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Editorial: The Journal's First 10 Years and Beyond

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Ten years ago, the *Journal of Gastrointestinal Surgery* (*JOGS*) launched its first issue in January, 1997 amid a storm of controversy. The contrarians within the Society for Surgery of the Alimentary Tract (SSAT) protested, "We don't need another surgical journal. We already have too many. The ones we have meet our needs satisfactorily." The supporters countered, "We need our own journal devoted to gastrointestinal surgery, one owned by the Society, a journal that will meet the needs of our members and of all surgeons in our country who practice gastrointestinal surgery, the largest segment of practice among the many general surgeons in the United States. The American College of Surgeons alone has 48,132 general surgeons among its current members. Moreover, the journal will reach out to surgeons practicing gastrointestinal surgery around the world." The discussion was vigorous at the Meeting of the SSAT Board of Trustees in October, 1995. The final vote came down in favor of a new journal. The name of the journal was quickly chosen, the coeditors were appointed, an editorial board established, and a contract signed with a publisher, Quality Medical Publishing, Inc. of St. Louis, MO, USA.

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Issue 1 of volume 1 appeared on time in January, 1997, as did the five other issues that year, and as have all subsequent issues over the last 10 years. The first issue was 96 pages in length. The issue contained two editorials, a review article, eight original scientific papers presented at the 1996 annual meeting of the SSAT, commentaries on those papers, three additional original scientific papers, and an obituary. A total of 596 pages were published in the six issues of volume 1. Of the 70 original scientific papers published that year, 81% were from the United States and 19% from foreign countries. Clinical papers comprised 61% of the total papers published and basic science papers 39%. The number of issues remained at six per year in volumes 1 through 5, but the number of pages increased by 18% from 596 pages in volume 1 to 706 pages in volume 5.

A new publisher, Elsevier, Inc., New York, NY, was recruited towards the end of year 5. The number of issues remained at six in volume 6, but the number increased to eight in volumes 7 and 8, and to nine in volume 9. By the time volume 9 was published the number of pages published per year had nearly doubled to 1,405 compared to the 596 pages of volume 1. A "How I Do It" section, a "Gastrointestinal Images" section, book reviews, guidelines for practice, supplements, announcements, abstracts from the American Hepato-Pancreato-Biliary Association (AHPBA) and the International Society for Digestive Surgery (ISDS) meetings, and letters to the editor had been added to the journal's material by this time. Also, the percent of clinical papers appearing in volume 9 had increased compared to that of volume 1. Clinical papers comprised 90% of the 152 scientific papers published in 2005, whereas only 10% were basic science papers. In addition, only 50% of the papers were from the United States, with the other 50% from foreign nations. Clearly, the journal had become more clinical and more international in

the first 9 years. Also, the number of members serving on the editorial board in 2006 increased somewhat to 55, compared to 47 serving when the journal was first published in 1997. Volume 10 of the journal had ten issues and 1,440 editorial pages.

Journal of Gastrointestinal Surgery has received high marks from the SSAT members, 88% of whom ranked it as very important or important in a membership survey done by an independent group in 2003. The members ranked 77% of the original, scientific articles in *JOGS* as very good or good, whereas 81% of the members read all or selected articles in the journal. The journal achieved an impact factor of 2.3 in 2005, placing it in the top 15% of the 139 surgical journals in our class. The SSAT and the journal have reached out to surgeons practicing gastrointestinal surgery in the US and in other parts of the world. The journal became the official journal of the AHPBA in 2002 and of the ISDS in 2003. Associations with other groups in other countries are pending.

We are pleased to begin our 11th year with a new publisher, Springer Science + Business Media, Inc., New York, NY. The submission, processing, and review of articles will soon be done online using the internet. Our editor's group has now grown to include two associate editors, Jeffrey B. Matthews, MD, of Chicago, IL, USA and Charles J. Yeo, MD, of Philadelphia, PA, USA. We expect to publish 12 issues in 2007 with 160 pages per issue, resulting in a total of 1,920 pages for the year.

We recognize the immense potential of the internet in facilitating communications around the world and plan to expand its use in the years to come. Using internet video to supplement the printed word seems likely to grow quickly in a field such as ours. Internet video will allow surgeons to demonstrate their operative techniques to others visually online just as though the viewers were in the operating room with the operating surgeon.

We believe the *JOGS* now serves a key role in our organization, the SSAT, and in the field of gastrointestinal surgery in our country and abroad. We thank the SSAT Board of Trustees, the SSAT members, our editorial board, our managing editors, our publishers, our authors, the AHPBA, the ISDS, our readers, and the many others who have been instrumental in making our journal a success over the last 10 years.

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Laparoscopic Restorative Proctocolectomy for Ulcerative Colitis

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Abstract Laparoscopic surgery of the colon has become an established method for the resection of both benign and malignant disease. Complex laparoscopic colon resections were once stigmatized due to their longer operating times and inherent technical difficulty. However, technological innovations and increased surgical experience with laparoscopy have advanced the field of complex laparoscopic surgery, including ileal pouch-anal anastomosis (IPAA) procedure, with safe feasible results. When these operations are broken down in a stepwise fashion, the complexity of the laparoscopic IPAA procedure becomes simplified, allowing one to effectively reproduce this operation. The systematic laparoscopic steps outlined establish a simple, reproducible approach to a laparoscopic IPAA procedure for ulcerative colitis patients. This approach to laparoscopic IPAA provides one with a viable approach to this complex operation.

Keywords Ileal pouch–anal anastomosis · Laparoscopy · Laparoscopic surgery

Introduction

Ileal pouch–anal anastomosis (IPAA) has become the surgical procedure of choice for chronic ulcerative colitis.[1] Technological innovations and increased surgical experience with laparoscopy have advanced the field of complex laparoscopic surgery to include operations such as the IPAA procedure.[2,4–6] Although early laparoscopic IPAA procedures had lengthy operative times, techniques utilized in today's operating forum have proven safe and efficient, with reduced operative times. When the technical steps are reviewed in a systematic fashion, the complexity of the laparoscopic IPAA procedure becomes simplified, allowing one to effectively reproduce this operation.[3]

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Positioning and Trocar Placement

The patient is placed in a combined synchronous position with both arms padded, protected, and tucked to the lateral aspect of the torso. The torso is secured with a chest strap in anticipation of frequent positional changes during the procedure. Legs are placed in Allen stirrups with careful attention to the height of the thighs, which should be level with the abdomen. Appropriate decompression is accomplished with a Foley catheter and an orogastric tube.

Four trocars are typically used, three 5-mm port sites and one 10–12-mm port site. At the proposed ileostomy site, a skin wheel is created and carried down into the abdomen in an open fashion. Through this, a 10–12-mm port is inserted. Once the pneumoperitoneum has been established, the 5-mm, 30 degree laparoscope is inserted and the abdomen surveyed. Prohibitive adhesions and unforeseen anatomical or inflammatory problems which preclude a laparoscopic approach should be assessed and immediate conversion initiated when appropriate.[3]

The remaining trocars are placed under direct visualization in a diamond configuration, in the left lower quadrant, suprapubic midline, and supraumbilically (Fig. 1a). In a patient in whom a hand-assisted-laparoscopic-surgery

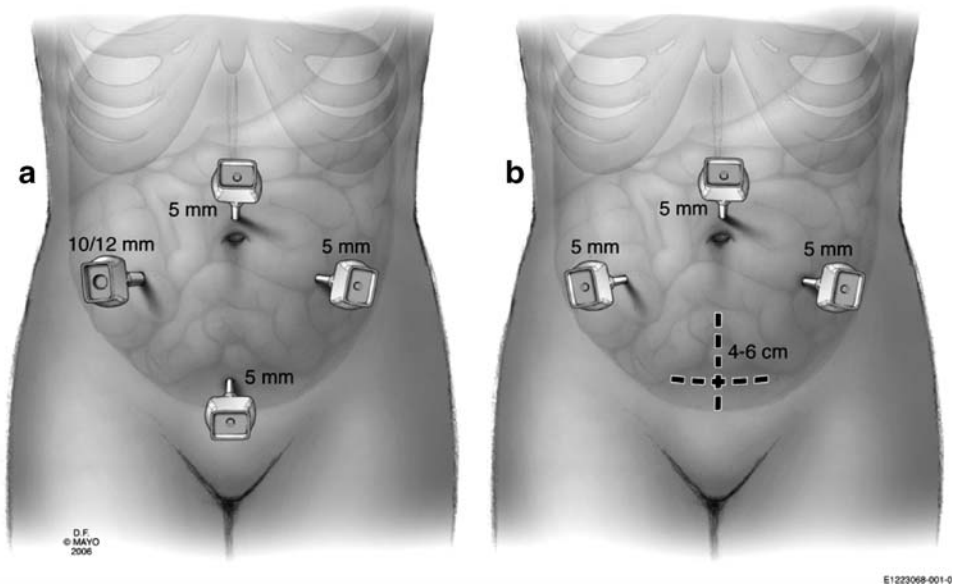

Figure 1 **a** Trocar placement for laparoscopic IPAA. **b** Trocar and handport placement for HALS IPAA.

(HALS) procedure is undertaken, the trocar placement is slightly different (Fig. 1b). Throughout the procedure, the first assistant will stand across from the surgeon, while the camera operator will most often share the surgeon's side of the table, utilizing the supraumbilical port.

Colectomy

The first two steps involve mobilization of the left side and the splenic flexure. The patient is placed in steep Trendelenburg with the left side elevated at a 30-degree angle to the ceiling.[3] With the surgeon on the patient's right side, the white line of Toldt is incised, reflecting the left colon medially as it is freed from its lateral peritoneal attachments (Fig. 2). Careful identification of the left ureter

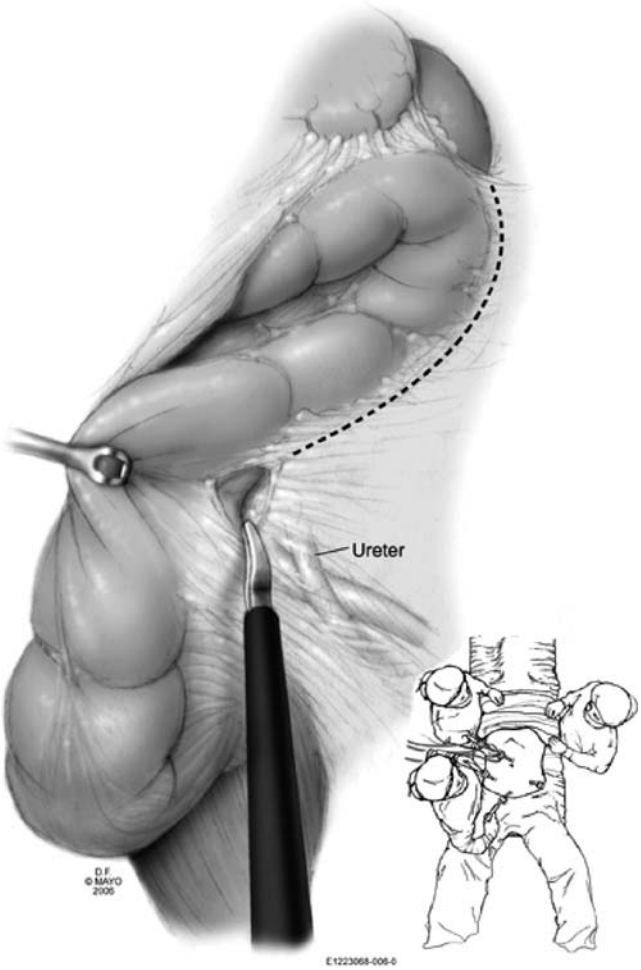

Figure 2 Left colon and sigmoid lateral dissection.

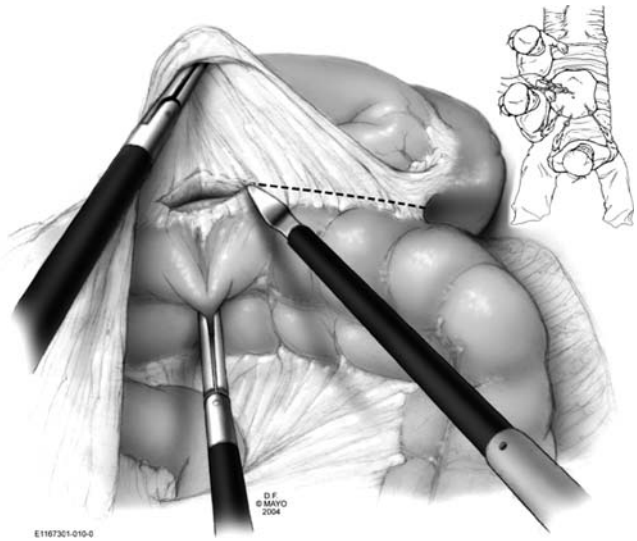

Figure 3 Splenic flexure takedown and dissection.

is paramount at this stage. To prevent undermining the kidney, one must remain focused on dissecting in the appropriate plane, which lies close to the colonic border.

To complete the mobilization of the splenic flexure, the patient is placed in reverse Trendelenburg, maintaining the right decubitus positioning. The surgeon moves from the patient's right side to the lithotomy position, utilizing the suprapubic and left lower quadrant ports for dissection.[6] The splenic flexure is mobilized off the retroperitoneum (Fig. 3). Once dissection has slowed, the surgeon may turn his/her attention to the lesser sac, which must be opened completely in a medial-to-lateral fashion. This technique ensures that splenic flexure mobilization is complete, allowing the flexure to drop to the level of the umbilicus and the left colon to lie medial to the left ureter.

The third and fourth steps involve mobilization of the right colon and the hepatic flexure. At this point, positioning is modified to facilitate the right-sided dissection. The patient is returned to Trendelenburg and the left side is placed in the lateral decubitus position. The surgeon and camera operator proceed to the patient's left side. The peritoneum surrounding the cecum and terminal ileum may be incised to reveal the retroperitoneal plane. The right ureter should be identified and protected. Once the colon's lateral attachments are incised, the medial attachments of the ileum mesentery are elevated above the level of the retroperitoneum. These medial peritoneal attachments are incised up to the duodenum to facilitate the surgeon's ability to achieve the maximum length of the small bowel mesentery (Fig. 4).[2]

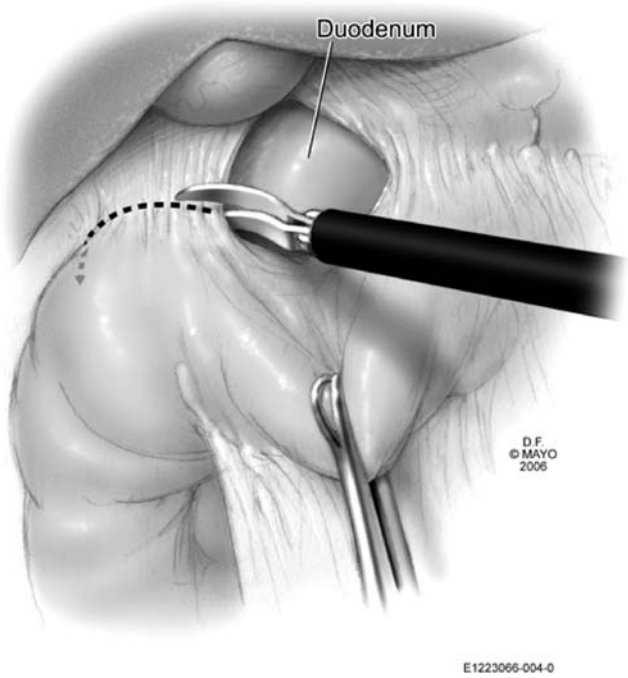

Figure 5 Hepatic flexure takedown and dissection.

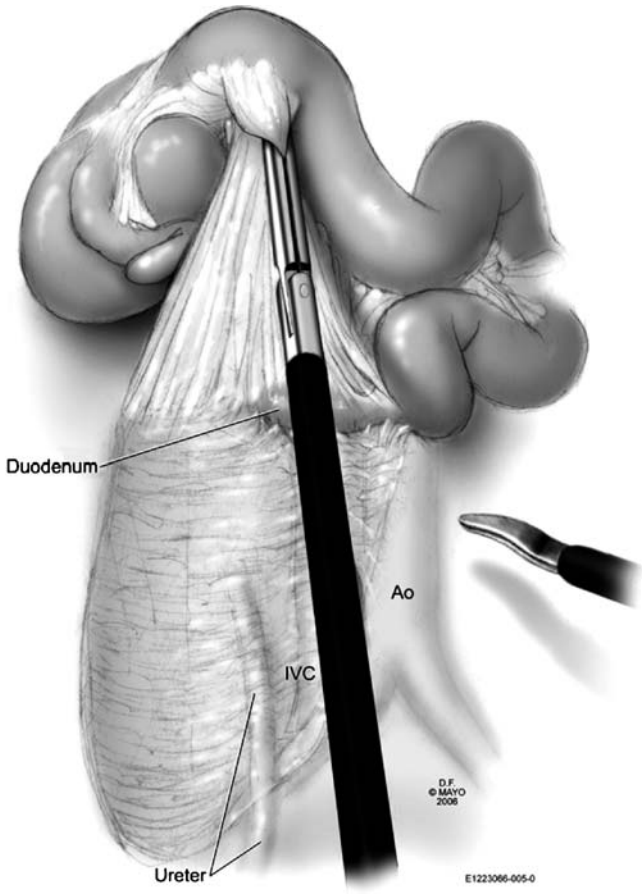

Figure 4 Right colon dissection.

Mimicking the dissection from the left side, the patient is now placed in reverse Trendelenburg, maintaining the left lateral decubitus position. With surgeon and camera operator on the patient's left side, the gastro-colic ligament is grasped near the bowel and elevated toward the abdominal wall.[2] Entering the space between the gastro-

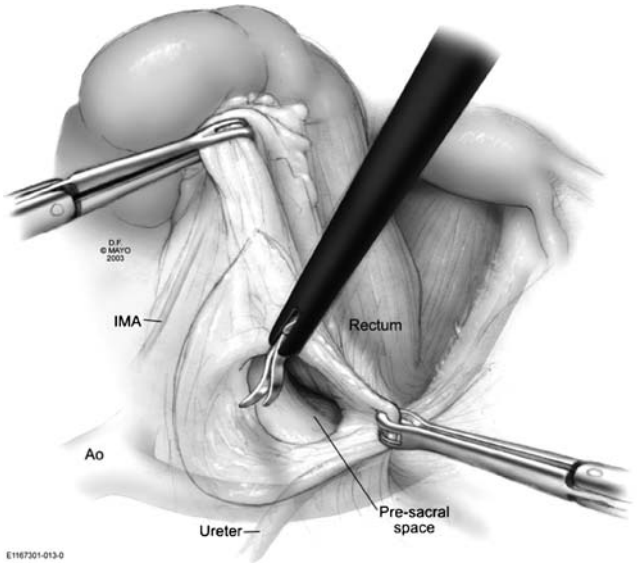

Figure 6 Rectal dissection.

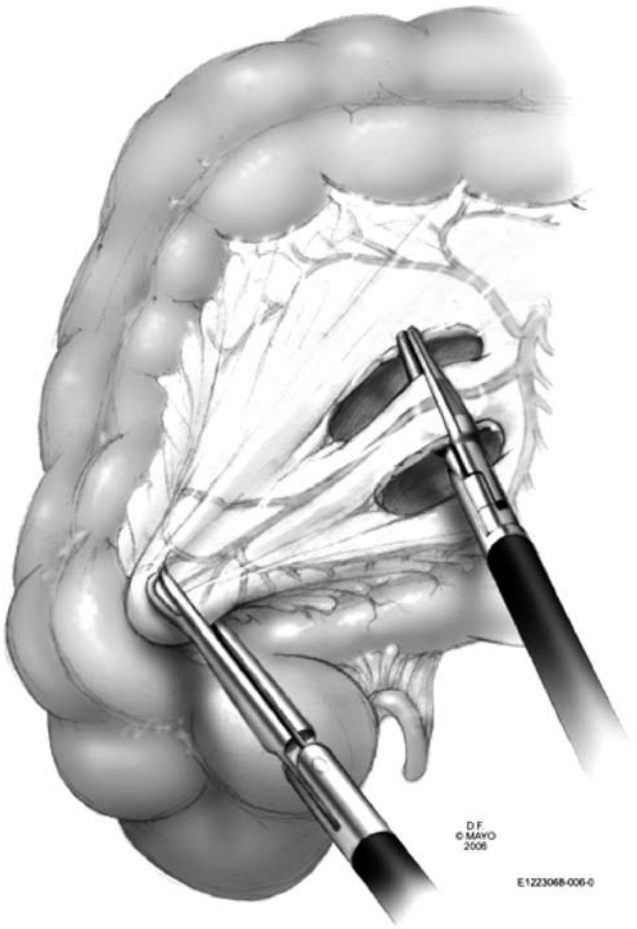

Figure 7 Intracorporeal vessel ligation.

colic ligament and the transverse mesocolon will facilitate mobilization of the hepatic flexure, which proceeds laterally. The duodenum is now identified form the superior aspect and protected (Fig. 5). Final steps include completely incising all remaining peritoneal attachments to the duodenum and the head of the pancreas.

Proctectomy

Completing the fifth and final step, one returns to the Trendelenburg position and the patient's horizontal position is flattened. The rectal dissection may proceed with a laparoscopic-assisted or hand-assisted technique. The systematic steps of a HALS rectal dissection are identical to a laparoscopic-assisted dissection, with the exception that, in HALS, the rectum is dissected through the handport site, and in a laparoscopic-assisted IPAA, the rectal dissection is completed with a laparoscopic technique.

The left pararectal fascia is addressed first, after reidentifying the ureters on both sides. Scoring the fascia to the left of the rectum, the presacral space is entered. Mirror dissection is then carried out on the right side of the rectum (Fig. 6). The surgeon alternates right to left until the two dissection planes meet posteriorly and the rectal dissection reaches the pelvic floor. Anterior dissection is facilitated by superior retraction of the vagina and uterus, either with a vaginal sponge stick, suspension clips, suture in the broad ligament, or laparoscopic retraction.[3] Circumferential dissection is then completed in the anterior and posterior positions. A digital rectal examination will confirm the level of distal dissection, which should be at the level of the pelvic floor. Once full mobilization has been accomplished, all vessels may be intracorporeally ligated with a vessel-sealing device (Fig. 7).

Deciding which technique to use for the rectal transection is based on surgeon preference and anatomical considerations. For the thin patient with a wide pelvis, intracorporeal stapling may be the technique of choice.

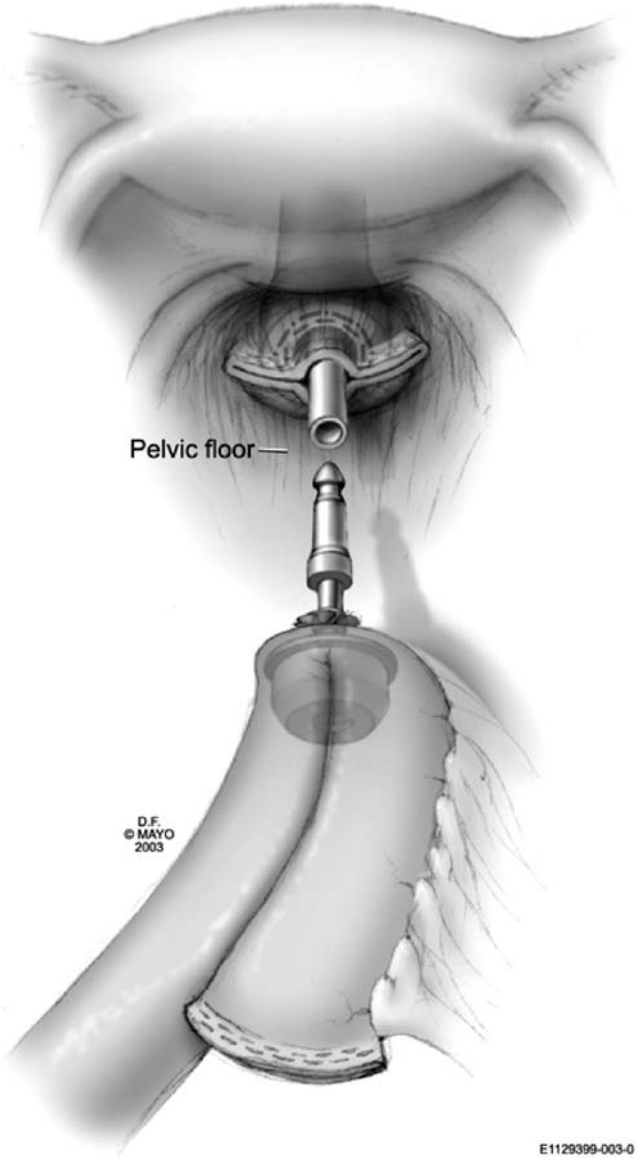

Figure 8 Creation of IPAA.

If the patient has a narrow pelvis or has an above-average BMI, one may need to utilize the exteriorization site to place the stapling device. With an assistant applying external perineal pressure, the laparoscopic reticulating stapler is inserted through the right 10–12-mm port, advanced to the pelvic floor, and fired. Care is taken to avoid including adjacent structures in the staple line.[4]

Exteriorization, Pouch Creation, and Anastomosis

Once all vessels are ligated, the colon is pulled into the pelvis, allowing the small bowel to drift superiorly under the colon. At this point, a 4–6-cm incision is created, depending on the patient's body habitus, to allow the exteriorization of the colon, rectum, and terminal ileum. This incision may be a Pfannenstiel incision or a subumbilical, low midline incision, at the surgeon's discretion. The terminal ileum is transected with a gastrointestinal anastomosis (GIA) linear stapler. The colon specimen is passed off the field and sent to pathology.

Through the incision, the pouch is created extracorporeally, similar to open surgery. Length is assessed, assuring that the pouch reaches below the pubic symphsis externally. The distal ileum is placed in a J configuration and a linear GIA stapler is inserted through an incision at the apex. The pouch is created upon stapling the septum. The anvil of the circular stapler is inserted into the apex of the pouch and a purse string is applied. The pouch is returned to the abdomen and the length is again assessed for adequacy.

The end-to-end anastomosis (EEA) stapler is inserted through the anus and brought out adjacent to the rectal staple line. The anvil exiting the pouch is grasped and connected with the rectal EEA stapler (Fig. 8). Correct positioning of the pouch, and pouch mesentery, is confirmed and the stapler is subsequently fired. The abdomen is then filled with irrigation fluid and the pouch–anal anastomosis insufflated with a proctoscope while laparoscopically assessing for an air leakage. Upon exiting the abdomen, a drain may be placed through the left 5-mm ports and positioned next to the pouch. Temporary fecal diversion is performed with a portion of proximal ileum. This loop ileostomy is brought through the previously created right lower quadrant site in standard fashion. All trocars are then removed, the fascia and skin incisions are closed, and the loop ileostomy matured.[3]

Discussion

Laparoscopic surgery of the colon has become an established method for the resection of both benign and malignant disease.[2,4–6] Complex laparoscopic colon resections were once stigmatized due to their longer operating times and inherent technical difficulty. The systematic laparoscopic steps outlined above establish a simple, reproducible approach to a laparoscopic IPAA procedure for ulcerative colitis patients.[3] This approach to laparoscopic IPAA confirms laparoscopy as a viable approach to complex colon procedures.

References

1. Farouk, R., Pemberton, J. H., Wolff, B. G., Dozis, R. R., Browning, S., & Larson, D. (2000). Functional outcomes after ileal pouch–anal anastomosis for chronic ulcerative colitis. *Annals of Surgery, 231*(6), 919–926.
2. Larson, D. W., & Nelson, H. (2004). Laparoscopic colectomy for cancer. *Journal of Gastrointestinal Surgery, 8*(5), 636–642.
3. Larson, D. W., & Young-Fadok, T.M. (2002). *Laparoscopic ileal pouch–anal anastomosis*. Mayo Clinic: Rochester.
4. Larson, D. W., Dozois, E. J., Piotrowicz, K., Cima, R. R., Wolff, B. G., & Young-Fadok, T. M. (2005). Laparoscopic-assisted vs. open ileal pouch–anal anastomosis: functional outcome in a case-matched series. *Diseases of the Colon and Rectum, 48*, 1845–1850.
5. Larson, D. W., Cima, R. R., Dozois, E. J., Davies, M., Piotrowicz, K., Barnes S. A., Wolff, B., & Pemberton, J. H. (2006). Safety, feasibility, and short-term outcomes of laparoscopic ileal-pouch anal anastomosis a single institution case-matched experience. *Annals of Surgery, 243*(5), 667–672.
6. Young-Fadok, T. M., & Nelson, H. (2000). Laparoscopic right colectomy: five-step procedure. *Diseases of the Colon and Rectum, 43*(2), 267–271; discussion 271–273.

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Anastomotic Leakage is Associated with Poor Long-Term Outcome in Patients After Curative Colorectal Resection for Malignancy

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Abstract The impact of anastomotic leakage on long-term outcomes after curative surgery for colorectal cancer has not been well documented. This study aimed to investigate the effect of anastomotic leakage on survival and tumor recurrence in patients who underwent curative resection for colorectal cancer. Prospectively collected data of the 1,580 patients (904 men) of a median age of 70 years (range: 24–94), who underwent potentially curative resection for colorectal cancer between 1996 and 2004, were reviewed. Cancer-specific survival and disease recurrence were analyzed using Kaplan Meier method, and variables were compared with log rank test. Cox regression model was used in multivariate analysis. The cancer was situated in the colon and the rectum in 933 and 647 patients, respectively. Anastomotic leakage occurred in 60 patients (clinical leakage: $n=48$; radiological leak: $n=12$). The leakage rate was significantly higher in patients with surgery for rectal cancer (6.3 vs 2.0%, $p<0.001$). The 5-year cancer-specific survivals were 56.9% in those with leakage and 75.9% in those without leakage ($p=0.012$). The 5-year systemic recurrence rates were 48.4 and 22.6% in patients with and without anastomotic leak, respectively ($p=0.001$), whereas the 5-year local recurrence rates were 12.9 and 5.7%, respectively ($p=0.009$). Anastomotic leakage remained an independent factor associated with a worse cancer-specific survival ($p=0.043$, hazard ratio: 1.63, 95% CI: 1.02–2.60) and a higher systemic recurrence rate (hazard ratio: 1.94, 95% CI: 1.23–3.06, $p=0.004$) on multivariate analysis. In rectal cancer, anastomotic leakage was an independent factor for a higher local recurrence rate (hazard ratio: 2.55, 95% CI: 1.07–6.06, $p=0.034$). In conclusion, anastomotic leakage is associated with a poor survival and a higher tumor recurrence rate after curative resection of colorectal cancer. Efforts should be undertaken to avoid this complication to improve the long-term outcome.

Keywords Anastomotic leakage · Colorectal cancer · Curative colorectal resection · Cancer-specific survival · Malignancy

This work was presented in the plenary session of the 47th Annual Meeting of the Society for Surgery of the Alimentary Tract at the Digestive Disease Week in Los Angeles on 22 May 2006.

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Introduction

Colorectal cancer is a common malignancy in Western countries. Its incidence is also increasing in many Asian societies and is currently the second most common cancer as well as the second cause of cancer-related mortality in Hong Kong.[1] Despite improvements in surgical techniques and perioperative management, anastomotic leakage remains one of the most dreadful complications after colorectal surgery. The reported incidences varied from 0.5 to over 30%,[2–11] depending on the inclusion criteria, the case mix, and the definition of leak. Leakage occurs more frequently in distal rectal anastomoses[7,10,12,13] and in patients undergoing emergency operations.[14] The severity of the septic consequence resulting from anastomotic leakage also varies from subclinical radiological evidence to generalized fecal peritonitis. It has been well documented that anastomotic leakage

adversely affects the short-term outcome after colorectal surgery, and patients with leakage have higher mortality and morbidity as well as a longer hospital stay.[4,6,11,15]

The effect of anastomotic leakage on long-term oncologic outcome is more controversial. A few recent studies showed that anastomotic leakage was associated with a poor survival as well as a high local recurrence rate.[2–6]

The aim of this study was to evaluate the impact of anastomotic leakage on the long-term survival and recurrences, both local and systemic, in patients who had undergone curative resection for colorectal cancer.

Patients and Methods

Consecutive patients who underwent potentially curative resection of primary adenocarcinoma of colon and rectum from January 1996 to December 2004 in the Department of Surgery, University of Hong Kong Medical Centre, were included in the study. Those patients with tumors associated with familial adenomatous polyposis or inflammatory bowel diseases, those with palliative resections, resections without an anastomosis, and local excision of rectal cancers were excluded. Data on the patients' demographics, operative details, postoperative outcomes, and disease status were collected prospectively.

The diagnosis of colorectal cancer was made by colonoscopy and biopsy unless there were contraindications of the procedure. In case of an elective operation, the patient received mechanical bowel preparation with polyethylene glycol electrolytes solution the day before surgery and prophylactic intravenous antibiotics were administered at the induction of anesthesia. During the study period, most of the procedures were performed or closely supervised by the same team of staff colorectal surgeons. Surgery for rectal and rectosigmoid cancers was performed with sharp perimesorectal dissection to keep the visceral pelvic fascia, which enveloped the mesorectum, intact. Total mesorectal excision was performed for patients with mid and distal rectal cancer, and diversion stoma was created selectively. In case of an upper and rectosigmoid tumor, the mesorectum was transected at the level of rectal transection, which was 4–5 cm distal to the tumor. Rectal anastomoses were performed with double stapling technique except in a small number of patients who underwent peranal coloanal anastomosis for ultralow tumors. After our analysis of patients with total mesorectal excision for mid and distal rectal cancer, diversion stoma was performed for all patients with total mesorectal excision with the anastomosis within 5 cm from the anal verge. In surgery for colonic cancer, the oncologic principle with adequate lymphadenectomy was observed. The method of anastomosis was decided by the surgeon, and a hand-sutured anastomosis was usually performed.

From 1996 to June 2000, the operations were performed through a midline incision. Laparoscopic approach, according to the same oncologic principle, was adopted in selected patients from June 2000.

Clinical anastomotic leak was considered to be present if any of the following features was observed: the presence of peritonitis caused by anastomotic dehiscence; the presence of feculent substances or gas from the drain; the presence of abscess with demonstration of anastomotic leak by clinical, endoscopic, or radiological examination. Contrast enema was routinely performed in patients with a diversion stoma after rectal surgery, and radiological leakage was defined as extravasation of contrast material during the radiological examination.

Operative mortality was defined as death that occurred within 30 days after the primary operation. In the analysis of survival and recurrences, patients with operative mortality were excluded.

Postoperative Surveillance

Patients were followed up at an interval of 2 to 3 months during the first 2 years and at 4- to 6-month interval from the third to fifth year. Thereafter, the patients were seen yearly. Full history, physical examination, blood tests, and serum carcinoembryonic antigen were performed at each follow-up visit. If recurrences were suspected, endoscopic examination and CT scan would be performed to confirm the diagnosis and to determine whether salvage surgery could be performed.

Statistical Analysis

Comparison of categorical variables was performed using chi-square test or Fisher's exact test where appropriate. Continuous variables were presented in median values and were compared using Mann–Whitney U test. Survival was analyzed using the Kaplan Meier method, and comparison of variables was performed with log rank test. Variables with p values less than 0.2 were put to multivariate analysis using Cox proportional hazards regression. P values of less than 0.05 were regarded as statistically significant.

Results

During the study period, 1,580 patients (904 men) with median age of 70 years (range: 24–94 years) underwent

potentially curative resection for primary colorectal cancer. The sites of the tumors are shown in Table 1. Rectal and rectosigmoid cancer constituted 40.4% of all cases. Diversion stoma was performed in 77.4% of patients with mid and distal rectal cancer (within 12 cm from the anal verge), 7.9% of patients with upper rectal cancer, and 1.3% of patients with colon cancer ($p<0.001$). Anastomotic leakage occurred in 60 patients (3.8%). Forty-eight patients had clinical leak, and 12 demonstrated subclinical radiological leak. Comparisons of the patients' characteristics and postoperative outcomes of those with and without anastomotic leakage are shown in Table 2. The only risk factor for anastomotic leakage was the site of the tumor, and patients with rectal cancer had a significantly higher incidence of leakage. In those patients with mid and distal rectal cancer, there was no difference in leakage in those with or without a diversion stoma (8.4 vs 9.3%, $p<0.694$). Anastomotic leak was associated with a higher reoperation rate, and 32 patients (53.3%) with anastomotic leakage required operative treatment. The median hospital stay was also significantly longer in the leakage group.

Thirty-five patients died within 30 days after the operations, and the operative mortality was 2.2%. Among them, six had anastomotic leakage (17.1%), and the 30-day mortality of patients who developed anastomotic leakage was 10%. Of the six patients who died of anastomotic leakage, five had colonic cancer and three underwent emergency operation for obstruction. The 30-day mortality rates of patients with leakage after rectal and colon cancer surgery were 2.5 and 26.3%, respectively ($p=0.01$).

Survival

The median follow-up period of the surviving patients was 46.2 months. The 5-year overall survival and cancer-specific survivals by Kaplan Meier method were 63.9 and 70.7%, respectively. The relationships between the cancer-specific survival and the patient and tumor characteristics are shown in Table 3. The 5-year cancer-specific survivals of patients with or without leakage were 56.9 and 75.9%, respectively ($p=0.012$) (Fig. 1). The presence of anastomotic leakage, stage-III and stage-IV disease, lymphovascular invasion, and emergency operations were independent factors associated with a poor cancer-specific survival on multivariate analysis (Table 3).

Table 1 Sites of the Tumors

	Frequency (%)
Cecum	92 (5.8)
Ascending colon	129 (8.2)
Hepatic flexure	91 (5.8)
Transverse	122 (7.7)
Splenic flexure	38 (2.4)
Descending	99 (6.3)
Sigmoid	372 (23.5)
Rectosigmoid	121 (7.7)
Rectum	516 (32.7)
Total	1,580 (100)

Table 2 Comparison of Characteristics and Outcomes of Patients With and Without Anastomotic Leakage

	Number without leak	Number with leak	*P* value
Male	864	40	0.145
Female	656	20	
Median age (IRQ)	70 (61–77)	69 (62–73.75)	0.151
Colon	914	19	<0.001
Rectum	606	41	
Medical illness	808	35	0.510
No medical illness	712	25	
Laparoscopic resection	267	6	0.163
Open resection	1,253	54	
Emergency operation	195	10	0.243
Elective operation	1,325	50	
Stages I and II	900	33	0.507
Stages III and IV	618	27	
30-day mortality			0.002
Yes	29	6	
No	1,491	54	
Reoperation			<0.001
Yes	35	32	
No	1,485	28	
Median hospital stay (IRQ)	8 (7–10)	19 (11.3–30.8)	<0.001

IRQ Interquartile range

Recurrence

The 5-year overall recurrence rate (including local and systemic recurrences) by Kaplan Meier method was 28.0%. The factors that affected overall recurrence are shown in Table 4. The 5-year recurrence rates in patients with and without anastomotic leakage were 53.8 and 27.0%, respectively ($p<0.001$). Multivariate analysis showed that anastomotic leakage remained an independent significant factor associated with disease recurrence (Table 4).

The 5-year local and systemic recurrence rates were 6.0 and 24.4%, respectively. Patients with anastomotic leakage had a significantly higher systemic recurrence rate when compared with that of patients without leakage (48.4 vs 22.6%, $p=0.001$) (Fig. 2). The 5-year local recurrence rate was also significantly higher in those with leakage (12.9 vs 5.7%, $p=0.009$) (Fig. 3). The relationships of other factors with local and systemic recurrences are shown in Table 5.

Table 3 Association of Cancer-Specific Survival with Patient and Tumor Characteristics

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Female	1	0.79–1.25	0.946			
Male	0.99					
Age ≤70	1	0.81–1.27	0.911			
Age >70	1.01					
Colon cancer	1	0.92–1.15	0.601			
Rectal cancer	1.03					
No medical illness	1	0.83–1.30	0.745			
Medical illness	1.04					
No diversion stoma	1	0.90–1.49	0.246			
Diversion	1.16					
Open resection	1	0.56–1.13	0.198	1	0.63–1.30	0.578
Laparoscopic resection	0.79			0.902		
Elective operation	1	1.57–2.75	<0.001	1	1.48–2.63	<0.001
Emergency operation	2.08			1.97		
Stages I and II	1	2.31–3.69	<0.001	1	1.94–3.17	<0.001
Stages III and IV	2.92			2.48		
No anastomotic leak	1	1.13–2.86	0.012	1	1.02–2.60	0.043
Anastomotic leak	1.80			1.63		
Lymphovascular invasion						
No	1	1.81–2.93	<0.001	1	1.27–2.12	<0.001
Yes	2.30			1.64		
Differentiation						
Well and moderate	1	1.29–2.59	0.002	1	0.95–1.94	0.091
Poor	1.83			1.36		

In those patients with total mesorectal excision for mid and distal rectal cancer, the presence of diversion stoma did not have any impact on the local or systemic recurrence rates ($p>0.05$).

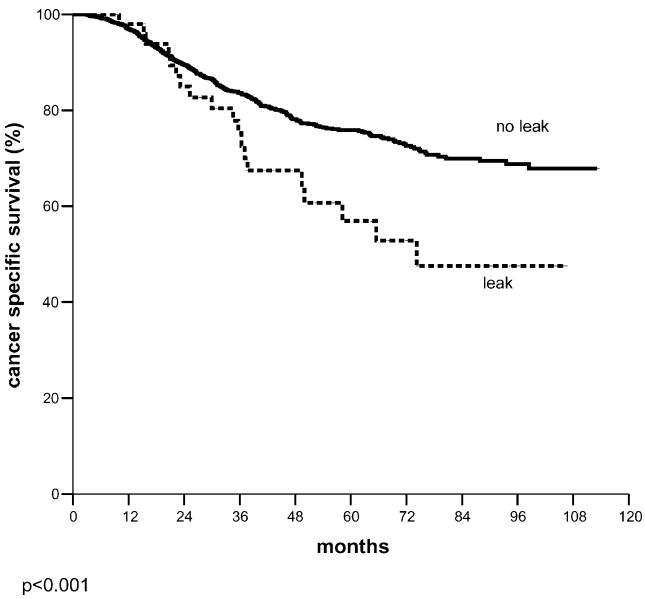

Figure 1 Comparison of cancer-specific survival of patients with and without anastomotic leak.

Multivariate analysis of factors associated with systematic recurrence demonstrated that anastomotic leakage remained an independent factor (hazard ratio: 1.94, 95% confidence interval: 1.23–3.06, $p=0.004$). Other independent factors included advanced stage, lymphovascular invasion, and emergency surgery (Table 6).

The independent factors associated with a higher incidence of local recurrence were advanced tumor stage, rectal cancer, and poor differentiation (Table 7). Anastomotic leakage was not an independent factor associated with increased local recurrence on multivariate analysis. However, in the subgroup analysis of patients with rectal cancer, advanced tumor stage (hazard ratio: 2.73, 95% confidence interval: 1.46–5.14, $p=0.002$) and the presence of anastomotic leakage (hazard ratio: 2.55, 95% confidence interval: 1.07–6.06, $p=0.034$) were the two independent risk factors associated with a higher local recurrence rate.

Discussion

The present study showed that the anastomotic leakage rate of patients who underwent curative resection for colorectal cancer was 3.8%, and this is comparable to other recently published series which included over 1,000 patients.[2,4,6,7,16] We also demonstrated that the incidences

Table 4 Association of Overall Tumor Recurrence with Patient and Tumor Characteristics

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Female	1	0.80–1.22	0.903			
Male	0.99					
Age ≤70	1	0.78–1.19	0.747			
Age >70	0.97					
Colon cancer	1	0.85–1.06	0.343			
Rectal cancer	0.95					
No medical illness	1	0.71–1.08	0.221			
Medical illness	0.877					
Open resection	1	0.54–1.01	0.058	1	0.58–1.09	0.152
Laparoscopic resection	0.739			0.79		
Elective operation	1	1.24–2.14	0.001	1	1.12–1.97	0.006
Emergency operation	1.63			1.48		
Stages I and II	1	2.19–3.37	<0.001	1	1.85–2.90	<0.001
Stages III and IV	2.72			2.32		
No anastomotic leak	1	1.41–3.29	<0.001	1	1.27–2.98	0.002
Anastomotic leak	2.16			1.95		
Lymphovascular invasion						
No	1	1.78–2.79	<0.001	1	1.27–2.06	<0.001
Yes	2.23			1.62		
Differentiation						
Well and moderate	1	1.32–2.52	<0.001	1	0.98–1.89	0.068
Poor	1.82			1.36		

and the characteristics of leakage in patients with colon and rectal cancers were different. In cases of surgery for colon cancer, the leakage rate was only 2.0% and was significantly lower than that of rectal cancer surgery. However, the septic consequences were more severe, and the operative mortality was significantly higher. This is because leakage after intraperitoneal anastomosis usually leads to generalized peritonitis and more severe sepsis, rendering reoperation necessary and resulting in a higher mortality. In our recently performed study on leakage after intraperitoneal anastomoses, surgery performed on an emergency setting and the high American Society of Anesthesiologist classes were the independent significant risk factors associated with a higher leakage rate (unpublished data).

In cases of mid and distal rectal cancer, with the widespread practice of total mesorectal excision in the recent two decades, leakage rates of more than 10% were usually reported.[10,12,17–19] The level of the anastomosis has

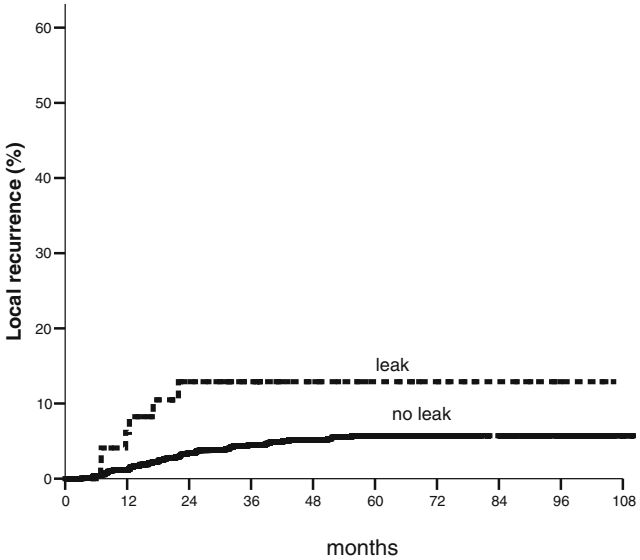

Figure 2 Comparison of local recurrence rate of patients with and without anastomotic leak.

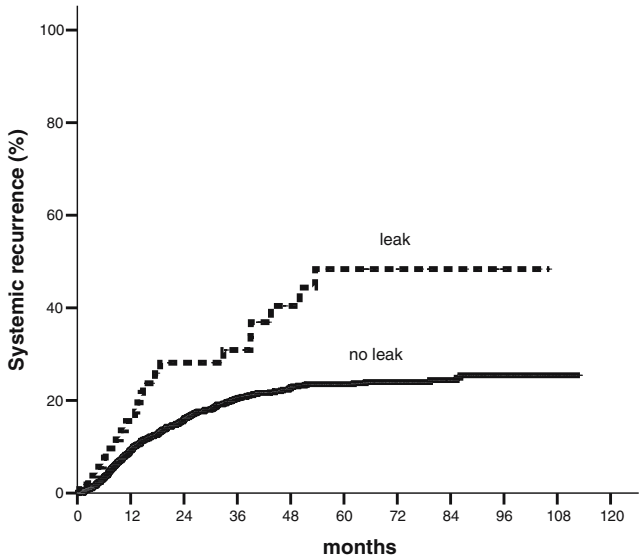

Figure 3 Comparison of systemic recurrence rates of patients with and without anastomotic leak.

Table 5 Analysis of Patient and Tumor Factors Affecting Local and Systemic Recurrences

	Local recurrence			Systemic recurrence		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Female	1	0.69–1.80	0.652	1	0.78–1.22	0.814
Male	1.17			0.97		
Age ≤70	1	0.57–1.48	0.721	1	0.76–1.19	0.653
Age >70	0.92			0.95		
Colon cancer	1	1.47–3.94	<0.001	1	0.76–1.20	0.709
Rectal cancer	2.41			0.96		
Medical illness	1	0.47–1.22	0.246	1	0.73–1.14	0.409
No medical illness	0.75			0.91		
Open resection	1	0.21–1.15	0.101	1	0.59–1.08	0.142
Laparoscopic resection	0.49			0.80		
Elective operation	1	0.41–1.98	0.804	1	1.34–2.39	<0.001
Emergency operation	0.91			1.78		
Stages I and II	1	1.59–4.23	<0.001	1	2.16–3.43	<0.001
Stages III and IV	2.59			2.72		
No anastomotic leak	1	1.26–4.75	0.009	1	1.32–3.27	0.001
Anastomotic leak	2.92			2.08		
Lymphovascular invasion						
No	1	1.25–3.45	0.005	1	1.81–2.93	<0.001
Yes	2.07			2.30		
Differentiation						
Well or moderate	1	1.13–4.55	0.014	1	1.18–2.40	0.004
Poor	2.33			1.68		

HR Hazard ratio, *CI* confidence interval

been shown to be the most important determinant of anastomotic leakage.[7,12,20,21] Karanjia et al.[10] reported a clinical leakage rate of 11% and a radiological leakage rate of 6.4% in patients after total mesorectal excision. All major leaks occurred in anastomoses below 6 cm from the anal verge, and diversion was suggested in patients with distal anastomoses.[10] In our previous study, we found that in patients undergoing anterior resection for rectal cancer, the performance of total mesorectal excision, and thus a distal rectal anastomosis, was associated with a higher leakage rate.[13] In patients treated with total mesorectal excision with the anastomosis within 5 cm from the anal verge, male gender and the absence of proximal diversion were the independent factors associated with a higher incidence of leak.[17]

Many studies, especially the early ones, did not demonstrate any association of anastomotic leakage with long-term outcomes.[10,20,22,23] With the improvement in perioperative care, more patients survived the septic consequences of anastomotic leakage, and long-term outcome can be analyzed in studies which included a larger number of patients.

In a study on 167 patients with colorectal cancer, Akyol et al.[24] showed that anastomotic leakage was associated with a higher overall and local recurrence rates as well as a higher cancer-specific mortality. Fujita et al.[5] showed similar results in a study of 980 patients operated on over a 20-year period. Subsequent studies on rectal cancer also demonstrated a higher local recurrence rate in patients with anastomotic leakage.[3,6,25,26] In our study, anastomotic

Table 6 Multivariate Analysis of Factors Associated with Systemic Recurrence

	HR	95.0% CI	*P* value
Advanced stage (stages III and IV)	2.30	1.81–2.93	<0.001
Emergency operation	1.64	1.23–2.20	0.001
Poor differentiation	1.22	0.84–1.75	0.297
Lymphovascular permeation	1.70	1.31–2.19	<0.001
Anastomotic leakage	1.94	1.23–3.06	0.004
Laparoscopic resection	0.84	0.60–1.19	0.310

HR Hazard ratio, *CI* confidence interval

Table 7 Multivariate Analysis of Factors Associated with Local Recurrence

	HR	95.0% CI	*P* value
Advanced stage (stage III and IV)	2.20	1.31–3.68	0.003
Poor differentiation	2.08	1.04–4.15	0.039
Lymphovascular permeation	1.28	0.74–2.22	0.379
Anastomotic leakage	2.05	0.88–4.77	0.097
Laparoscopic surgery	0.53	0.23–1.24	0.143
Rectal cancer	0.68	0.53–0.87	0.003

HR Hazard ratio, *CI* confidence interval

leakage was associated with local recurrence in univariate analysis but not in multivariate analysis when both colon and rectal cancers were included. However, in the subgroup analysis of rectal cancer, anastomotic leakage was shown to be an independent factor for a higher incidence of local recurrence. This is similar to the results from the multicenter study performed by Branagan and Finnis.[6]

Poor survival in patients with anastomotic leakage has recently demonstrated in two studies, each of which included over 1,500 patients. In an Australian study on 1,722 patients who underwent curative resection with colorectal anastomosis in a single institution over 20 years, Walker et al.[2] demonstrated that anastomotic leakage was associated with poor overall survival and cancer-specific survivals. McArdle et al.[4] also reported similar results in a multicenter study of 2,235 patients in the United Kingdom. Our study included a sizable of patients managed within a relatively short period of time (over 9 years), and the operations were performed by the same surgical team. Thus, variations in surgical technique and treatment protocol, which could be important determinants of oncologic outcome, were avoided.

We demonstrated that anastomotic leakage is an independent significant factor associated with a poor cancer-specific survival as well as a higher overall and systemic recurrence rates. The poor survival is likely to be the direct results of a higher recurrence rate.

The mechanisms for a high recurrence rate, and thus a poor survival after anastomotic leakage, have not been elucidated. The presence of viable tumor cells at the site of the anastomosis as well as the staple line has been demonstrated.[27–29] Viable exfoliated cells can be deposited and implanted in the pelvis in the situation of anastomotic leakage, accounting for recurrence of the disease. Actually, patients with perforated tumors have been reported to have poor survival.[30] Moreover, occult distant metastasis and circulating tumor cells in patients with curative resection for colorectal cancer are not uncommon.[31–33] The progress and growth of these viable tumor cells involve an interaction with the host's response. The systemic inflammatory response has been shown to be associated with poor outcome in patients with curative treatment of colorectal cancer.[34–36] With the sepsis associated with anastomotic leakage, the systemic inflammatory response is exaggerated. The release of the proinflammatory cytokines may alter the host defense and promote the growth of the residual or implanted tumor cells.

With increasing evidence showing the association of poor survival and increased recurrence with anastomotic leakage after colorectal resection for cancer, it is of utmost importance to pay attention to every detail of the operation to avoid an anastomotic leak. Moreover, aggressive adjuvant therapy and close postoperative surveillance should also be offered to patients with leakage, which is a risk factor for poor long-term outcomes.

In conclusion, the present study showed that the anastomotic leakage was an independent factor associated with a poor cancer-specific survival and high overall and systemic recurrence rates in patients who underwent curative resection for colorectal cancer. In patients with rectal cancer, anastomotic leakage was also an independent factor associated with a higher local recurrence rate. Thus, measures to minimize the risk of anastomotic leakage are important to improve long-term outcomes in surgery for colorectal cancer.

References

1. Hong Kong Cancer Registry Hong Kong Hospital Authority. Hong Kong Cancer Registry. Cancer Incidence and Mortality in Hong Kong. http://www.ha.org.hk/cancereg/ [Accessed May 2006].
2. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH, et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004;240:255–259.
3. Petersen S, Freitag M, Hellmich G, Ludwig K. Anastomotic leakage: Impact on local recurrence and survival in surgery of colorectal cancer. Int J Colorectal Dis 1998;13:160–163.
4. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg 2005;92:1150–1154.
5. Fujita S, Teramoto T, Watanabe M, Kodaira S, Kitajima M. Anastomotic leakage after colorectal cancer surgery: A risk factor for recurrence and poor prognosis. Jpn J Clin Oncol 1993;23:299–302.
6. Branagan G, Finnis D. Prognosis after anastomotic leakage in colorectal surgery. Dis Colon Rectum 2005;48:1021–1026.
7. Vignali A, Fazio VW, Lavery IC, Milsom JW, Church JM, Hull TL, et al. Factors associated with the occurrence of leaks in stapled rectal anastomoses: A review of 1,014 patients [see comments]. J Am Coll Surg 1997;185:105–113.
8. Stewart BT, Woods RJ, Collopy BT, Fink RJ, Mackay JR, Keck JO. Early feeding after elective open colorectal resections: A prospective randomized trial. Aust NZ J Surg 1998;68:125–128.
9. Pakkastie TE, Ovaska JT, Pekkala ES, Luukkonen PE, Jarvinen HJ. A randomised study of colostomies in low colorectal anastomoses. Eur J Surg 1997;163:929–933.
10. Karanjia ND, Corder AP, Bearn P, Heald RJ. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of the rectum. Br J Surg 1994;81:1224–1226.
11. Isbister WH. Anastomotic leak in colorectal surgery: A single surgeon's experience. ANZ J Surg 2001;71:516–520.
12. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355–358.
13. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: A prospective evaluation of 622 patients. Ann Surg 2004;240:260–268.
14. Bokey EL, Chapuis PH, Fung C, Hughes WJ, Koorey SG, Brewer D, et al. Postoperative morbidity and mortality following resection of the colon and rectum for cancer. Dis Colon Rectum 1995;38:480–486.
15. Alves A, Panis Y, Trancart D, Regimbeau JM, Pocard M, Valleur P. Factors associated with clinically significant anastomotic

leakage after large bowel resection: Multivariate analysis of 707 patients. World J Surg 2002;26:499–502.
16. Fazio VW, Tekkis PP, Remzi F, Lavery IC. Assessment of operative risk in colorectal cancer surgery: The Cleveland Clinic Foundation colorectal cancer model. Dis Colon Rectum 2004;47:2015–2024.
17. Law WI, Chu KW, Ho JW, Chan CW. Risk factors for anastomotic leakage after low anterior resection with total mesorectal excision. Am J Surg 2000;179:92–96.
18. Peeters KC, Tollenaar RA, Marijnen CA, Klein KE, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005;92:211–216.
19. Schmidt O, Merkel S, Hohenberger W. Anastomotic leakage after low rectal stapler anastomosis: Significance of intraoperative anastomotic testing. Eur J Surg Oncol 2003;29:239–243.
20. Eriksen MT, Wibe A, Norstein J, Haffner J, Wiig JN. Anastomotic leakage following routine mesorectal excision for rectal cancer in a national cohort of patients. Colorectal Dis 2005;7:51–57.
21. Yeh CY, Changchien CR, Wang JY, Chen JS, Chen HH, Chiang JM, Tang R. Pelvic drainage and other risk factors for leakage after elective anterior resection in rectal cancer patients: A prospective study of 978 patients. Ann Surg 2005;241:9–13.
22. Phillips RK, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following 'curative' surgery for large bowel cancer: I. The overall picture. Br J Surg 1984;71:12–16.
23. Sauven P, Playforth MJ, Evans M, Pollock AV. Early infective complications and late recurrent cancer in stapled colonic anastomoses. Dis Colon Rectum 1989;32:33–35.
24. Akyol AM, McGregor JR, Galloway DJ, Murray GD, George WD. Anastomotic leaks in colorectal cancer surgery: A risk factor for recurrence? Int J Colorectal Dis 1991;16:179–183.
25. Bell SW, Walker KG, Rickard MJ, Sinclair G, Dent OF, Chapuis PH, Bokey EL. Anastomotic leakage after curative anterior resection results in a higher prevalence of local recurrence. Br J Surg 2003;90:1261–1266.
26. Merkel S, Wang WY, Schmidt O, Dworak O, Wittekind C, Hohenberger W, Hermanek P. Locoregional recurrence in patients with anastomotic leakage after anterior resection for rectal carcinoma. Colorectal Dis 2001;3:154–160.
27. Fermor B, Umpleby HC, Lever JV, Symes MO, Williamson RC. Proliferative and metastatic potential of exfoliated colorectal cancer cells. J Natl Cancer Inst 1986;76, 347–349.
28. van den Tol PM, van Rossen EE, van Eijck CH, Bonthuis F, Marquet RL, Jeekel H. Reduction of peritoneal trauma by using nonsurgical gauze leads to less implantation metastasis of spilled tumor cells. Ann Surg 1998;227:242–248.
29. Umpleby HC, Fermor B, Symes MO, Williamson RC. Viability of exfoliated colorectal carcinoma cells. Br J Surg 1984;71:659–663.
30. Slanetz CA Jr. The effect of inadvertent intraoperative perforation on survival and recurrence in colorectal cancer. Dis Colon Rectum 1984;27:792–797.
31. Finlay IG, McArdle CS. Occult hepatic metastases in colorectal carcinoma. Br J Surg 1986;73:732–735.
32. Denis MG, Lipart C, Leborgne J, LeHur PA, Galmiche JP, Denis M, Ruud E, Truchaud A, Lustenberger P. Detection of disseminated tumor cells in peripheral blood of colorectal cancer patients. Int J Cancer 1997;74:540–544.
33. Molnar B, Ladanyi A, Tanko L, Sreter L, Tulassay Z. Circulating tumor cell clusters in the peripheral blood of colorectal cancer patients. Clin Cancer Res 2001;7:4080–4085.
34. Nielsen HJ, Christensen IJ, Sorensen S, Moesgaard F, Brunner N. Preoperative plasma plasminogen activator inhibitor type-1 and serum C-reactive protein levels in patients with colorectal cancer. The RANX05 Colorectal Cancer Study Group. Ann Surg Oncol 2000;7:617–623.
35. McMillan DC, Canna K, McArdle CS. Systemic inflammatory response predicts survival following curative resection of colorectal cancer. Br J Surg 2003;90:215–219.
36. Balkwill F, Mantovani A. Inflammation and cancer: Back to Virchow? Lancet 2001;357:539–545.

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Cytokine Network in Chronic Perianal Crohn's Disease and Indeterminate Colitis After Colectomy

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Abstract Antitumor necrosis factor alpha (anti-TNF-α) therapy in perianal Crohn's disease (CD) is widely established but recent studies suggest that the underlying fistula tract and inflammation may persist. Treatment with a monoclonal antibody against interleukin (IL)-12 was reported to induce clinical responses and remissions in patients with active CD. The aim of our study was to analyze the cytokine network (TNF-α, IL-12, IL-1β, and IL-6) in 12 patients with chronic perianal CD and a Crohn's disease activity index (CDAI) score <150 to exclude active intestinal disease, in 7 patients with indeterminate colitis (IC) after restorative proctocolectomy with perianal complications, in 7 patients with active intestinal CD without perianal manifestations, and in 19 healthy controls. Nonparametric Mann–Whitney U test and Spearman's rank correlation test were used. Serum TNF-α levels were significantly higher in patients with IC than perianal CD patients and healthy controls. Serum TNF-α levels significantly correlated with perianal CDAI score and with the presence of anal fistulas. Serum IL-12 levels correlated with the presence of anal strictures and were similar in all groups. Serum IL-6 levels were significantly higher in the presence of perianal fistulas and lower in the presence of anal strictures. Our study confirmed that TNF-α plays a major role in the perianal and intestinal CD. Furthermore, the significantly higher TNF-α serum levels in patients with IC suggest the use of anti-TNF-α in such patients. On the contrary, according to our results the efficacy of anti-IL-12 antibodies appears doubtful in chronic perianal CD or IC without anal strictures. The role of IL-6 as a systemic mediator for active chronic inflammation was confirmed and a possible role for its monoclonal antibody was suggested.

This study was presented at the 47th annual meeting of the Society for Surgery of the Alimentary Tract (Digestive Disease Week), May 20–24, 2006 Los Angeles CA, USA, as a poster.

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Keywords Perianal Crohn's disease · Cytokines · Indeterminate colitis

Introduction

The incidence of perianal involvement in Crohn's disease (CD) ranges from 3.8% in some series[1] to 60–80% in others.[2] In 64–68% of patients, perianal disease occurs contemporaneously or after the diagnosis of intestinal disease.[3,4] Williams et al.[3] reported that 74% of these patients develop perianal lesions within 10 years of diagnosis of intestinal disease. In 20–36% perianal disease precedes intestinal disease. The recent identification of a susceptibility locus on chromosome 5 supports the fact that perianal disease is a distinct phenotype of CD.[5] Perianal CD may include a variety of manifestations such as perianal skin lesions (anal

skin tags and hemorrhoids), anal canal lesions (fissures, ulcers, and anorectal strictures), perianal fistulas and abscesses, rectovaginal fistulas, and cancer.[6]

Cytokines represent the inflammatory cells' messengers so they play a central role in the modulation of intestinal inflammation. For this reason they can be the target of neutralizing antibodies that, now, are a valid option in the treatment strategy. In fact, there are evidences of increased levels of tumor necrosis factor alpha (TNF-α) in the physiopathology of CD.[7] The consequent strategy was to use neutralizing antibodies, of which the two most widely described are infliximab (cA2/remicade) and CDP571.[8,9] Infliximab is a murine/human chimeric monoclonal antibody directed toward soluble and membrane-bound TNF-α. Present et al.[10] reported that three infusions of infliximab, 5 or 10 mg/kg, at weeks 0, 2, and 6 yielded a complete perianal fistula closure in 46% of patients. The median length of time the fistula remained closed was 12 weeks, and the response rate was higher with the 5-mg/kg dose. Farrell et al.[11] reported similar results. On the other hand, recent studies suggest that in spite of an initial clinical response to infliximab the underlying fistula tract and inflammation persist.[12,13]

Interleukin (IL)-12) is a key cytokine that drives the inflammatory response mediated by type 1 helper T cells. Crohn's disease is characterized by increased production of IL-12 by antigen-presenting cells in intestinal tissue and interferon-γ and TNF-α by intestinal lymphocytes and macrophages. A recent study reported that treatment with a monoclonal antibody against IL-12 might induce clinical responses and remissions in patients with active intestinal CD.[14]

The aim of our study was to analyze the systemic cytokine network (TNF-α, IL-12, IL-1β, and IL-6) in chronic perianal CD, in indeterminate colitis (IC) after restorative proctocolectomy (RPC) with perianal complications, in intestinal CD, and in healthy controls. The levels of these cytokines were then correlated to parameters of natural immunity and acquired immunity.

Materials and Methods

Patients

We enrolled 12 patients with active perianal CD and a Crohn's disease activity index (CDAI) score <150 to minimize the inflammatory cytokine production from an active intestinal disease; 7 patients with IC submitted to RPC with perianal complications; 7 patients with active intestinal CD without perianal manifestations; and 19 healthy controls sex- and age-matched with the perianal CD and the IC groups. We also excluded CD or IC patients affected by extraintestinal manifestations such as arthritis, cholangitis, or other inflammatory pathology that could have interfered with the dosage of inflammatory cytokines. Patients' characteristics are shown in Table 1.

Clinical Parameters

During the physical examination of the patients that included a rigid proctoscopy, we recorded the presence of any perineal, anal, or rectal pathology. In particular, we focused on the presence of fissures, fistulas, abscesses, and/or anal strictures. The perianal disease activity was assessed with the perianal Crohn's disease activity index (PCDAI) score.[15] The PCDAI includes five categories: discharge, pain, restriction of sexual activities, type of perianal disease, and degree of induration, which are graded on a 5-point Likert scale ranging from no symptoms (0) to severe symptoms (14).

In our perianal CD group, we included patients with a CDAI score lower than 150 to have CD patients with insignificant disease activity at bowel levels. In fact, the CDAI score (number of liquid stools, abdominal pain, general well-being, extra intestinal complications, use of antidiarrhoic drugs, abdominal mass, hematocrit, and body weight) ranges from 0 to approximately 600.[16,17] The disease is considered quiescent under the score of 150, mildly active between 150 and 219, moderately active between 220 and 450, and severe over the score of 450.

Immunoassays

Blood samples were taken from all fasting patients. We took into exam the serum levels of the following cytokines:

Table 1 Patient Characteristics

	Perianal CD	IC	Intestinal CD	Healthy controls
Number of patients	12	7	7	19
Sex (M/F)	7/5	4/3	4/3	11/8
Age (years)	39.6±9.6	38.5±4.7	46±18.2	38.7±13.9
Age at diagnosis (years)	26.5±8.9	22.3±7.7	37±18.2	
Duration of disease (years)	12.6±4	16.2±5.3	9±9.1	
CDAI	90.03±40.7	122.8±47.3	97.6±61.2	
PCDAI	5.3±3.5	4.2±2.2		
Past intestinal resections	7	7 (colectomy)	7	
Perianal fistulas	11	5		
Perianal abscesses	2	2		
Anal stenosis	4	0		
Fissures	2	0		
Extraintestinal manifestations	7	4	3	

IL-1β, IL-6, IL-12, and TNF-α. IL-1β, IL-6, and TNF-α were measured with immunometric assays (Immulite analyzer; Diagnostics Products Corporation DPC, Los Angeles, CA, USA); quantitative detection of IL-12 was performed with IL-12 enzyme-linked immunosorbent assay (ELISA) (Bender MedSystems, Vienna, Austria). The sensitivity of the assays was 1.5 pg/ml (IL-1β), 2 pg/ml (IL-6), 1.7 pg/ml (TNF-α), and 12.6 pg/ml (IL-12).

Inflammation Status

The inflammatory activity was also assessed by quantifying erythrocyte sedimentation rate (ESR), white blood cell count (WBC), platelets blood count (PLT), and C-reactive protein (CRP). ESR was measured by the Westergren method.[18] CRP was detected by immunonephelometry.[19] Total proteinemia and albuminemia were assessed with the biuret method.[20] WBC and hemoglobinemia were obtained with standard full blood cell count.

Antineutrophil Cytoplasmic Antibody

The acquired immunity was studied by the quantitative evaluation of perinuclear antineutrophil cytoplasmic antibody (pANCA). Detection of pANCA was performed by an indirect immunofluorescence technique on ethanol-fixed buffy coat leukocytes. A fluorescein isothiocyanate-conjugated rabbit anti-human IgG antibody (Rabbit/Kaninchen/Lapin/Anti-human/Humain-Dako, Copenhagen, Denmark) was used for the detection of bound IgG antibodies, followed by an initial 1:20 and progressively higher dilutions in phosphate-buffered saline. Staining patterns that were considered positive were cytoplasmic (cANCA) and perinuclear (pANCA) staining of neutrophils. Samples that were scored positive were further analyzed by ELISA (ALIFAX) for antiproteinase 3 (29 kDa) in the first case and antimyeloperoxidase (23 kDa) antibodies in the second case.

Statistical Analysis

Data were presented as mean ± SE. Data elaboration was performed with Statsoft Statistica 5.0 software. Nonparametric Mann–Whitney U two-tailed test was used to compare cytokines levels according to dichotomous variables. Linear association between cytokines serum levels and continuous variables was quantified using Spearman's rank correlation test. Statistical significance was set at $p<0.05$.

Results

The comparison with Mann–Whitney U test demonstrated that serum TNF-α levels significantly correlated with the presence of perianal fistulae ($R=0.36$, $p=0.01$). In fact, as shown in Table 2, serum TNF-α levels were significantly higher in patients with active perineal fistulae. Serum TNF-α levels also significantly correlated with the number of daily stools ($R=0.48$, $p<0.01$) and PCDAI ($R=0.40$, $p<0.01$) as shown in Table 3 and illustrated by Fig. 1. Furthermore, patients with IC who were submitted to RPC, which was complicated in the long-term follow-up by perianal complications, were reported to have high TNF-α levels than perianal CD patients and healthy controls (25.7±15.2 vs 21.9±13.3 and vs 7.1±0.5, $p<0.05$).

Spearman's correlation test showed that IL-12 significantly correlated with the presence of anal strictures ($R=0.33$, $p=0.03$) and presented an inverse correlation with the platelet count ($R=-0.50$, $p=0.03$, respectively). As illustrated in Table 2, IL-12 levels were significantly higher in patients with anal strictures ($p=0.03$). On the other hand, serum IL-12 levels were similar in perianal CD patients group, in intestinal CD group, in IC group, and in healthy controls. There were no other correlations with any of the other parameters (age, sex, age at diagnosis, CD duration, CD site, operation, weight, CDAI, fissure, abscess, WBC, PMN, and HB) considered.

Table 2 Cytokines Levels Compared with Mann–Whitney U Two-tailed Test According to Disease Groups and the Presence of Fistulae and Strictures

	Patients	IL-12 (pg/ml)	TNF-α (pg/ml)	IL-1β (pg/ml)	IL-6 (pg/ml)
Disease groups					
Perianal CD	12	72.9±14.5	21.9±13.3[a]	5.0±0	8.4±2.6
IC	7	100.0±27.5	25.7±15.2	5.0±0	3.9±1.0
CD	7	115.5±20.3	9.1±2.3	5.0±0	2.6±0.5
Healthy controls	19	71.2±18.3	7.1±0.5	5.0±0	2.2±0.1[b]
Fistulae					
Yes	16	88.5±15.4	26.3+/11.4[c]	5.0±0	7.1±2.0[c]
No	29	80.3±13.4	7.5±0.6	5.0±0	2.6±0.2
Strictures					
Yes	4	88.4±10.7[d]	15.0+/4.8	5.0±0	3.9±0.9[d]
No	40	32.3±7.3	7.5±0.5	5.0±0	6.1±0.8

[a] Perianal CD vs IC; $p=0.05$
[b] Healthy controls vs perianal CD, intestinal CD, and IC; $p<0.05$
[c] Presence of active fistula vs absence; $p<0.05$
[d] Presence of anal stricture vs absence; $p<0.05$

Table 3 Spearman Rank Correlation Test Analysis: Cytokines Serum Levels were Correlated to the Main Clinical and Serological Parameters

Spearman rank correlation test	IL-12			TNF-α			IL-1β			IL-6		
	Pts	*R*	*p* Level	Pts	*R*	*p* Level	Pts	*R*	*p* Level	Pts	*R*	*p* Level
Disease groups	44	−0.12	0.425	44	−0.25	0.096	45			45	−0.57	0.000
Daily stools	44	0.26	0.083	44	0.48	0.001	45			45	0.38	0.009
PCDAI	44	0.19	0.214	44	0.40	0.008	45			45	0.58	0.000
Fistulae	44	−0.10	0.516	44	−0.36	0.015	45			45	−0.37	0.013
Anal stricture	44	0.33	0.029	44	0.01	0.968	45			45	−0.40	0.006
PLT	24	−0.44	0.032	23	−0.17	0.452	24	0.00	1.000	24	0.30	0.149
ESR	25	0.01	0.951	24	0.05	0.817	25			25	0.45	0.023
CRP	25	−0.04	0.833	24	−0.07	0.748	25			25	0.46	0.020
ALB	23	0.01	0.975	22	−0.09	0.685	23	0.00	1.000	23	−0.61	0.002

Parameters relative to disease history or activity were not available for healthy controls so these patients were not included in these respective analyses.
ALB = albumin

Among the clinical variables, IL-6 showed a strong relation with the number of daily stools (R=0.38, p<0.01) and PCDAI (R=0.57, p<0.01) as shown in Table 3. As expected, serum IL-6 levels significantly correlated with ESR (R=0.45, p=0.02), CRP (R=0.46, p=0.02), and albuminemia (R=−0.61, p<0.01). Furthermore, IL-6 levels significantly correlated with the presence of active fistulas (R=0.36, p=0.01). On the contrary, we observed an inverse correlation with the presence of anal strictures (R=−0.40, p<0.01) with significantly lower IL-6 levels in patients with anal stenosis. Last, but not least, IL-6 significantly correlated with different disease groups (R=0.56, p<0.01) and the comparison among the four groups showed that the healthy controls had significantly lower IL-6 levels than perianal CD and complicated post-RPC ulcerative colitis (UC) patients (p=0.05).

IL-1β resulted to be undosable in all patients and control subjects of our study.

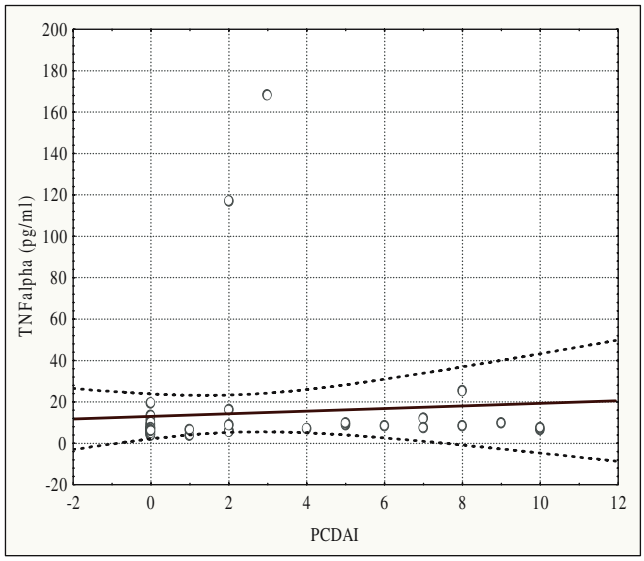

Figure 1 Serum TNF-α levels significantly correlated with PCDAI (Spearman's correlation test R=0.40, p<0.01).

Discussion

The management of Crohn's perianal disease has changed since the introduction of anti-TNF-α monoclonal antibodies (infliximab)[7] that determine the complete recovery of fistulas in 46% of the patients treated. Recent studies have demonstrated the ability of both intestinal and peripheral macrophages to secrete a considerable quantity of TNF-α and IL-1β in patients with active inflammatory bowel disease. Two randomized trials assessed the efficacy of anti-TNF treatment of fistulas in patients with CD.[9,10] But recent studies propose that, although there is a clinical response with infliximab, the fistulous tract and inflammation may persist.[11,12] A role on this type of inflammation could be played by IL-12. In fact, CD is characterized by an increased production of IL-12 by antigen-presenting cells in the intestinal tissue and also by an increased production of interferon-γ and of TNF-α by intestinal lymphocytes and macrophages. Recently, Mannon et al. assumed that treatment with a monoclonal antibody against IL-12 could induce clinical response and remission in patients with fistulizing CD.

The aim of our study was to search for possible immunologic therapeutic targets of chronic perianal CD in patients without an active intestinal disease. Cytokine (IL-1β, IL-6, IL-12, and TNF-α.) serum levels were compared in patients with perianal CD in patients with IC submitted to RPC with perianal complications, in patients with active intestinal CD without perianal manifestations, and in

healthy controls. Cytokine levels were correlated with systemic inflammation parameters (ESR, CRP, and WBC) and with specific immunologic response parameters (ANCA).

Serum levels of TNF-α were significantly higher in patients with UC after RPC with perianal complications than in patients with intestinal CD and healthy controls. Moreover, a significant direct correlation between TNF-α serum levels and daily stools, PCDAI, and the presence of perianal fistulas was found. In our study, group patients with perianal complications after RPC for IC were those with the most active disease as demonstrated by PCDAI scores, so there was no surprise to find that their TNF-α levels resulted higher than those of control groups. On the contrary, these findings seem to confirm a possible role for infliximab in this complication of RPC as suggested by a preliminary study for the treatment of refractory pouchitis complicated by fistula after ileal pouch-anal anastomosis for UC.[21] Nevertheless, the correlation with PCDAI additionally confirms TNF-α's leading part in establishing inflammation and the consequent clinical picture in perianal CD as demonstrated by the results of a multicentric study where perianal fistulas predicted a better response to infliximab than other types of fistulas.[22]

Whereas no significant relations were demonstrated with anamnestic parameters, IL-12 presented an inverse relationship with platelet count. On the other hand, IL-12 serum levels were significantly higher in the presence of anal strictures and this result might be a clue of a possible role of IL-12 in the postinflammatory repairing mechanism. However, in spite of the demonstration of the presence of more colonic dendritic cells that produce IL-12 and IL-6 in active CD than in UC[23] there were no statistically significant differences in the serum levels of IL-12 between the diseased groups and the healthy controls. Furthermore, in a recent study, active CD was shown to be associated with high levels of IL-12p70 and this cytokine production is downregulated by treatment with anti-IL-12 p40 monoclonal antibody.[24] These data seem to suggest a double peak in IL-12 expression in perianal CD: a first peak, according to the literature data,[25] in the acute phase, then a "chronic" phase with active fistulae when this cytokine is not particularly elevated, and another peak during the post inflammatory repairing phase. The role of IL-12 as a target for monoclonal antibodies in the chronic stage may appear doubtful although it would be rather interesting to evaluate it during the repairing stage such as in the presence of an anal stricture. Preventing the stricture recurrence in abdominal CD would be a major advancement in CD therapy and anal stricture may be an easy model to monitor.

The practically undosable serum levels of IL-1β confirmed the fact that the patients were not in an acute stage of disease. This cytokine, typically expressed in the pyretic stages of inflammation, was undosable in all patients of our study. This data confirms the findings by experimental studies that have demonstrated low levels of IL-1β in chronic inflammation.[26]

As expected, IL-6 showed an important direct correlation with the PCDAI, the number of stools/die, ESR, and CRP, and indirectly correlated with albuminemia.[27] Moreover, serum IL-6 levels were significantly higher in the presence of both perianal fistulas. IL-6 is the cytokine that stimulates the hepatocyte production of CRP, which is the protein described as a disease activity marker for CD that correlates with all inflammatory parameters.[28,29] This result confirms that, differently from IL-1β, which increases just in acute inflammation, IL-6 contributes to the maintenance of active chronic inflammation such as perianal fistulae.[30] The significantly lower level observed in patients with the presence of anal strictures may suggest that when fibrosis starts to play its role in the postinflammatory repairing mechanism, IL-6 expression is downregulated. Ito et al.[31] published the first clinical trial of humanized anti-IL-6 receptor monoclonal antibody in CD in which a biweekly 8 mg/kg infusion was well tolerated and normalized the acute-phase responses, suggesting a clinical effect in active CD. Furthermore, because healthy controls had significantly lower IL-6 levels than perianal CD and complicated post-RPC IC patients, anti-IL-6 receptor could be associated in both diseases, with anti-TNF-α or anti-IL-12 according to the presence of perianal fistulas or anal strictures, respectively.

Conclusion

Our study confirmed that TNF-α plays a major role in perianal CD as demonstrated by the correlation with the perianal activity index. Furthermore, the significantly higher TNF-α serum levels in patients with IC after restorative proctocolectomy with perianal complications suggest the use of anti-TNF-α in such patients. On the contrary, according to our results the efficacy of anti-IL12 antibodies appears doubtful in chronic perianal CD or IC without anal strictures. The role of IL-6 as a systemic mediator for chronic inflammation was confirmed and a possible role for its monoclonal antibody was suggested.

References

1. Sangwan YP, Schoetz DJ Jr, Murray JJ, Roberts PL, Coller JA. Perianal Crohn's disease. Results of local surgical treatment. Dis Colon Rectum 1996;39:529–535.
2. McClane SJ, Rombeau JL. Anorectal Crohn's disease. Surg clin North Am 2001;81:169–183.

3. Williams DR, Coller JA, Corman ML, Nugent FW, Veidenheimer MC. Anal complications in Crohn's disease. Dis Colon Rectum 1981;24:22–24.
4. Keighley MR, Allan RN. Current status and influence of operation on perianal Crohn's disease. Int J Colorectal Dis 1986;1:104–107.
5. Armuzzi A, Ahmad T, Ling KL, de Silva A, Cullen S, van heel D, Orchard TL, Welsh KI, Marshall KE, Jewel DP. Genotype–phenotype analysis of the Crohn's disease susceptibility haplotype on chromosome 5q31. Gut 2003;52:1133–1139.
6. Sandborn WJ, Fazio VW, Feagan BG, Hanauer SB. American Gastroenterological Association Clinical Practice Committee. AGA technical review on perianal Crohn's disease. Gastroenterology 2003;125:1508–1530.
7. Plevy SE, Landers CJ, Prehn J, Carramanzana NM, Deem RL, Shealy D, Targan SR. A role for TNF-alpha and mucosal T helper-1 cytokines in the pathogenesis of Crohn's disease. J Immunol 1997;159:6276–6282.
8. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, De Woody KL, Schaible TF, Rutgeerts PJ. A short-term study of chimeric monoclonal antibody cA2 to tumour necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. N Engl J Med 1997;337:1029–1035.
9. Sandborn WJ, Feagan BG, Hanauer SB, Present DH, Sutherland LR, Kamm MA, Wolf DC, Baker JP, Hawkey C, Archaumbalt A, Bernstein CN, Novak C, Heath PK, Targan SR. CDP571 Crohn's Disease Study Group. An engineered human antibody to TNF (CDP571) for active Crohn's disease: A randomized double-blind placebo-controlled trial. Gastroenterology 2001;120:1330–1338.
10. Present DH, Rutgeerts P, Targan S, Hanauer S, Mayer L, von Hogezand RA, Podolsky DK, Sands BE, Braakman T, De Woody KL, Schaible TF, van Deventer SJ. Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med 1999;340:1398–1405.
11. Farrell RJ, Shah SA, Lodhavia PJ, Alsahli M, Falchuk KR, Michetti P, Peppercorn MA. Clinical experience with infliximab therapy in 100 patients with Crohn's disease. Am J Gastroenterol 2000;95:3490–3497.
12. van Bodegraven AA, Sloots CE, Felt-Bersma RJ, Meuwissen SG. Endosonographic evidence of persistence of Crohn's disease-associated fistulas after infliximab treatment, irrespective of clinical response. Dis Colon Rectum 2002;45:39–45.
13. Van Assche G, Vanbeckevoort D, Bielen D, Coremans G, Aerden I, Noman M, D'Hoore A, Penninckx F, Marchal G, Cornillie F, Rutgeerts P. Magnetic resonance imaging of the effects of infliximab on perianal fistulizing Crohn's disease. Am J Gastroenterol 2003;98:332–339.
14. Mannon PJ, Fuss IJ, Mayer L, Elson CO, Sandborn WJ, Present DH, Goodman N, Groden C, Hornung RL, Quezado M, Neurath MF, Salfeld J, Veldman GM, Schwertschlag U, Strober W. Anti-interleukin-12 antibody for active Crohn's disease. N Engl J Med 2004;351:2069–2079.
15. Irvine EJ. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. McMaster IBD Study Group. J Clin Gastroenterol 1995;20:27–32.
16. Best WR, Becktel JM, Singleton JW, Kern F Jr. Development of a Crohn's disease activity index. National Cooperative Crohn's Disease Study. Gastroenterology 1976;70:439–444.
17. Winship DH, Summers RW, Singleton JW, Best WR, Becktel JM, Lenk LF, Kern F Jr. National Cooperative Crohn's Disease Study: Study design and conduct of the study. Gastroenterology 1979,77:829–842.
18. ICSH recommendations for measurement of erythrocyte sedimentation rate. International Council for Standardization in Haematology (Expert Panel on Blood Rheology). J Clin Pathol 1993;46:198–203.
19. Dominici R, Luraschi P, Franzini C. Measurement of C-reactive protein: two high sensitivity methods compared. J Clin Lab Anal 2004;18:280–284.
20. Brooks SP, Lampi BJ, Sarwar G, Botting HG. A comparison of methods for determining total body protein. Anal Biochem 1995;226:26–30.
21. Viscido A, Habib FI, Kohn A, Papi C, Marcheggiano A, Pimpo MT, Vernia P, Cadau G, Caprilli R. Infliximab in refractory pouchitis complicated by fistulae following ileo-anal pouch for ulcerative colitis. Aliment Pharmacol Ther 2003;17:1263–1271.
22. Orlando A, Colombo E, Kohn A, Biancone L, Rizzello F, Viscido A, Sostegni R, Benazzato L, Castiglione F, Papi C, Meucci G, Riegler G, Mocciaro F, Cassinotti A, Cosintino R, Geremia A, Morselli C, Angelucci E, Lavagna A, Rispo A, Bossa F, Scimeca D, Cottone M. Italian multicentric study group on infliximab. Infliximab in the treatment of Crohn's disease: predictors of response in an Italian multicentric open study. Dig Liver Dis 2005;37:559–563.
23. Hart AL, Al-Hassi HO, Rogby RJ, Bell SJ, Emmanuel AV, Knight SC, Kamm MA, Stagg AJ. Characteristics of intestinal dendritic cells in inflammatory bowel diseases. Gastroenterology 2005;129:50–65.
24. Fuss IJ, Becker C, Yang Z, Groden C, Hornung RL, Heller F, Neurath MF, Strober W, Mannon PJ. Both IL-12p70 and IL-23 are synthesized during active Crohn's disease and are down-regulated by treatment with anti-IL-12 p40 monoclonal antibody. Inflamm Bowel Dis 2006;12(1):9–15 Jan.
25. Nielsen OH, Kirman I, Rudiger N, Hendel J, Vainer B. Upregulation of interleukin-12 and -17 in active inflammatory bowel disease. Scand J Gastroenterol 2003;38:180–185.
26. Boggess KA, Price WA, Preisser JS, Moise KJ Jr, Offenbacher S. Insulin-like growth factor and interleukin-1beta levels and subsequent fetal size response to chronic Porphyromonas gingivalis exposure in the pregnant rabbit. Am J Obstet Gynecol 2005;193:1219–1223.
27. Aleksandra NA, Nederby NJ, Schmedes A, Brandslund I, Hey H. Saliva Interleukin-6 in patients with inflammatory bowel disease. Scand J Gastroenterol 2005;40:1444–1448.
28. Mazlam MZ, Hodgson HJ. Interrelations between interleukin-6, interleukin-1beta, plasma C-reactive protein values, and in vitro C-reactive protein generation in patients with inflammatory bowel disease. Gut 1994;35:77–83.
29. Vermeire S, Van Assche G, Rutgeerts P. C-reactive protein as a marker for inflammatory bowel disease. Inflamm Bowel Dis 2004;10:661–665.
30. Atreya R, Neurath MF. Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer. Clin Rev Allergy Immunol 2005;28:187–196.
31. Ito H, Takazoe M, Fukuda Y, Hibi T, Kusugami K, Andoh A, Matsumoto T, Yamamura T, Azuma J, Nishimoto N, Yoshizaki K, Shimoyama T, Kishimoto T. A pilot randomized trial of a human anti-interleukin-6 receptor monoclonal antibody in active Crohn's disease. Gastroenterology 2004;126:989–996.

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Trends and Predictors for Vagotomy When Performing Oversew of Acute Bleeding Duodenal Ulcer in the United States

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Abstract
Background In the era of *Helicobacter pylori* treatment, the role of vagotomy in bleeding duodenal ulcers is debatable. National outcomes were evaluated to determine the current surgical treatment and use of vagotomy for bleeding duodenal ulcers.
Methods Data from the Nationwide Inpatient Sample (NIS) were used from years 1999 to 2003. Patients were selected using diagnostic codes for acute duodenal ulcer bleed and procedure codes for simple oversew of a bleeding ulcer and vagotomy. Data were analyzed using multiple linear and logistic regression.
Results Between 1999 and 2003, 100,931 patients with an acute bleeding duodenal ulcer were identified. Over time, there was a decrease in the number of acute bleeding ulcers ($p=0.027$) and a decrease in the number of vagotomies ($p=0.027$). A high co-morbidity index [odds ratio (OR), 0.60, $p=0.017$], operation in the Midwest (OR 0.50, $p<0.001$) and operation in the West (OR 0.68, $p=0.034$) were predictive of no vagotomy during surgery for a bleeding duodenal ulcer.
Conclusions A vagotomy is not commonly performed during surgical treatment of an acute bleeding duodenal ulcer. This variation in practice was not fully explained by patient characteristics. We must seek new evidence to determine the safety of combined medical and surgical management of this clinical problem.

Keywords Vagotomy · Duodenal ulcer · Bleeding · Outcomes

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Introduction

Upper gastrointestinal (UGI) bleeding has always been a life-threatening condition and it still carries up to a 10% mortality rate.[1] Overall mortality has been reduced by recent advances in medical and endoscopic management of this critical problem.[2] While endoscopy has quickly become the standard for initial management of a duodenal bleed, surgical treatment remains the mainstay for life-threatening hemorrhage or failure of endoscopic treatment. The surgical dictum of the era "no acid, no ulcer" guided surgeons to perform operations such as vagotomy and pyloroplasty and distal gastric resections.[1,3] More recently, acid reduction procedures have been replaced with minimal procedures such as oversew combined with postoperative eradication of *Helicobacter pylori* (*H. pylori*) and treatment with proton pump inhibitors.[4–6] Current practice patterns and indications for minimal surgical procedures have not been well defined and that combined with a lack of

prospective data further clouds management principles for significant duodenal bleeding.

This study utilizes a large national database to determine if there are predictor variables for the use of a surgical vagotomy in the face of oversew for an acute bleeding duodenal ulcer. It also examines the most recent national trends for duodenal ulcer surgery in the United States.

Material and Methods

The most recent 5 years of the Nationwide Inpatient Sample (NIS), 1999 to 2003, were used to identify a subpopulation of inpatients treated for an acute bleeding duodenal ulcer. The NIS is the largest, all-payer inpatient database available that represents a 20% sample of all hospital discharges from nonfederal facilities within the United States. This database is maintained by the Agency for Healthcare Cost and Utilization Project. Hospitals are selected to represent five strata of hospital characteristics and weights based on sampling probabilities for each stratum are used in the analysis so hospitals are representative of all U.S. hospitals.

Patient identification was based on the 2003 International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes. Codes were evaluated for changes to previous years, dating back to 1999. ICD-9 diagnosis codes of 532.0 and 533.0 were used to identify acute bleeding duodenal ulcers. ICD-9 procedure codes of 44.40, 44.42, and 44.49 were used to identify patients who went to surgery for an oversew procedure for management of their acute bleed. ICD-9 procedure codes of 44.00, 44.01, 44.02, 44.03 were used to identify patients who underwent surgical vagotomy (not otherwise specified, truncal, highly selective, or other selective, respectively). Additionally, ICD-9 codes for endoscopy were used to identify those patients who went on to endoscopy with an acute bleeding duodenal ulcer (44.43, 45.13, 45.16). Patient co-morbidities were identified using the up to 15 ICD-9 diagnosis codes for each patient. Individual co-morbidities were then combined into a summary Charlson co-morbidity index score.[7] This index is a score of patient comorbidity based on ICD-9 diagnostic codes for diseases and risk factors for perioperative complications.

Complication rate between simple oversew and surgical vagotomy was compared among the following categories: wound, infection, urinary, pulmonary, gastrointestinal, cardiovascular, systemic, and procedural complications, based on the coding scheme developed by Guller et al.[8] Wound complications include postoperative hematoma, seroma, disruption of wound, or persistent fistula. Infection complications include intraabdominal or stitch abscess, skin abscess, septic wound complications, infected seroma. Urinary complications include postoperative urinary retention, acute renal failure, or acute tubular necrosis due to procedure. Pulmonary complications include postoperative respiratory insufficiency, iatrogenic pneumothorax, adult respiratory distress syndrome, iatrogenic pulmonary embolus, pulmonary edema. Gastrointestinal complications include small bowel obstruction, postoperative ileus, pancreatitis, blind loop syndrome, postoperative emesis, peritoneal adhesions, paralytic ileus, postgastric surgery syndromes (dumping, poastgastrectomy, postvagotomy), malnutrition after gastrointestinal surgery and persistent postoperative fistula. Cardiovascular complications include cardiac arrest, stroke, pulmonary embolus, or deep venous thrombosis. Systemic complications include postoperative shock, fever, or systemic inflammatory response syndrome. Procedural complications include foreign body accidentally left during procedure, bleeding complication, air embolism, subcutaneous emphysema from surgical procedure. Overall complications include all of the above complications.

Statistical analysis included multiple logistic regression to assess independent predictors for use of a surgical vagotomy. Variables assessed in the model were: age, sex, race, admission type (elective, urgent, emergency), hospital teaching status, hospital location (rural or urban), geographical hospital region (Northeast, South, Midwest or West), co-morbid diseases based on the Charlson co-morbidity index, payer information, household income and hospital volume based on total discharges (Table 2). Length of stay comparisons were made using the two-sample t test using equal variances. Additional regression analysis was performed with gender, race, hospital teaching status, hospital geographic region, and patient income in the regression model. We used logistic regression models to assess the occurrence of in-hospital complications between patients undergoing simple oversew versus surgical vagotomy for a bleeding duodenal ulcer. All models were adjusted for patient factors (age, gender, race, family income) and hospital factors (geographic hospital region, hospital teaching status).

Population sampling weights from the NIS were applied to all statistical computations. Significance for all statistical tests was set at a p value of less than 0.05. All p values are two-tailed. All analyses were performed using statistical computer software (STATA 9.0, STATA Corporation, College Station, TX, USA).

Results

A total of 419,132 inpatients were identified with ICD-9 diagnostic codes for a bleeding duodenal ulcer. Of these, 100,931 inpatients were identified with an acute bleeding duodenal ulcer using ICD-9 definitions.

Table 1 Bleeding Duodenal Ulcer Data for the United States, 1999 to 2003

	1999	2000	2001	2002	2003
Total number of bleeding duodenal ulcers (acute and chronic)	85,070	85,118	85,953	82,389	80,602
Number of acute bleeding duodenal ulcers	24,719	23,325	20,939	16,353	15,595
Percent to the OR	4.8%	4.8%	5.2%	4.6%	4.5%
Percent undergoing vagotomy	53.0%	49.1%	35.5%	45.2%	45.3%

There was a statistically significant decrease in the number of acute bleeding ulcers per year (p=0.040) and total number of vagotomies performed per year (p=0.027) (Tables 1 & 2). However, the percentage of bleeding ulcers that need operative intervention as well as the percentage of patients undergoing vagotomy each year remained relatively stable (Table 1). Over the 5-year-study period, on average, 45.6% of patients with an acute bleeding duodenal ulcer will undergo a surgical vagotomy as part of an oversew procedure. The majority of these patients will receive a truncal vagotomy (between 50 and 65% by year). Vagotomy, not otherwise specified (NOS), made up the next most common type of vagotomy performed with the minority of patients receiving a type of selective vagotomy (Table 2).

There were no significant differences in patient characteristics between the two study groups (those who received a surgical vagotomy during operation for an acute bleeding duodenal ulcer and those who did not receive a vagotomy, Table 3). Original regression models focused on predictors for a surgical vagotomy; however, strong predictors of not undergoing vagotomy were more prominent. All predictor variables tested appear in Table 4). In the univariate analysis, hospitals in the Midwest and West and high Charlson co-morbidity score were significant predictors for simple oversew only (no vagotomy). Univariate analysis showed that patients with higher household income were less likely to undergo vagotomy (OR 0.85, p=0.03). There was a trend towards performing a surgical vagotomy at teaching hospitals [odds ratio (OR) of 1.2, 95% confidence interval (CI) of 0.92 to 1.57, p=0.168]. Independent predictors for not undergoing a surgical vagotomy when performing oversew for an acute bleeding duodenal ulcer are hospital location in the Midwest (OR 0.50, CI 0.35–0.72, p<0.001), hospital location in the West (OR 0.68, CI 0.48–0.97, p=0.034) and high co-morbidity index (>7) (OR 0.60, CI 0.39–0.91, p=0.017) (Fig. 1). Length of stay

Table 2 Type of Vagotomy Performed during Oversew of Acute Bleeding Duodenal Ulcer by Year

	1999 (%)	2000 (%)	2001 (%)	2002 (%)	2003 (%)
Truncal	50	51	51	65	53
Highly Selective	9	3	3	7	4
Other Selective	11	18	11	6	14
Vagotomy, NOS	30	28	35	22	29

All values are percentage of total vagotomies performed per year.
NOS=Not otherwise specified

Table 3 Patient Characteristics by Surgical Vagotomy vs Oversew Only

Characterisitcs	Acute Bleeding Ulcer		
	Vagotomy	No Vagotomy	P value
Age	66.89±15.12	67.94±15.77	0.29[£]
Gender			
Male	66%	62%	0.20[¥]
Female	34%	38%	
Race			
White	86%	84%	0.32[§]
Black	5%	7%	
Hispanic	4%	3%	
Asian/Pacific Islander	3%	3%	
Native American	<1%	<1%	
Other	1%	3%	
Geographic Region			
Northeast	22%	21%	0.54[§]
Midwest	18%	26%	
South	38%	28%	
West	22%	25%	
Hospital Teaching Status			
Teaching Hospital	36%	68%	0.17[¥]
Non-teaching Hospital	64%	32%	
Hospital Location			
Rural	17%	19%	0.23[¥]
Urban	83%	81%	
Admission Type			
Emergency	73%	75%	0.32[§]
Urgent	19%	18%	
Elective	8%	7%	
Charlson Comorbidity Index			
0–3	30%	28%	0.11[§]
4–7	63%	59%	
8–11	7%	10%	
12–15	<1%	3%	
>15	0%	0%	

All numbers are expressed as percentage of total, except for age. All data are based on 20% stratified sample of the NIS.
[£] t test
[¥] Chi^2
[§] Wilcoxon-Mann–Whitney

Table 4 Variables Tested for Significance in Predicting a Surgical Vagotomy during Oversew of an Acute Bleeding Duodenal Ulcer

Age—by decade	
0–9	
10–19	
20–29	
30–39	
40–49	
50–59	
60–69	
70–79	
80–89	
90–99	
Gender	
Hospital Teaching Status	
Hospital Region	
Northeast	(CT, MA, ME[a], NJ, NY, PA, RI[£], VT[£], NH[¢])
South	(FL, GA, KY[¥], MD, NC[¥], SC, TN, TX[¥], VA, WV[¥])
Midwest	(IL, IA, KS, MI[£], MN[£], MO, NE[£], OH[§], SD[§], WI, IN[¢])
West	(CA, CO, HI, NV[§], OR, UT, WA, AZ[¢])
Patient Co-morbidity (by Charlson Co-Morbidity Index Score—0–15, grouped 0–7, 8–15)	
Patient Race	
White	
Black	
Hispanic	
Asian/Pacific Islander	
Native American	
Other	
Pay Type	
Medicare	
Medicaid	
Private Insurance, including HMO's	
Self-pay	
No charge	
Other	
Hospital Location	
Rural	
Urban	
Patient Family Income by Zip Code:	
$1–$24,999	
$25,000–$34,999	
$35,000–$44,999	
>$45,000	

[a] =Data not available for 2003
[¥] =added in 2000
[£] =added in 2001
[§] =added in 2002
[¢] =added in 2003

was not different between patients undergoing simple oversew versus a surgical vagotomy when evaluated by *t* test or regression analysis (p=0.79 and p=0.14, respectively). Regression analysis comparing complication rates for surgical wounds, post operative infection, urinary complications, pulmonary complications, intestinal complications, cardiac complications, systemic complications, procedural complications, and overall complications were not different between simple oversew and surgical vagotomy (p=0.35, p=0.31, p=0.06, p=0.77, p=0.58, p=0.67, p=0.44, p=0.65, p=0.72, respectively).

Discussion

Successful management of an acute bleeding duodenal ulcer can be handled in a variety of ways. One of the most common surgical procedures for a bleeding duodenal ulcer for more than 30 years has been truncal vagotomy and antrectomy. However, because of complications such as dumping, diarrhea, or alkaline reflux, alternative operations were developed to reduce surgical morbidity.[9] Current recommendations for surgical management of a bleeding duodenal ulcer still involve an element of surgical acid reduction. These include truncal vagotomy for a compromised patient or a highly selective or truncal vagotomy for an ideal surgical candidate.[10] Still, the goals of ulcer surgery have not changed: safe correction of the bleeding, avoidance of perioperative morbidity and mortality, and freedom from disabling postoperative side effects. However, with the advances in endoscopic management of duodenal bleeds, improvements in medical therapy for acid hypersecretion and recognition of the role of *H. pylori* in ulcer pathogenesis, acid reducing surgical therapy for a bleeding duodenal ulcer appears to have gone by the wayside.

No study to date has attempted to evaluate national practice patterns for use of a surgical vagotomy. As modern surgical practice evolves, it is valuable to reevaluate the role of a procedure whose utility is no longer as clear. Endoscopic therapy has become a dominant first-line therapy for a bleeding duodenal ulcer. Studies have demonstrated the effectiveness of endoscopy as primary therapy and even as a repeat therapy in the event of a rebleed from a duodenal ulcer.[11,12]

Several randomized controlled trials have also shown benefit of proton pump inhibitors over histamine blockers for decreasing upper gastrointestinal bleeding, need for blood transfusions, and maintaining gastric pH at a less acidic level.[13–15] In addition, the discovery of the role of *H. pylori* in ulcer pathogenesis and its treatment has dramatically changed the recurrence rates for peptic ulcer disease.[16–17] Despite this and other compelling evidence, there are no large clinical trials at this point evaluating combined surgical and medical therapy with modern-day therapies of proton pump inhibitors and triple therapy for *H. pylori*.

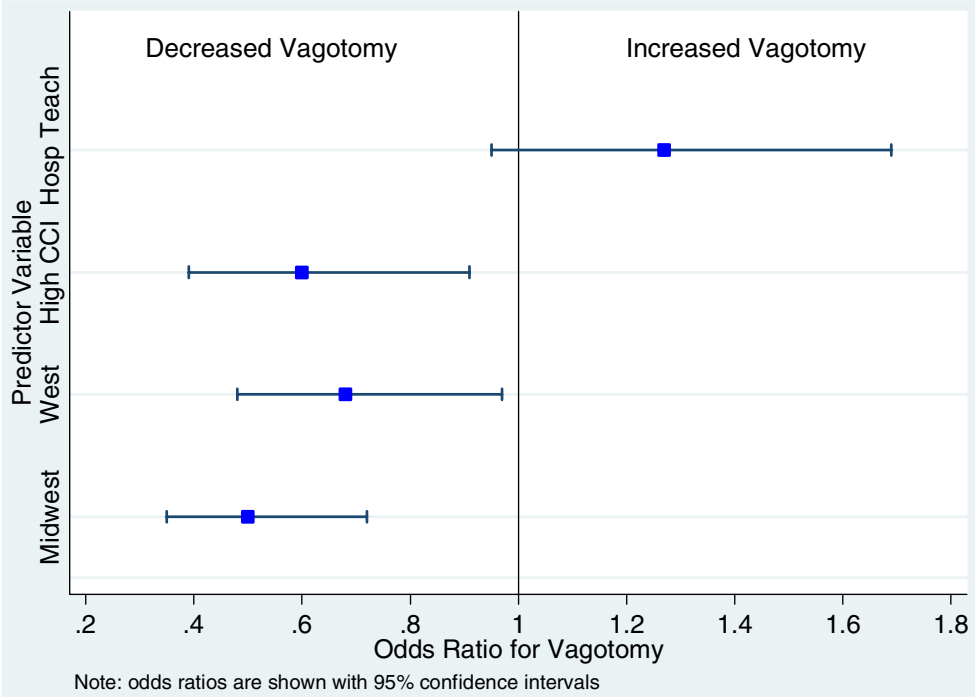

Figure 1 Odds ratios and 95% confidence intervals describing the likelihood of undergoing a surgical vagotomy given the four predictor variables modeled after stepwise evaluation in a univariate analysis.

As we have shown, there has been a significant decrease in the overall incidence of bleeding duodenal ulcers over the 5-year study period. Whether this trend is a result of improvements in endoscopic therapy, increased awareness and treatment of *H. pylori* or increasing use of proton pump therapy is unknown. Our study demonstrates a surgical vagotomy rate for bleeding duodenal ulcers of about 45%. Also of interest is the percentage of patients going to the operating room for surgical treatment of their bleeding ulcer. This has remained relatively stable over the study period, perhaps reflecting the patient population with significant or life-threatening hemorrhage, which is poorly treated by endoscopic means. The actual rate of surgical vagotomy is lower than expected, given the clinical evidence and current recommendations in the literature. The safety of such a combined minimal surgical procedure and postoperative medical therapy remains to be definitively proven.

This study also identified geographic trends in utilization of a surgical vagotomy for treatment of a bleeding duodenal ulcer. Patients in the Midwest and West had equal surgical risk as evidenced by their Charlson co-morbidity score. Why then would they be less likely to undergo vagotomy? Our analysis did not uncover any large variations in the number of bleeding duodenal ulcers between the four regions, which would argue against a lower incidence secondary to a lack of surgical cases. From a surgical perspective, exploration of this geographic variability may help to not only understand the rationale in various locations but also to examine outcomes to determine the efficacy of conservative treatment of this complex problem. These variations may be a reflection of provider preferences, patient differences, or a reflection of teaching practices. Although a thorough investigation of patient demographics (Table 5) between our two study groups did not define any differences, perhaps there are other patient factors such as surgical history, nutritional status, or physical condition, which play a part in decision-making and are not quantifiable by our database.

We know from the recent literature that academic programs are performing fewer ulcer operations than in

Table 5 Patient Characteristics by Geographic Region

	Northeast	South	Midwest	West
Age	70.3±14.5	68.3±14.4	65.7±16.0	66.5±16.3
Gender				
Male	57%	62%	70%	65%
Female	43%	38%	30%	35%
CCI				
0–3	22%	24%	33%	33%
4–7	64%	61%	61%	57%
8–11	11%	13%	5%	8%
12–15	3%	2%	1%	2%
Insurance				
Medicare	68%	64%	60%	51%
Medicaid	6%	6%	7%	7%
Private/HMO	22%	25%	23%	31%
Self-pay	4%	4%	7%	6%
No charge	0%	0%	<1%	0%
Other	<1%	<1%	2%	5%
Length of Stay (days)	21±19	16±14	16±13	16±17

the past.[4–6,18] In striking contrast to this trend, our data show that teaching hospitals tend to perform more surgical vagotomies than private hospitals. If university hospitals are performing these procedures, even at a greatly reduced volume, residents are theoretically still exposed to the procedure and should be able to perform it on their own once in practice. Most of the evidence in the surgical literature for bleeding duodenal ulcers is dated and does not utilize either current therapy for *H. pylori* or proton pump inhibitors.[1,19–22] Other authors have stated that surgery "if necessary, should aim at stopping the hemorrhage and not curing the disease".[23] Statements such as these are based on theory, and we must either await better information to come forth or continue with our best judgment.

As part of our evaluation, we have also compared in-hospital complications between minimal surgery and vagotomy as well as length of stay between these two procedures. Interestingly, the complication rate as well as length of stay are not different between patient populations receiving simple oversew and those receiving a surgical vagotomy. This current study does not provide definitive support for the use of minimal surgery for acute bleeding ulcers; however, it shows the current outcomes and trends, and highlights the need for further studies to determine the long-term safety and efficacy of the newer classes of drugs for the treatment of *H. pylori* and management acid hypersecretion.

One of the aims of this study was to determine clinical predictors for performing a surgical vagotomy. Ultimately, when analyzing the univariate models, there were stronger negative predictors. Common clinical predictors were thought to include age, the teaching status of the hospital, the patient co-morbidity status, and the socioeconomic status of the patient (as related to *H. pylori* prevalence). Our univariate analysis did confirm that higher socioeconomic status did confer a lower rate of surgical vagotomy. This was not found to be significant in the multivariate model and thus unlikely that the surgeon took into mind the endemic locale of the patient. One of the greatest concerning factors when operating on a patient with several co-morbidities is the risk of a re-bleed event. Most studies in the past comparing minimal therapy with conventional operations demonstrate a significantly lower re-bleed rate with conventional surgery, but conflicting reports on overall mortality.[1,24,25] Given these discrepancies and lack of large center trials, determination of the ideal surgical management is often left up to surgeon experience and training and therefore individual predictor variables are difficult to discern.

The use of an administrative database does provide benefits as well as impose several limitations. The benefits of a large administrative database include the assimilation of a large number of patient data into one large accessible database. Data from the NIS can be extrapolated for the entire United States and gives us valuable information on current practices in the United States today. There is no reporting bias on behalf of the individual. All information is coded independently of the individual practitioner. On the other hand, the database relies heavily on ICD-9 codes, which can be, at times, vague for certain surgical procedures. Coding errors can cause misinformation within the database and missing data can become difficult to deal with and interpret. This may also cause an underestimation of the number of bleeding ulcers and surgical vagotomies in the database. The NIS is also inpatient data and patient information is at the discharge level. There is no information on 30-day-patient outcomes. In addition, we lack a thorough history on the patients and are unable to stratify the patients based on a prior history of a gastrointestinal bleed, *H. pylori* status, medication history, or prior ulcer surgery. Nevertheless, this study represents national data for the most recent 5 years of the NIS database and demonstrates the dramatic change in management of a very difficult clinical problem.

Conclusion

A vagotomy is performed less than 50% of the time during surgical treatment of an acute bleeding duodenal ulcer. This may reflect the current understanding of the role of *H. pylori* in ulcer pathogenesis as well as improvements in our armamentarium of medical therapy. Our study also demonstrates geographic variations in surgical treatment in the United States. These variations may also be due to variations in training or unquantifiable patient factors absent from our database. As clinical medicine continues to evolve and progress, we must seek new evidence to determine the safety of combined medical and minimal surgical therapy in the management of this clinical problem.

References

1. Poxon, V. A., Keighley, M. B., Dykes, P. W., Hepinstall, K., & Jaderberg, M. (1991). Comparison of minimal and conventional surgery in patients with bleeding peptic ulcer: A multicentre trial. *British Journal of Surgery, 78*(11), 1344–1345.
2. Lau, J., Schmid, C. H., & Chalmers, T. C. (1995). Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. *Journal of Clinical Epidemiology, 48*(1), 45–57.
3. Weil, P. H., & Buchberger, R. (1999). From Billroth to PCV: A century of gastric surgery. *World Journal of Surgery, 23*, 736–742.
4. Parsa, C. J., Organ, C. H., & Barkan, H. (2000). Changing patterns of resident operative experience from 1990 to 1997. *Archives of Surgery, 135*, 570–573.

5. Schwesinger, W. H., Page, C. P., Sirinek, K. R., Gaskill, H. V., Melnick, G., & Strodel, W. E. (2001). Operations for peptic ulcer disease: Paradigm lost. *Journal of Gastrointestinal Surgery, 5*, 438–443.
6. Espat, N. K., Ong, E. D., Helton, W. S., & Nyhus, L. M. (2004). 1990–2001 US general surgery chief resident gastric surgery operative experience: Analysis of a pagadigm shift. *Journal of Gastrointestinal Surgery, 8*, 471–478.
7. Charlson, M. E., Popmei, P., Ales, K. L., & MacKenzie, C. R. (1987). A method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *Journal of Chronic Diseases, 40*, 373–383.
8. Guller, U., Hervey, S., Pruves, H., Muhlbaier, L. H., Peterson, E. D., Eubanks, S., et al. (2004). Laparoscopic versus open appendectomy: Outcomes based on a large administrative database. *Annals of Surgery, 239*(1), 43–52.
9. Welch, C. E., Rodkey, G. V., & von Ryll Gryska, P. (1986). A thousand operations for ulcer disease. *Annals of Surgery, 204*(4), 454–467.
10. Donahue, P. (2000). Parietal cell vagotomy versus vagotomy–antrectomy: Ulcer surgery in the modern era. *World Journal of Surgery, 24*, 264–269.
11. Kapetanakis, A. M., Kyprizlis, E. P., & Tsikrikas, T. S. (1997). Efficacy of repeated therapeutic endoscopy in patients with bleeding ulcer. *Hepatogastroenterology, 44*(13), 288–293.
12. Sacks, H. S., Chalmers, T. C., Blum, A. L., ZBerrier, J., & Pagano, D. (1990). Endoscopic hemostasis. An effective therapy for bleeding peptic ulcers. *JAMA, 264*(4), 494–499.
13. Lin, H. J., Lo, W. C., Lee, F. Z. Y., Perng, C. L., & Tseng, G. Y. (1998). A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. *Archives of Internal Medicine, 158*(1), 54–58.
14. Khoshbaten, M., Fattahi, E., Naderi, N., Khaleghian, F., & Rezailashkajani, M. (2006). A comparison of oral omeprazole and intravenous cimetidine in reducing complications of duodenal peptic ulcer. *ZBMC Gastroenterol, 11*(6), 2.
15. Conrad, S. A., Gabrielli, A., Margolis, B., Quartin, A., Hata, J. S., Frank, W. O., et al. (2005). Randomized, double-blinded comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Critical Care Medicine, 33*(4), 760–765.
16. Tomita, T., Fukuda, Y., Tamura, K., Tanaka, J., Hida, N., Kosaka, T., et al. (2002). Successful eradication of Helicobacter pylori prevents relapse of peptic ulcer disease. *Alimentary Pharmacology & Therapeutics, 16*(Suppl 2), 204–209.
17. Ng, E. K., Lam, Y. H., Sung, J. J., Yung, M. Y., To, K. F., Chan, A. C., et al. (2000). Eradication of Helicobacter pylori prevents recurrence of ulcer after simple closure of duodenal ulcer perforation: Randomized controlled trial. *Annals of Surgery, 231*(2), 159–160.
18. Smith, B. R., & Stablie, B. E. (2005). Emerging trends in peptic ulcer disease and damage control surgery in the H. pylori era. *Am Surgeon, 71*(9), 797–801.
19. Thompson, J. C., & Wiener, I. (1984). Evaluation and surgical treatment of duodenal ulcer: Short- and long-term effects. *Clinics in Gastroenterology, 13*, 569–600.
20. Mulholland, M. W., & Debas, H. T. (1987). Chronic duodenal and gastric ulcer. *Surgical Clinics of North America, 67*, 489–507.
21. Johnson, A. G., & Chir, M. (2000). Proximal gastric vagotomy: Does it have a place in the future management fo peptic ulcer? *World Journal Surgery, 24*, 259–263.
22. Feliciano, D. (1992). Do perforated duodenal ulcers need an acid-decreasing surgical procedure now that omeprazole is available? *Surgical Clinics of North America, 72*, 369–380.
23. Ohmann, C., Imhof, M., & Roher, H. D. (2000). Trends in peptic ulcer bleeding and surgical treatment. *World Journal of Surgery, 24*, 284–293.
24. Kubba, A. K., Choudari, C., Rajgopal, C., & Palmer, K. R. (1996). The outcome of urgent surgery for major peptic ulcer haemorrhage following failed endoscopic therapy. *European Journal of Gastroenterology & Hepatology, 8*(12), 1175–1178.
25. Dousset, B., Suc, B., Doudet, M. D., Cherqui, D., Rotman, N., Julien, M., et al. (1995). Surgical treatment of severe ulcerous hemorrhages: Predictive factors of operative mortality. *Gastro-enteÂrologie Clinique et Biologique, 19*(3), 259–265.

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Gastrectomy as a Remedial Operation for Failed Fundoplication

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Abstract The decision for, and choice of, a remedial antireflux procedure after a failed fundoplication is a challenging clinical problem. Success depends upon many factors including the primary symptom responsible for failure, the severity of underlying anatomic and physiologic defects, and the number and type of previous remedial attempts. Satisfactory outcomes after reoperative fundoplication have been reported to be as low as 50%. Consequently, the ideal treatment option is not clear. The purpose of this study was to evaluate the outcome of gastrectomy as a remedial antireflux procedure for patients with a failed fundoplication. The study population consisted of 37 patients who underwent either gastrectomy (n=12) with Roux-en-Y reconstruction or refundoplication (n=25) between 1997–2005. Average age, M/F ratio, and preoperative BMI were not significantly different between the two groups. Outcome measures included perioperative morbidity, relief of primary and secondary symptoms, and the patients' overall assessment of outcome. Mean follow up was 3.5 and 3.3 years in the gastrectomy and refundoplication groups, respectively (p=0.43). Gastrectomy patients had a higher prevalence of endoscopic complications of GERD (58% vs 4%, p=0.006) and of multiple prior fundoplications than those having refundoplication (75% vs 24%, p=0.004). Mean symptom severity scores were improved significantly by both gastrectomy and refundoplication, but were not significantly different from each other. Complete relief of the primary symptom was significantly greater after gastrectomy (89% vs 50%, p=0.044). Overall patient satisfaction was similar in both groups (p=0.22). In-hospital morbidity was higher after gastrectomy than after refundoplication (67% vs 20%, p=0.007) and new onset dumping developed in two gastrectomy patients. In select patients with severe gastroesophageal reflux disease (GERD) and multiple previous fundoplications, primary symptom resolution occurs significantly more often after gastrectomy than after repeat fundoplication. Gastrectomy, however, is associated with higher morbidity. Gastrectomy is an acceptable treatment option for recurrent symptoms particularly when another attempt at fundoplication is ill advised, such as in the setting of multiple prior fundoplications or failed Collis gastroplasty.

Keywords Gastrectomy · Fundoplication · Gastroesophageal reflux disease

Introduction

Laparoscopic Nissen fundoplication has become the most commonly performed surgical procedure for control of gastroesophageal reflux disease (GERD). Although long-term studies suggest an approximately 80–90% life-long symptom relief after a Nissen procedure, 10 to 20% of patients will develop recurrent symptoms and are referred for consideration of reoperative surgery.[1–5] Achievement of a successful outcome with remedial antireflux surgery is a challenge and depends upon many factors including the symptoms responsible for failure, the severity of underlying anatomic and physiologic defects, and the number and type of previous operative attempts. Experience has shown that

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failure after refundoplication is higher than after a first-time fundoplication. Further, the greater number of repairs a patient has undergone, the higher the incidence of a poor outcome, with resolution of symptoms occurring in as few as 50% of patients after multiple attempts.[6–8] With each reoperation at the gastroesophageal junction, the recreation of an anatomically functional barrier becomes more difficult and is sometimes impossible.

An alternative to refundoplication is resection of all or part of either the esophagus or stomach. The decision for resection is complex in the setting of failed antireflux surgery, and outcomes are not well documented. Although esophagectomy is an alternative, it is a major surgical undertaking associated with considerable morbidity and may involve extirpation of what often is an anatomically and functionally normal organ. This leaves gastrectomy as perhaps the most attractive resection option. The perioperative risks, symptomatic outcome, side effects, and patient satisfaction after gastrectomy as a remedial antireflux procedure are poorly understood and form the basis for this study.

Methods

Study Population

Approval from our institutional review board was obtained before the start of this study. Thirty-seven patients with failed fundoplication who underwent remedial antireflux surgery by a single surgeon (TJW) during the years 1997 to 2005 were retrospectively evaluated. Twenty-five patients underwent refundoplication and 12 patients underwent gastrectomy with Roux-en-Y reconstruction as a remedial procedure. Patients who underwent esophagectomy for failed fundoplication were not included in this study.

Preoperative symptoms and evaluation, past surgical history, and perioperative data for both groups of patients were collected through retrospective review of both inpatient and outpatient charts. Routine preoperative evaluation included flexible upper endoscopy, barium upper gastrointestinal radiography, and stationary esophageal manometry. Ambulatory esophageal pH monitoring and gastric emptying scintigraphy were used selectively, depending upon clinical need.

Outcome Assessment

Patients were contacted after remedial surgery via telephone and interviewed regarding current symptoms and change in symptom frequency. Both typical (heartburn, regurgitation, dysphagia) and atypical (odynophagia, chest pain, epigastric pain, cough, choking, nausea, vomiting) symptoms were queried. The primary symptom was considered the presenting symptom documented preoperatively as most bothersome to the patient. Additional symptoms were considered secondary. Both pre- and postoperative symptoms were assigned a standardized symptom severity score (Table 1). Patients were also asked to give an overall subjective assessment of their outcome. Specifically, they were asked whether they considered themselves improved, cured or worsened, whether they were satisfied with the result of their surgery, and whether they would undergo the same remedial operation again if given the choice.

Mean follow up after surgery was 3.3 and 3.5 years in the refundoplication and gastrectomy groups, respectively ($p=0.43$). Follow-up was obtained in 88% (22/25) of patients who underwent refundoplication and 83% (10/12) of patients who had a gastrectomy. Outcome measures included perioperative morbidity, relief of primary and secondary symptoms, and the patients' overall assessment of outcomes.

Statistics

The Student t test was used to compare continuous data between individual groups. Chi-square or Fischer exact test was used to compare proportions between individual groups. The Wilcoxon or Mann–Whitney U test was used for paired and unpaired, independent, nonparametric data. A p value of less than 0.05 defined statistical significance.

Results

Clinical Features

Demographic data for the refundoplication and gastrectomy patients are shown in Table 2. There was no significant difference in age or gender between the groups. Mean preoperative body mass index (BMI) was also similar, as was the prevalence of typical and atypical symptoms. Weight loss was observed in both groups after remedial surgery, with refundoplication patients losing significantly less weight than those in the gastrectomy group ($p=0.004$). Mean postoperative BMIs, however, remained within

Table 1 Symptom Severity Score

Score	Symptom severity
4	Symptom occurs daily.
3	Symptom occurs less than once per day.
2	Symptom occurs less than once per week.
1	Symptom occurs less than once per month.
0	Asymptomatic

Table 2 Demographic Data

	Refundoplication (n=25)	Gastrectomy (n=12)	p value
Mean age	50±10	51±9.9	0.83
M/F	7:18	2:10	0.25
Preoperative BMI	28.9±5.3 (range 19.3–41.2)	29.6±6.7 (range 17.6–40.4)	0.83
Postoperative BMI	26.8±4.6 (range 20.4–41.1)	21.6±4.1 (range 16.3–29.3)	0.004*
Primary symptom:			0.104
Typical	68% (n=17)	91.7% (n=11)	
Atypical	32% (n=8)	8.3% (n=1)	
Endoscopic disease:	4.0% (1/25)	58.3% (7/12)	0.006*
Esophagitis	1	7	
Barrett's	0	1	
Stricture	0	1	

*p<0.05 considered statistically significant

normal range. More than half (58%) of patients undergoing gastrectomy had endoscopic evidence of esophagitis, stricture or Barrett's esophagus (BE) representing more complicated GERD than those in the refundoplication group (p=0.006). All patients undergoing gastrectomy had adequate preoperative esophageal body function established by video esophagography or stationary esophageal manometry. No patient who underwent refundoplication had evidence of severe gastroparesis, as determined by either gastric emptying scintigraphy or upper endoscopy.

Table 3 shows the number and type of prior antireflux procedures in each treatment group. Patients undergoing gastrectomy had a significantly higher incidence of more than one prior antireflux procedure (75%) compared to patients who underwent refundoplication (24%; p=0.004). Of the patients undergoing refundoplication, 19 (76%) had one previous fundoplication and six (24%) had two. No patients in this group had more than two prior procedures. Of patients undergoing gastrectomy, three (25%) had one prior fundoplication, seven (58.3%) had two, one (8.3%) patient had three and one (8.3%) patient had four. In the three patients with only one prior fundoplication, gastrectomy was chosen because of prior Collis gastroplasty (n=2) or because of concomitant severe gastroparesis (n=1).

Remedial Operations and Mechanisms of Failure

Remedial surgery in the refundoplication group consisted of 20 left transthoracic and five open transabdominal fundoplications. One patient who had a transabdominal fundoplication underwent a concomitant distal esophageal myotomy. Remedial surgery in the gastrectomy group consisted of six near-total, four proximal, and two total gastrectomies, all with Roux-en-Y reconstruction. The proximal extent of gastrectomy was determined by intraoperative assessment of the suitability of the proximal stomach for reconstruction, with the intent of leaving a minimal proximal gastric remnant. Near-total gastrectomy was defined by resection of at least 85–90% of the distal stomach, whereas with proximal gastrectomy a distal gastric remnant was preserved. The Roux limb was typically 45 to 60 cm in length.

Intraoperative assessment of the mechanism of failure of the prior fundoplication was carried out in all patients. Recurrent hiatal hernia was identified in 91% (21/23) of the refundoplication group. Of these patients, eight had an associated slipped fundoplication and one had a complete disruption. Of the two refundoplication patients without hiatal hernia, one was thought to have an intact but loose fundoplication and one was found to have a slipped fundoplication. Recurrent hiatal hernia was also present in the majority (66.6%, 8/12) of those undergoing gastrectomy. Of these patients, two also had a slipped fundoplication, two had previous Collis gastroplasty and one had complete disruption of the fundoplication. Of the remaining

Table 3 Number and Type of Previous Antireflux Operations

Number of Previous Fundoplications	Refundoplication (n=25)		Gastrectomy (n=12)	
	Number of Patients	Surgery Type	Number of Patients	Surgery Type
One	19	14 LAP 5 TA	3	1 LAP 1 TA/COLLIS 1 TT/COLLIS
Two	6	2 TA: TA 2 LAP: TA 2 LAP: LAP	7	1 TA: TA 1 TA: TT 2 TA: TA/COLLIS 2 LAP: TA 1 LAP: LAP
Three	0		1	1 Angelchik: TA: TA
Four	0		1	1 LAP: LAP: LAP: Attempted Redo TA

TA=Open transabdominal fundoplication, TT=Transthroacic fundoplication, LAP=Laparoscopic fundoplication

gastrectomy patients without hiatal hernia, one patient was found to have a tight fundoplication secondary to mesh placed at the hiatus, two patients had an intact fundoplication but an improperly tailored Collis gastroplasty, and one patient had an intact fundoplication with previous gastrojejunostomy and severe gastroparesis.

Outcomes

Complications occurred in 20% (5/25) of patients after refundoplication and 67% (8/12) of patients after gastrectomy (p=0.007). The number and nature of complications in each group are shown in Table 4. One patient died after gastrectomy secondary to ARDS and sepsis. Median hospital stay was shorter for patients undergoing refundoplication (6 days, range 3–12) compared to those undergoing gastrectomy (10 days, range 6–38; p<0.001).

Complete relief of the primary symptom was significantly less likely after refundoplication (50%) than after gastrectomy (89%; p=0.044, Fig. 1). Before refundoplication, primary symptoms included heartburn (n=10), dysphagia (n=4), regurgitation (n=3), epigastric pain (n=4), chest pain (n=1), choking (n=2) and vomiting (n=1). Before remedial gastrectomy, primary symptoms included heartburn (n=7), dysphagia (n=2), regurgitation (n=2), and chest pain (n=1).

When defined as complete relief of the primary symptom and no further surgery required, success was achieved in 47.8% of refundoplication patients and in 89% of gastrectomy patients (p=0.035). Four of the patients in the refundoplication group failed remedial surgery. Of these, three went on to have a gastrectomy and one underwent a third fundoplication. The reason for failure in two of the patients who went on to gastrectomy was symptomatic recurrent hiatal hernia. The remaining two failures underwent remedial surgery for unknown reasons. No patient who failed fundoplication, however, had preexisting esophageal body dysfunction or gastroparesis.

Figure 2 shows the mean change in symptom severity scores before and after refundoplication or gastrectomy.

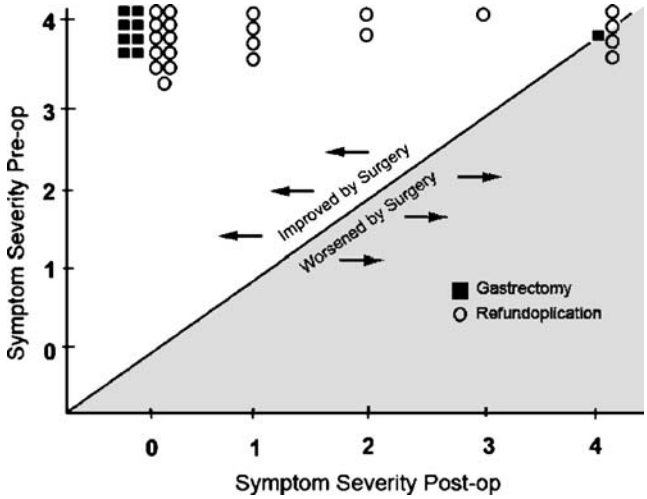

Figure 1 Relief of primary symptom after refundoplication (n=22) versus gastrectomy (n=9) in patients with previous failed fundoplication. Complete primary symptom resolution, as defined by a postoperative symptom severity score of zero, was seen in 50% of patients following refundoplication and 89% of patients following gastrectomy (p=0.004). All data points above or below the centerline indicate improvement or worsening of symptom severity, respectively. Data points on the centerline indicate no change in symptom severity.

Marked improvements in mean symptom scores were seen for all symptoms in both groups. Further, mean pre- and postoperative symptom scores were not significantly different between groups. Postoperative dumping syndrome was reported by two of the gastrectomy patients.

Eighty-two percent of patients after refundoplication and 85% of patients after gastrectomy considered themselves improved or cured (p=0.351). Eighty-three percent of patients after refundoplication and 67% of patients after gastrectomy were satisfied with their outcome (p=0.220). When asked whether they would undergo the same reoperative procedure again if given the choice, 83% of patients after refundoplication and 34% of patients after gastrectomy would do so (p=0.011). In the refundoplication group, the reasons cited for not choosing to undergo the same remedial surgery again were postoperative pain (n=1) and persistent symptoms (n=2). In the gastrectomy group,

Table 4 Perioperative Complications

Refundoplication (5/25) 20%*		Gastrectomy (8/12) 67%*	
Wound infection	1	Wound infection	4
Pulmonary:	2	Pulmonary:	3
Intraop pneumothoraxrequiring chest tube	2	Pneumonia	2
		Respiratory failure	1
Phlebitis	2	Anastomotic leak	2
Bacteremia	1	Hepatic abscess	1
Urinary tract infection	1	Pancreatitis (Violation of pancreatic head intraop, drain left)	1
		Evisceration	1
		Death	1

*p=0.007

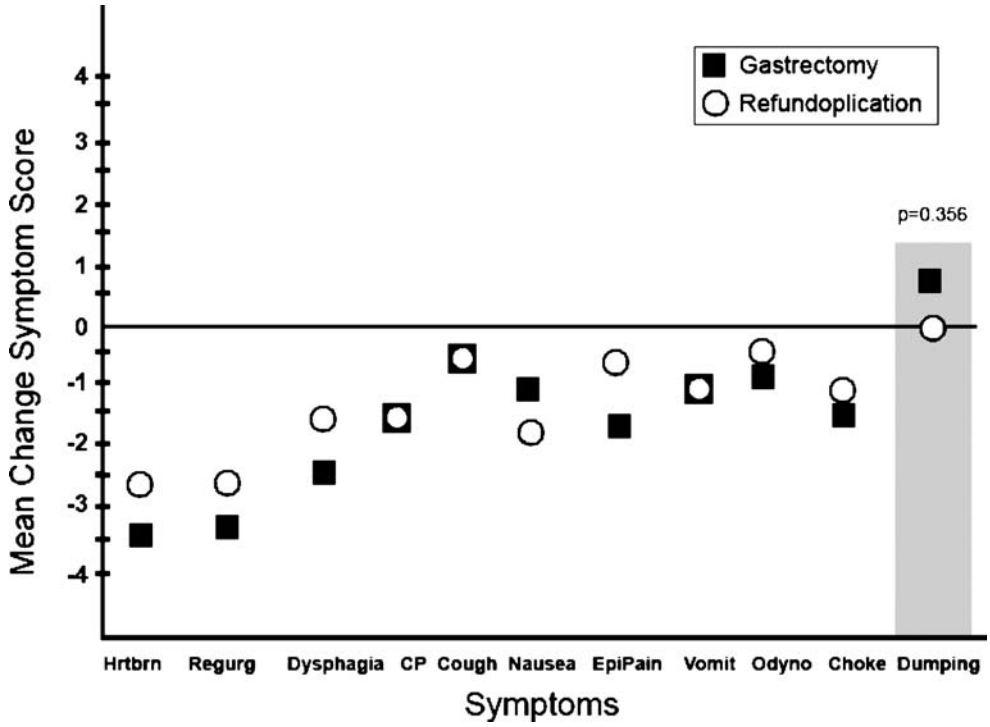

Figure 2 Mean change in symptom severity scores before and after refundoplication or gastrectomy. Marked improvement in mean symptom scores was seen for all symptoms in both groups. New onset dumping syndrome was seen in the gastrectomy group (p=0.356).

the reasons cited were prolonged postoperative course (n=4) and the development of dumping syndrome (n=2).

Discussion

Patients referred with a failed fundoplication present a surgical challenge. Our data demonstrate that in select patients with severe GERD and failed fundoplication, primary symptom resolution occurs significantly more often after gastrectomy than after repeat fundoplication. These results occurred despite the fact that patients undergoing gastrectomy had a higher prevalence of complications of GERD including persistent esophagitis, stricture, and BE than those undergoing refundoplication. In addition, patients undergoing gastrectomy had a higher prevalence of multiple prior fundoplications, making refundoplication a poor option owing to the severity of the anatomical and functional derangements involving the gastroesophageal junction or stomach.

When comparing pre- and postoperative symptoms, mean severity scores were markedly improved by both refundoplication and gastrectomy. Not only was the magnitude of improvement similar between the two groups, but the severity of postoperative symptoms was also similar. On the other hand, complete resolution of the primary symptom was significantly more likely after gastrectomy (89%) than after refundoplication (50%). Further, four of the refundoplication patients went on to undergo another remedial procedure. If these patients are considered surgical failures, the outcome difference is further enhanced between the patients undergoing gastrectomy and those undergoing refundoplication. There was a cost to the choice of gastrectomy, however, reflected in a higher perioperative morbidity and new onset of dumping, which developed in two patients. Based on these findings, we conclude that in select patients with severe GERD having undergone multiple previous fundoplications, gastrectomy is an acceptable treatment option for recurrent symptoms. This conclusion is particularly true when another attempt at fundoplication is ill-advised, such as in the setting of two or more prior fundoplications, failed Collis gastroplasty, or severe gastroparesis. We would not consider gastrectomy after a first-time failed fundoplication, unless anatomic or physiologic circumstances, such as described above, prohibited refundoplication.

The decision to attempt a repeat fundoplication can be difficult. Many factors must be considered, including the nature and severity of ongoing symptoms, the anatomic or physiologic parameters contributing to failure, the type of prior antireflux procedures performed, the patient's underlying comorbidities and body habitus, and the success of nonsurgical therapies in controlling symptoms. Refundoplication in the setting of a failed Collis gastroplasty, for instance, may not be technically feasible. Similarly, refundoplication in the setting of severe gastroparesis would be expected to lead to a poor functional outcome and should be avoided. In addition, reoperation in patients who have had two or more prior fundoplications has been associated with poor outcomes.

Whereas some authors have reported acceptable outcomes after first time refundoplication[7–11] reports after two or more refundoplications have been less than desirable. In reviewing the experience from 1973 to 1989 of 413 patients who underwent fundoplication for GERD, Skinner et al. found that 28% required reoperation. Although a good clinical outcome was seen in a majority of first-time refundoplications, success fell to 66% after a third repair and to less than 50% after a fourth-time repair.[6] In a more recent prospective evaluation of 1892 patients who underwent fundoplication between 1991 and 2004, Smith et al. found an initial revision rate of 2.8%. In a subset of 22 of these patients who required more than one refundoplication, the rate of revision was found to be more than twice this initial rate.[8] Thus, the success of fundoplication appears to decrease with each additional reoperation.

When patients referred for remedial surgery are considered poor candidates for refundoplication, the decision commonly becomes whether to perform an esophagectomy or gastrectomy for persistent severe symptoms. Although we have performed esophagectomy for failed fundoplication, the number of patients who underwent this procedure is small, and we chose not to include them in this analysis. Outcomes after esophagectomy for benign disease, however, have been extensively reported in the literature.[12–15] The morbidity of esophageal replacement can be considerable. In patients with failed fundoplication, the esophagus may be normal both anatomically and physiologically, which argues for its preservation. An esophagectomy, by definition, positions a replacement organ in the thorax predisposing the patient to regurgitation. In addition, esophagectomy in the reoperative setting may require more than one incision, such as a thoracotomy or cervicotomy in addition to a laparotomy. In our opinion, patients with normal esophageal motility, as assessed by video esophagography or stationary esophageal manometry, would better be served by gastrectomy rather than esophagectomy when foregut replacement is contemplated.

Compared to esophagectomy, gastric resection is associated with a number of potential benefits. The native esophagus is left intact, which allows propagation of a food bolus distally and acts as a barrier against the reflux of gastric or intestinal contents into the pharynx or airway. In addition, gastric resection typically can be completed through a laparotomy incision alone. End-stage reflux disease is frequently associated with gastric stasis or delayed gastric emptying, which is addressed via a gastric resection. Finally, in the setting of significant obesity, weight loss from gastric diversion can be a significant associated medical benefit. The use of partial gastrectomy or antrectomy with Roux-en-Y reconstruction as a treatment for patients with severe esophagitis and stricture formation has been described. Salo et al. reported the outcome of partial gastrectomy as a remedial treatment for six patients with persistent esophagitis after fundoplication and found complete endoscopic resolution in 83%.[16] A subsequent study by this same group reevaluated these patients along with two additional patients after a follow-up of 4 years and found all patients to be asymptomatic with complete endoscopic resolution of esophagitis. In addition, postoperative ambulatory esophageal pH monitoring normalized.[17]

Csendes et al. reported on vagotomy and antrectomy with long-limb Roux-en-Y gastrojejunostomy as the preferred treatment option for patients with long-segment BE.[18,19] This choice of operation was based on the observations that fundoplication in the setting of BE is associated with a relatively high long-term failure rate, and that a small proportion of patients with BE develop dysplasia or carcinoma in follow-up. As duodenogastric reflux is common in patients with BE, and as components of the duodenal refluxate are thought to be carcinogenic or injurious to the esophageal mucosa, antrectomy with Roux-en-Y diversion theoretically diverts the damaging components of the gastric refluxate from the esophageal mucosa. Because of the added complexity and potential morbidity of such a reconstruction compared to fundoplication, especially when the latter can be performed via a laparoscopic approach, the operation as proposed by Csendes has not gained wide acceptance in the US and Europe.

An issue of controversy is whether the distal gastric remnant need be removed after proximal gastrectomy. Whereas such a resection is typically not performed in the setting of Roux-en-Y gastric bypass (RYGBP) for obesity, resection does appear to reduce or eliminate the potential risks of hemorrhage from the blind gastric pouch, the occurrence of gastrogastric fistula, the development of marginal ulceration due to a retained antrum effect, bacterial overgrowth in the excluded pouch, or development of a subsequent carcinoma, which is not amenable to surveillance.[20] RYGBP with distal gastric resection clearly is more time-consuming and requires more extensive dissection than RYGBP without distal resection. Whether the benefits of distal gastric resection outweigh the disadvantages merits further study and follow-up.

Conclusion

Based on our findings, we conclude that in select patients with severe GERD and multiple previous fundoplications, primary symptom resolution occurs significantly more often after gastrectomy than after repeat fundoplication. Gastrectomy, however, is associated with higher morbidity. Gastrectomy is an acceptable treatment option for recurrent symptoms

particularly when another attempt at fundoplication is ill-advised, such as in the setting of multiple prior fundoplications, failed Collis gastroplasty, or severe gastroparesis. The indications for gastrectomy with Roux-en-Y reconstruction in the reoperative setting, the pros and cons relative to esophagectomy, whether to resect the distal gastric remnant, and the situations where a repeat attempt at fundoplication should be abandoned require further elucidation.

References

1. Granderath FA, Kamolz T, Schweiger UM, Pasiut M, Haas CF, Wykepiel H, Pointner R. Long-term results of laparoscopic antireflux surgery. Surg Endoscopy 2002;16:753–757.
2. Deschamps C, Trastek VF, Allen MS, Pairolero PC, Johnson JO, Larson DR. Long-term results after reoperation for failed antireflux procedures. J Thorac Cardiovasc Surg 1997;113:545–551.
3. Lundell L, Miettinen P, Myrvold HE, Pedersen SA, Liedman B, Hatlebakk JG, Julkonen R, Levander K, Carlsson J, Lamm M, Wiklund I. Continued (5-year) follow-up of a randomized clinical study comparing antireflux surgery and omeprazole in gastroesophageal reflux disease. J Am Coll Surg 2001;192:172–181.
4. Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen B, Monami B, Jehaes C. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endoscopy 2006;20:159–165.
5. Pessaux P, Armaud JP, Delattre JF, Meyer C, Baulieux J, Mosnier H. Laparoscopic antireflux surgery: Five-year results and beyond in 1340 patients. Arch Surg 2005;140:946–951.
6. Skinner DB. Surgical management after failed antireflux operations. World J Surg 1992;16:359–363.
7. Little A, Ferguson M, Skinner D. Reoperation for failed antireflux operations. J Thorac Cardiovasc Surg 1986;91:511–517.
8. Smith CD, McClusky DA, Rajad MA, Lederman AB, Hunter JG. When fundoplication fails redo? Ann Surg 2005;241(6):861–871.
9. Coelho JCU, Goncalves CG, Claus CMP, Andrigueto PC, Ribeiro MN. Late laparoscopic reoperation of failed antireflux procedures. Surg Laparosc Endosc Percutan Tech 2004;14(3):13–117.
10. Dutta S, Bamehriz F, Boghossian T, Pottruff CG, Anvari M. Outcome of laparoscopic redo fundoplication. Surg Endoscopy 2005;18(3):440–443.
11. Wykypiel H, Kamolz T, Steiner P, Klinger A, Granderath FA, Pointner R, et al. Austrian experiences with redo antireflux surgery. Surg Endoscopy 2005;19:1315–1319.
12. Watson TJ, DeMeester TR, Kauer WKH, Peters JH, Hagen JA. Esophageal replacement for end-stage benign esophageal disease. J Thorac Cardiovasc Surg 1998;115:1241–1249.
13. Young MM, Deschamps C, Trastek VF, Allen MS, Miller DL, Schleck CD et al. Esophageal reconstruction hfor benign disease: early morbidity, mortality, and functional results. Ann Thorac Surg 2000;70:1651–1655.
14. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy for treatment of benign and malignant esophageal disease. World J Surg 2001;25:196–203.
15. Young MM, Deschamps C, Allen MS, Miller DL, Trastek VF, Schleck CD, Pairolero PC. Esophageal reconstruction for benign disease: self-assessment of functional outcome and quality of life. Ann Thorac Surg 2000;70:1799–1802.
16. Salo JA, Lempinen M, Kivilaakso E. Partial gastrectomy with Roux-en Y reconstruction in the treatment of persistent or recurrent oesophagitis after Nissen fundoplication. Br J Surg 1985;72(8):623–625.
17. Salo JA, Ala-Kulju KV, Heikkinen LO, Kivilaakso EO. Treatment of severe peptic esophageal stricture with Roux-en Y partial gastrectomy, vagotomy, and endoscopic dilation. A follow-up study. J Thorac Cardiovasc Surg 1991;101(4):649–653.
18. Csendes A, Braghetto I, Burdiles P, Korn O. Roux-en-Y long limb diversion as the first operation for patients who have Barrett's esophagus. Chest Surg Clin North Am 2002;12(1):157–184.
19. Csendes A, Braghetto I, Burdiles P, Smok G, Henriquez A, Parada F. Regression of intestinal metaplasia to cardiac or fundic mucosa in patients with Barrett's esophagus submitted to vagotomy, partial gastrectomy and duodenal diversion. A prospective study of 78 patients with more than 5 years of follow up. Surgery 2006;139(1):46–53.
20. Csendes A, Burdiles P, Papapietro K, Diaz JC, Muluenda F, Burgos A, Rojas J. Results of gastric bypass plus resection of the distal excluded gastric segment in patients with morbid obesity. J Gastrointest Surg 2005;9:121–131.

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Predicting Unresectability in Pancreatic Cancer Patients: The Additive Effects of CT and Endoscopic Ultrasound

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Abstract
Background A standardized method for predicting unresectability in pancreatic cancer has not been defined. We propose a system using CT and endoscopic ultrasound (EUS) to assess patients for unresectable pancreatic cancers.
Methods Radiologic and surgical data from 101 patients who underwent exploration/resection for pancreatic cancer were reviewed. Chi-squares were used to identify five factors significantly correlated with unresectability, which were incorporated into a scoring system (one point for each factor).
Results The resectability rates were 84, 56, and 10% for patients with scores of 0, 1, and 2, respectively. All four patients with three risk factors for unresectability had unresectable tumors. The most accurate results were achieved in patients evaluated with both CT and EUS.
Discussion This scoring system stratifies pancreatic cancer patients into three groups: (1) patients with a score of zero (likely to undergo successful resection), (2) patients with a score of one (likely to benefit from laparoscopic staging prior to attempting resection), and (3) patients with a score of two or higher (low probability of successful resection, who may be better served by neoadjuvant therapy).

Keywords Pancreatic cancer · CT scan · Endoscopic ultrasound

Introduction

Pancreatic cancer represents one of the greatest challenges in oncology. In 2004, more than 30,000 new cases were diagnosed, with a dismal overall survival rate of only 4%.[1] Surgery remains the cornerstone of curative treatment. Among patients with resectable disease, 5-year survival is approximately 20% with multimodality treatment.[2] However, in unresectable patients (even those who receive

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aggressive multimodality treatment), 2-year survival is only 10% and long-term survival is rare.[3,4,5,6] Consequently, many pancreatic cancer patients are referred for surgery in the hope of achieving a successful resection, even when imaging is concerning for unresectable disease. A systematic and accurate method of predicting unresectable disease could spare these patients the morbidity and mortality associated with nontherapeutic surgery. Further, by accurately predicting resectable disease, such a method could maximize the number of patients who are able to undergo a potentially curative procedure.

The major contraindications to surgical resection of pancreatic adenocarcinoma include proven metastatic disease and definitive evidence on imaging of superior mesenteric artery/vein, portal vein, or celiac axis involvement by tumor. Traditionally, angiography, computed tomography (CT) scans, and open laparotomy were the primary methods of evaluating patients for resectability. Newer diagnostic tools such as thin section high-resolution multislice spiral CT, magnetic resonance imaging/magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS), and laparoscopy allow increasingly accurate diagnosis and preoperative staging of pancreatic cancer. However, the optimal use of these tests in selecting unresectable patients has not been definitively established. There remains a clinically significant subset of patients who appear on imaging studies to have resectable tumors, yet have locally unresectable or metastatic disease at exploratory laparotomy.

There are a number of benefits to increasing the accuracy of preoperative staging in pancreatic cancer patients. Identifying patients with unresectable tumors would reduce the morbidity and mortality associated with a nontherapeutic laparotomy. In such patients, symptoms such as duodenal obstruction, pain, and jaundice can often be palliated with nonsurgical procedures.[7,8,9,10] By avoiding a laparotomy, one can also eliminate the delays in starting palliative chemotherapy that are associated with the postlaparotomy recovery period. Additionally, patients who are accurately classified as high risk for unresectability would be more appropriate for laparoscopic staging than open surgical exploration. Effective preoperative staging methods would also help select the most appropriate candidates for aggressive neoadjuvant radiation and chemotherapy. Finally, more accurate preoperative staging would allow better comparison of outcomes among different institutions. In the absence of a systematic method of predicting resectability, the selection of operable patients is inherently subjective and highly variable from one institution to another. This variability among different institutions complicates comparisons of the accuracy of diagnostic testing, as well as of the effectiveness of multidisciplinary interventions in the treatment of pancreatic cancer.

The goals of this investigation were to identify characteristics common to patients who were found to have unresectable pancreatic adenocarcinoma without definitive evidence on imaging of unresectability, and to compare these characteristics with those of patients at the same institution who underwent successful resection. We looked carefully for CT and EUS findings that were predictive for patients who were ultimately found to have unresectable pancreatic cancer but whose preoperative imaging did not demonstrate obvious unresectability (i.e., metastatic disease or vessel encasement/thrombosis).

Materials and Methods

Patient Selection

One hundred and one consecutive patients of a single surgeon, who underwent exploration and either resection or palliation for pancreatic adenocarcinoma, were identified. All surgeries were performed between September 2000 and October 2005. Patients with tumors of the endocrine pancreas, cholangiocarcinoma, or nonpancreatic periampullary tumors were excluded from the analysis.

Data Analysis

Data on tumor size, vascular abutment, distant metastases, and pathologically enlarged lymph nodes (defined as larger than 1 cm in the short axis) were collected by reviewing reports of EUS procedures and CT scans. For purposes of this study, abdominal CT scans both from this institution and from outside facilities were reviewed by one of our institution's radiologists specializing in the interpretation of abdominal imaging. The EUS procedures were performed by gastroenterologists at one institution with specific experience in pancreatic ultrasonography. EUS features considered suspicious for vascular invasion (but not encasement/thrombosis) include loss of interface between the mass and adjacent vessels without tumor in the lumen and/or irregular appearance of the wall of the vessel (but the vessel still has flow by Doppler examination). CT features considered suspicious for unresectability include the presence of liver lesions too small to characterize or biopsy percutaneously, as well as compression, abutment, or deformation of the superior mesenteric artery/vein. All patients with definite evidence on CT scan of thrombosis or encasement of a significant length of the superior mesenteric artery/vein were determined to be unresectable preoperatively, as were those with liver lesions large enough to confirm malignancy on biopsy percutaneously. These patients were not included in this study. Symptoms present at the time of surgery were determined from

previously documented preoperative history and physical examinations. Preoperative hemoglobin, bilirubin, alkaline phosphatase, and CA19-9 levels were also documented. Operative notes were reviewed for information about surgery performed, as well as reasons for aborting an attempted resection. Tumor size, histology, pathologic staging, and nodal status were obtained from surgical pathology reports.

The chi-square method was used to identify five radiologic factors that were significantly correlated with unresectability. The scoring system incorporates these five individual factors; patients were assigned one point for each of the factors associated with unresectability, so that a higher score was associated with a greater chance of unresectability. Chi-square analysis was then repeated based on total point scores of one, two, and three (no patient who underwent exploration received a score higher than three of a potential five). Sensitivity, specificity, and accuracy were also calculated for each identified factor, as well as each total score level.

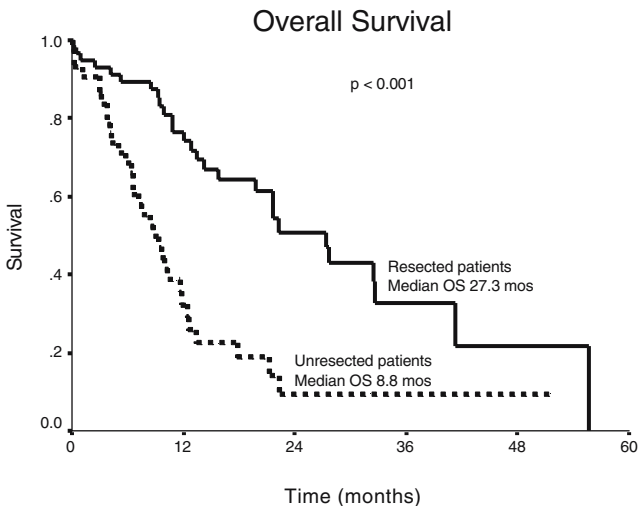

Figure 1 Kaplan–Meier survival curve, overall survival.

Table 1 Patient Characteristics

Characteristic	Number	Percent
Sex		
Female	48	48
Male	53	52
Presenting symptom		
Jaundice	72	71
Pain	16	16
Incidental finding	4	4
Weight loss	3	3
Pancreatitis	3	3
Nausea/vomiting	2	2
Duodenal obstruction	1	1
AJCC stage group		
IA	4	4
IB	10	10
IIA	7	7
IIB	36	36
III	16	16
IV	27	27
Pathologic CR	1	1
Resected		
Yes	58	58
No	43	42
Reason unresectable		
Metastases	27	63
Locally unresectable	16	37
Site of metastasis		
Liver	17	63
Peritoneum	9	33
Bowel	1	4
Surgery performed		
Pylorus-sparing Whipple	41	40
Classic Whipple	10	11
Distal pancreatectomy	7	8
Exploratory laparotomy (+/− bypass)	37	37
Laparoscopic biopsy	3	3
Angiogram	1	1

Survival was calculated from the date of surgery in all patients. Follow-up was conducted by review of medical records, interviews with patients/families, and searches of the Social Security Death Index, and was available in 100/101 patients (99%). Actuarial survival analysis was performed using the Kaplan–Meier method, with the log-rank test used to compare survival curves. All statistical analyses were performed with SPSS (version 10.0 for

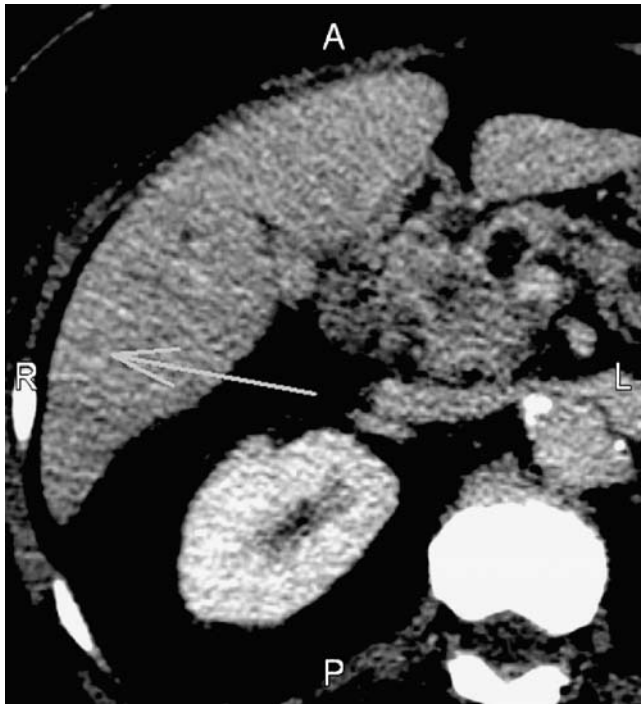

Figure 2 Abdominal CT scan with indeterminate but suspicious lesion in the liver (*arrow*).

Figure 3 CT scan of the abdomen with a pathologically enlarged lymph node in the celiac region (*arrow*).

Windows®). Statistical significance was defined as $p<0.05$. The collection and reporting of these data were approved by the institutional review board at the University of Maryland.

Results

Patient Data

A total of 101 patients were analyzed in this study. Median age was 64 years (range 36–86 years), and 48% of the patients were women. Detailed demographic and clinical patient characteristics are presented in Table 1. The most common presenting symptom was obstructive jaundice (71%), followed by pain (16%). A majority of patients (58%) underwent curative-intent resection, with the remainder undergoing exploratory laparotomy or laparoscopic biopsy. Six of the Whipple resections included a partial superior mesenteric vein (SMV) resection. In every case, these were resections of a "knuckle" of SMV, i.e., a small piece and not a circumferential resection. In none of these cases was SMV reconstruction necessary. One patient proved to be unresectable by angiography and was therefore never explored. Among the 58 patients who ultimately underwent resection, the most common (70%) surgery was a pylorus-preserving Whipple procedure (pancreatico-duodenectomy), followed by a classic Whipple procedure (17%), and a distal pancreatectomy with splenectomy (14%). Of the 43 patients found to be unresectable, 27 (63%) were unresectable because of distant

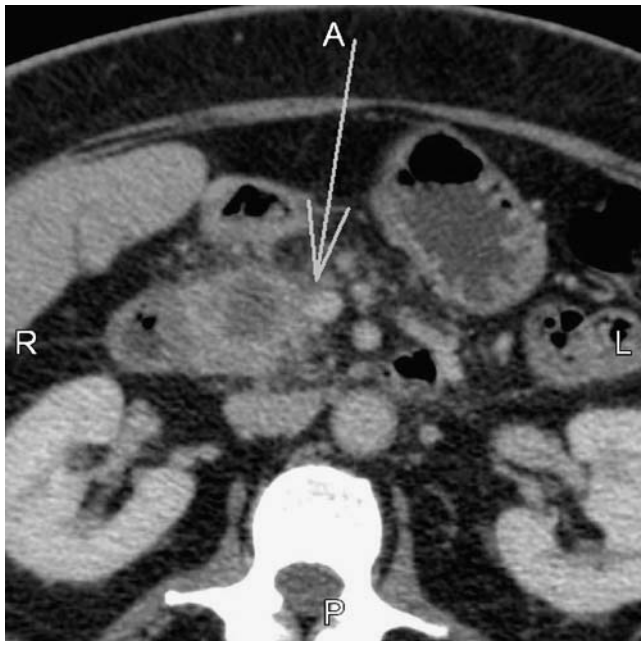

Figure 4 Abdominal CT scan showing tumor in the pancreas abutting and deforming the SMV (*arrow*).

Figure 5 EUS image with pathologically enlarged lymph node (marked by *dashed lines*).

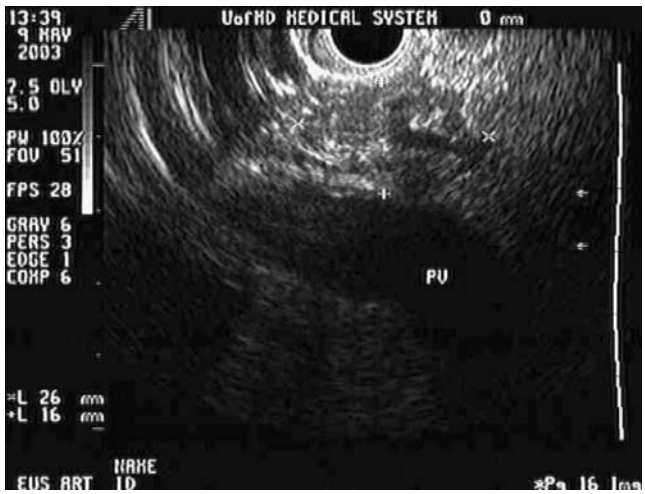

Figure 6 EUS image with tumor abutment of the portal vein (*plus sign*).

Table 2 Criteria Which Individually Predicted Unresectability

Criterion	*n*	*p*[a]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	RR[b]
Vascular abutment, CT	16	<0.001	94	74	44	98	3.16 (2.12–4.70)
Adenopathy >1 cm, CT	29	<0.001	76	74	69	80	2.88 (1.63–5.10)
Liver lesion, CT	10	0.06	70	60	18	94	1.77 (1.09–2.88)
Vascular abutment, EUS	18	0.004	72	67	42	88	2.17 (1.35–3.48)
Adenopathy >1 cm, EUS	13	0.03	69	64	30	90	1.91 (1.16–3.15)

PPV = positive predictive value, NPV = negative predictive value, RR = relative risk
[a] *p* vs resectable patients
[b] 95% CI are in parentheses

metastases. The most common site of metastasis was the liver. The remainder of inoperable patients had locally unresectable disease secondary to vascular involvement. Three patients had received neoadjuvant chemotherapy.

Survival

Median survival for the entire group was 13.5 months. As expected, patients who underwent a resection had significant improvement in median survival when compared with unresectable patients: 27.3 vs 8.8 months, $p<0.001$ (see Fig. 1).

Imaging

Ninety-three of the 101 patients had a preoperative CT scan report available for evaluation. Forty-seven (51%) of these patients did not have a discrete mass seen on CT. Among these patients (i.e., those who did not have a discrete mass on CT), 35 underwent further evaluation with EUS, which demonstrated a mass in 33 patients. This yielded a sensitivity of 94% for EUS detection of a pancreatic mass in the setting of a CT that was negative for a focal mass. Overall, EUS identified a mass in 65/71 (92%) patients who underwent the test.

Predicting Unresectability

Through univariate analysis, we identified five criteria that were associated with a higher risk of unresectability: (1) suspicious liver lesions that were too small to characterize or biopsy percutaneously, (2) intra-abdominal adenopathy (>1 cm in short axis) identified by CT, (3) vascular abutment or deformation on CT, (4) intra-abdominal adenopathy (>1 cm) identified by EUS, and (5) vascular abutment or deformation on EUS. These findings are depicted in Figs. 2, 3, 4, 5, and 6; statistical analyses of these five criteria are summarized in Table 2.

A number of other variables were analyzed but did not significantly predict unresectability in univariate analysis. Notably, these factors included tumor size, CA19-9 levels, and the presence of pain preoperatively; all of which have been suggested as possible markers for unresectable disease by other investigators.

As described in the "Materials and Methods" section, each patient was assigned a score of 0–5 based on the number of criteria that they fulfilled. Eighty four percent (41/49) of the patients with a score of "0" had a resectable tumor, but only 56% (15/27) of the patients with a score of "1" had a resectable tumor (see Tables 3, 4, and 5). In the group of 52 patients who had a score of "≥1," 35 (67%) were unresectable, yielding a relative risk for unresectability in this group of patients (when compared with patients with a score of "0") of 2.7 [95% confidence interval (CI) 1.3–5.8]. Accuracy in predicting unresectability improved further with a score of "≥2" (see Table 6). That is, 56/58, or 97%, of the resectable patients had a score of "0" or "1," whereas 23/25, or 92%, of patients with a score "≥2" were unresectable (see Table 4). Of the four patients who had three risk factors for unresectability, none were found to have a resectable tumor. None of the patients

Table 3 Resectability Rates by Total Score

Score	# Resectable	# Unresectable
0	41/49 (84%)	8/49 (16%)
1	15/27 (56%)	12/27 (44%)
≥1	17/52 (33%)	35/52 (67%)
2	2/21 (10%)	19/21 (90%)
≥2	2/25 (8%)	23/25 (92%)
3	0/4 (0%)	4/4 (100%)

Table 4 Resectability Rates by Total Score (Among Patients Who Had Preoperative CT and EUS)

Score	# Resectable	# Unresectable
0	27/29 (93%)	2/29 (7%)
1	9/21 (43%)	12/21 (57%)
≥1	17/46 (37%)	29/46 (63%)
2	2/18 (11%)	16/18 (89%)
≥2	2/22 (9%)	20/22 (91%)
3	0/4 (0%)	4/4 (100%)

Table 5 Resectability by Score of 0 vs 1

	Score=1	Score=0	Total
Unresectable	12	8	20
Resectable	15	41	56
	27	49	76

Relative risk for unresectability, score of 1 vs score of 0=2.7 (1.3–5.8). $p \leq 0.01$

had a score greater than three. The most accurate results were achieved in the group of 72 patients who were evaluated with both CT and EUS, as shown in Tables 4 and 7; in this group of patients, 29/31 (94%) of the unresectable patients had a score ≥1, with a relative risk for unresectability (when compared with patients with a score of "0") of 9.8 (95% CI 2.5–37.8). These radiographic features were also statistically significant in tumors of the pancreatic body and tail (n=11).

Discussion

A number of recent studies have evaluated the ability of CT and EUS to diagnose and stage pancreatic cancers. DeWitt et al. described 104 patients who underwent preoperative EUS and CT. In this study, EUS and CT correctly predicted for unresectability in 68 and 64% of cases, respectively.[11] Ahmad et al. reported on 89 patients evaluated for resectability with EUS.[12] This study found no significant difference in resectability rates between patients whose tumors were staged by EUS as T4 (locally unresectable) vs those who were staged as T3, suggesting that EUS alone is not a satisfactory modality for predicting local resectability. Contemporary CT techniques are better able to predict resectability than unresectability; recent studies have reported that thin-slice helical CT scan correctly predicted resectability in 74[13] to 88%[14] of patients. However, one bias that should be considered when evaluating these studies is that patients who are determined to be "unresectable" by radiographic criteria generally do not undergo surgical exploration. Because of this, radiographic findings cannot be confirmed at surgery, and thus, institutional variation in what is deemed "resectable" and "unresectable" invariably

Table 6 Resectability by Score ≥2

	Score≥2	Score≤1	Total
Unresectable	23	20	47
Resectable	2	56	58
	29	76	101

Relative risk for unresectability, score of ≥2 vs score of ≤1=3.5 (2.4–5.2). $p \leq 0.001$

Table 7 Resectability by Score ≥1, Patients Who Had CT and EUS

	Score≥1	Score=0	Total
Unresectable	29	2	31
Resectable	14	27	41
	43	29	72

Relative risk for unresectability, score of ≥1 vs score of 0=9.8 (2.5–37.8). $p \leq 0.001$

influences results. Presumably, studies from centers that use stricter radiographic criteria will report a relatively high success rate for CT in predicting resectability.

We would like to emphasize that the unexpected finding of unresectability in those patients with adenopathy described on CT was not secondary to pathologic nodal involvement. In fact, CT was not sensitive for the diagnosis of pathologically positive lymph nodes (18.2% sensitivity, 71.4% specificity). Among the 22 unresectable patients with adenopathy >1 cm (in short axis) on CT scan, eight patients had locally unresectable disease, and 14 had metastatic disease. A possible explanation for this correlation is that locally advanced/metastatic disease may worsen low-grade cholangitis (from obstruction) or low-grade pancreatitis (from atrophy/inflammation of the gland involved by tumor).

Other studies have identified nonradiographic factors that predict for unresectability, including carbohydrate antigen 19-9 (CA19-9) levels above 150 units/ml,[15] positive peritoneal cytology,[16] and the presence of pain before surgery.[17] We were unable to replicate the results of Schlieman et al., who reported on CA19-9 as a significant predictor of unresectability. This is most likely due to the relatively small proportion of patients (30%) that had preoperative CA19-9 levels available for review. At our institution, peritoneal cytology is not routinely used in the preoperative evaluation of pancreatic cancer.

We believe that the scoring system described in this paper provides an effective method of stratifying pancreatic cancer patients into three groups. The first group would include patients with a score of zero and a high probability of undergoing successful resection. The second group includes patients with a score of one who are likely to benefit from laparoscopy to look for metastatic disease. In the absence of metastatic disease, the majority of patients in this group would still be resectable. The third group is comprised of patients with a score of two or higher who have a low probability of undergoing successful resection and are therefore more likely to benefit from expedited chemotherapy and radiation therapy. Patients who had no risk factors (i.e., a score of zero) had an 84% chance of resectability. In the presence of only one risk factor (i.e., a score of one), resectability rates dropped to 56%. That is, of the 27 patients with only one risk factor present, 12 were

unresectable (eight due to metastatic disease). We feel that this subgroup of patients—with only one risk factor for unresectability—would be ideal candidates for laparoscopic staging before laparotomy. In fact, in this series, after the patients in this group with metastatic disease are excluded, 18 of 23 (78%) patients were resectable. In our study, laparoscopic staging could have prevented eight unnecessary laparotomies by detecting metastatic disease. Patients with more than two risk factors (i.e., a score of two) are ideal patients for whom to consider neoadjuvant therapy protocols with the intent to downstage the tumor because greater than 85% of this group of patients had unresectable tumors. Even if attempts to downstage the primary tumor are unsuccessful, these patients would still benefit from nonsurgical methods of palliation, including endoscopic stent placement for biliary decompression, percutaneous or endoscopic celiac plexus block for pain control, and palliative chemotherapy/radiotherapy to decrease tumor burden.

Conclusion

In this paper, we propose a scoring system derived from both CT and EUS imaging data for predicting resectability and unresectability in patients with pancreatic cancer. We also present a previously unreported radiologic risk factor for unresectability, namely, the presence of intra-abdominal adenopathy >1 cm (in short axis) on CT scan and/or EUS. Our results suggest that by combining data from both CT and EUS, a clinically relevant scoring system can be utilized to help select appropriate interventions and therapy for patients with pancreatic cancer.

References

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. CA Cancer J Clin 2005;55:10–30.
2. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. 201 patients. Ann Surg 1995;221(6):721–731.
3. Moertel CG, Frytak S, Hahn RG, et al. Therapy of locally unresectable pancreatic carcinoma: a randomized comparison of high dose (6000 rads) radiation alone, moderate dose radiation (4000 rads + 5-fluorouracil), and high dose radiation + 5-fluorouracil: the Gastrointestinal Tumor Study Group. Cancer 1981;48(8):1705–1710.
4. Gastrointestinal Tumor Study Group. Radiation therapy combined with adriamycin or 5-fluorouracil for the treatment of locally unresectable pancreatic carcinoma. Cancer 1985;56(11):2563–2568.
5. Klaassen DJ, MacIntyre JM, Catton GE, et al. Treatment of locally unresectable cancer of the stomach and pancreas: a randomized comparison of 5-fluorouracil alone with radiation plus concurrent and maintenance 5-fluorouracil—an Eastern Cooperative Oncology Group study. J Clin Oncol 1985;3(3):373–378.
6. Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. J Natl Cancer Inst 1988;80(10):751–755.
7. Mittal A, Windsor J, Casey P, et al. Matched study of three methods of palliation for malignant pyloroduodenal obstruction. Br J Surg 2004 Feb;91(2):205–209.
8. Maetani I, Tada T, Ukita T, et al. Comparison of duodenal stent placement with surgical gastrojejunostomy for palliation in patients with duodenal obstructions caused by pancreaticobiliary malignancies. Endoscopy 2004 Jan;36(1):73–78.
9. Levy M, Wiersema M. EUS-guided celiac plexus neurolysis and celiac plexus block. Gastrointest Endosc 2003;57(7):923–930.
10. Espat N, Brennan MF, Conlon KC. Patients with laparoscopically staged unresectable pancreatic adenocarcinoma do not require subsequent surgical biliary or gastric bypass. J Am Coll Surg 1999 Jun;188(6):649–655.
11. Dewitt J, Devereaux B, Chriswell M. et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for diagnosis and staging of pancreatic cancer. Ann Intern Med 2004 Nov 16;141(10):753–763.
12. Ahmad N, Lewis J, Ginsberg G. EUS in preoperative staging of pancreatic cancer. Gastrointest Endosc 2000 Oct;52(4):463–468.
13. Valls C, Andia E, Sanchez A. Dual-phase helical CT of pancreatic adenocarcinoma: assessment of resectability before surgery. AJR Am J Roentgenol 2002 Apr;178(4):821–826.
14. Fuhrman GM, Charnsangavej C, Abbruzzese JL. Thin-section contrast-enhanced computed tomography accurately predicts the resectability of malignant pancreatic neoplasms. Am J Surg 1994 Jan;167(1):104–111; discussion 111–113.
15. Schlieman MG, Ho HS, Bold RJ. Utility of tumor markers in predicting resectability of pancreatic cancer. Arch Surg 2003 Sep;138(9):951–955.
16. Merchant NB, Conlon KC, Saigo P, et al. Positive peritoneal cytology predicts unresectability of pancreatic adenocarcinoma. J Am Coll Surg 1999;188(4):421–426.
17. Kelsen DP, Portenoy R, Thaler H, et al. Pain as a predictor of outcome in patients with operable pancreatic carcinoma. Surgery 1997 Jul;122(1):53–59.

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Declining Morbidity and Mortality Rates in the Surgical Management of Pancreatic Necrosis

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Abstract Surgical management of patients with pancreatic necrosis (PN) has evolved over the last two decades to include prophylactic antibiotics, initial medical management, and delayed surgical intervention. The purpose of this study is to identify changes in morbidity and mortality rates as our methods of surgical management have evolved. One hundred two consecutive patients (59 males and 43 females, mean age 53±16 years) with PN managed surgically were classified as group I (1993–2001), after the routine use of prophylactic antibiotics (N=55), and group II (2002–2005), after the use of International Association of Pancreatology (IAP) guidelines for intervention (N=47). Age, sex, etiology of pancreatitis, percent of necrosis, infected necrosis, and acute physiology and chronic health evaluation II scores were similar between groups. Despite a significant worsening of Balthazar computed tomography scoring in group II patients ($p<0.0001$), operative morbidity (49 [89%] vs 34 [72%], $p=0.03$), mortality (10 [18%] vs 2 [4%], $p=0.03$), and hospital length of stay (38±33 days vs 26±23 days, $p=0.04$) were significantly less in group II patients. Current methods of surgical management utilizing IAP guidelines have resulted in a decreased operative morbidity, mortality, and hospital length of stay in patients with PN.

Keywords Severe acute pancreatitis · Pancreatic necrosis · Pancreatic debridement · Morbidity · Mortality · Pancreatic fistula

Introduction

Pancreatic necrosis (PN) is either a diffuse or focal area of nonviable pancreatic parenchyma that has lost its microvascular blood supply as a consequence of an episode of severe acute pancreatitis (SAP).[1,2] Dynamic contrast-enhanced computed tomography (CT) is currently the gold standard in confirming this diagnosis.

Once identified, the presence of PN increases patients' risk for secondary pancreatic infection and the need for surgical debridement.[3,4] Our understanding of the pathophysiology and natural history of SAP and PN has evolved over the last two decades: This knowledge forms the basis for the evidence-based treatment guidelines from the International Association of Pancreatology (IAP) for the surgical management of acute pancreatitis (Table 1).[5] Treatment in our own unit was centralized, and the surgical management has evolved to include the routine use of prophylactic broad spectrum antibiotics[6]; delayed surgical intervention for specific indications; and use of organ-preserving debridement with abdominal closure over drains.[7] The purpose of this study was to assess changes in the morbidity and mortality rate in 102 consecutive patients with PN treated by operative debridement over a 12-year period as our methods of surgical management have evolved.

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Table 1 Summary of the official IAP Guidelines for the Surgical Management of Acute Pancreatitis[26]

IAP Guidelines
1. Mild acute pancreatitis is not an indication for pancreatic surgery.
2. The use of prophylactic broad-spectrum antibiotics reduces infection rates in CT-proven necrotizing pancreatitis but may not improve survival.
3. FNAB should be performed to differentiate between sterile and infected PN in patients with sepsis syndrome.
4. Infected PN in patients with clinical signs and symptoms of sepsis is an indication for intervention including surgery and radiologic drainage.
5. Patients with sterile PN (FNAB-negative) should be managed conservatively and only undergo intervention in selected cases.
6. Early surgery within 14 days after onset of the disease is not recommended in patients with necrotizing pancreatitis unless there are specific indications.
7. Surgical and other forms of interventional management should favor an organ-preserving approach, which involves debridement or necrosectomy combined with a postoperative management concept that maximizes postoperative evacuation of retroperitoneal debris and exudate.
8. Cholecystectomy should be performed to avoid recurrence of gallstone-associated acute pancreatitis.
9. In mild gallstone-associated acute pancreatitis cholecystectomy should be performed as soon as the patient has recovered and ideally during the same hospital admission.
10. In severe gallstone associated acute pancreatitis, cholecystectomy should be delayed until there is sufficient resolution of the inflammatory response and clinical recovery.
11. Endoscopic sphincterotomy is an alternative to cholecystectomy in those who are not fit to undergo surgery in order to lower the risk of recurrence of gallstone-associated acute pancreatitis. There is, however, a theoretical risk of introducing infection into sterile PN.

Methods

Between July 1993 and February 2005, 1,970 patients were admitted to Indiana University Medical Center with the diagnosis of acute pancreatitis (ICD-9 code=577.0). Of these, we identified 102 (5%) patients with the diagnosis of PN who required pancreatic and/or peripancreatic debridement. This study was carried out after approval from our human research review committee (Indiana University–Purdue University Indianapolis Institutional Review Board Study Number 0505-68). All patients had PN confirmed by contrast-enhanced CT showing zones of nonenhancing pancreas (<50 Hounsfield units) larger than 3 cm or involving more than 30% of the volume of the pancreas. Seventy-nine patients (77%) were referred from outside facilities, and 23 (23%) were admitted directly to our hospital. Acute physiology and chronic health evaluation (APACHE) II scores were calculated in all patients at the time of their admission to our facility.[8] Patients with either a pancreatic abscess (circumscribed collection of pus with no or minimal PN) or an infected pancreatic pseudocyst (collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue) based on the Atlanta criteria[1] were excluded.

Based on our management algorithm for patients with PN, all patients admitted or transferred within 7 days of their initial bout of SAP were treated with a drug showing good penetration into pancreatic tissue for 14 days.[5,9] Many patients received antibiotics at outside institutions before being transferred, but these data were not captured accurately for this study. Initial medical management at our hospital included withholding oral intake, aggressive fluid resuscitation, pain control using narcotic analgesics, antiemetics, and nutritional support. Enteral feeding via a nasogastric or nasojejunal tube was instituted in 48 (47%) patients whereas 54 (53%) patients received alimentation by parenteral nutrition (TPN). If nausea and vomiting were present, decompression was instituted utilizing a nasogastric tube. All patients received an intravenous proton pump inhibitor for peptic ulcer prophylaxis and subcutaneous heparin (fractionated or unfractionated) for deep vein thrombosis prophylaxis.

Our indications for surgery remained consistent throughout this 12-year period and included (1) infected PN (N=76), as evidence by gas identified in necrosis or peripancreatic fluid collections on contrast-enhanced CT scan, or by positive gram stain or culture on percutaneous fine needle aspiration[10]; (2) symptomatic sterile necrosis (N=23) defined as patients with sterile PN who were managed medically for at least 4 weeks after their initial episode of SAP who have persistent "unwellness," malaise, fatigue, nausea, inability to eat, low-grade fevers, poor glycemic control, plateau in their clinical progress, or recovery from organ dysfunction[11]; or (3) deteriorating clinical course with progressive organ failure despite appropriate medical therapy (N=3).

Operations were carried out through a bilateral subcostal incision. The retroperitoneum was entered through the lesser sac by mobilizing the omentum off the transverse colon. Utilizing preoperative CT imaging as a guide, specific areas of pancreatic and peripancreatic necrosis and associated fluid sequestration were targeted. Fluid collections were evacuated and devitalized tissue was removed by blunt and

occasionally careful sharp debridement. Necrotic tissue and peripancreatic fluid was routinely cultured for bacteria (aerobic and anaerobic) and fungus. Extension of the necrotic process down the paracolic gutters prompted mobilization of either the hepatic flexure, splenic flexure, or both. Once the main cavity containing necrosis was entered, multiple extension of the process in the retroperitoneum were identified by gentle digital palpation, which demonstrated communicating spaces and extensions of the necrosis debris.[12] Debridement often extended into the peripancreatic fat of the transverse mesocolon or small bowel mesentery. If technically feasible, cholecystectomy was performed with intraoperative cholangiogram in those with presumed gallstone pancreatitis.

Closed suction 19-french Jackson-Pratt drains were placed at the time of operation with the number predicated by the extent of debridement and concern for postoperative pancreatic fistula. All patients had gastrojejunal feeding tubes (18 or 22 French MIC tubes) placed at the time of operation via a Stamm-type gastrostomy with the jejunal segment of the catheter directed past the ligament of Treitz. When early surgical intervention (<3 weeks after initial bout of SAP) was required or when the necrosis was found too poorly demarcated to allow for complete debridement, patients were treated with repeated operations every 48–72 h until the surgeon felt the necrotic process was adequately controlled. At the time of final laparotomy, the abdomen was closed over drains. No patient in this series was treated by laparostomy or open abdominal packing. Postoperatively, all patients were managed on the surgical service by attending surgeons and house staff; return to the operating room was dictated by the clinical course.

Patients were divided into two groups: group I—patients treated between July 1, 1993 and December 31, 2001 after the introduction of routine prophylactic antibiotic use in patients with SAP at our institution, and group II—patients treated between January 1, 2002 and February 2005 when IAP guidelines for intervention were adopted. Multiple clinical variables were abstracted from the medical record and copied into a secure clinical database. These included admission APACHE II score, age, sex, etiology, length of hospital stay, ICU stay, time from onset of pancreatitis attack to surgery, number of reoperations, complications, hospital morbidity and mortality, and bacteriology. For patients transferred to our facility, if outside records were unattainable, lab values and vital signs at the time of admission to our institution were used for calculating initial APACHE II scores. If radiologic imaging from the initial episode of SAP was unavailable from an outside institution, the earliest contrast-enhanced CT or magnetic resonance imaging (MRI) done at our institution was used for analysis. All 47 patients in group II had their CT scans graded in a blinded fashion by a dedicated pancreatic radiologist (K.S.) for Balthazar scoring, percent PN, and the presence or absence of a disconnected pancreatic segment.[3,13]

SAS version 9.0 (SAS Institute, Cary, NC) was used to perform all the statistical analysis. Pearson chi-square or Fisher's exact test was used as appropriate to compare categorical variables; Student's *t* test or Wilcoxon rank-sum test were used to compare the mean or median values of parametric data. A two-sided *p* value of less than 0.05 was considered significant.

Results

Over a 12-year period (July 1993–February 2005), 102 consecutive patients with PN confirmed by contrast-enhanced CT or MRI underwent operation at our institution. There were 59 men and 43 women with a mean age of 53±16 years. The patients were divided into two time periods of treatment: group I—treated from 1993–2001 (*N*=55) and group II—treated from 2002–2005 (*N*=47). Groups I and II patients

Table 2 Patient Demographics, Etiology of Pancreatitis, and Initial Clinical Characteristics of 102 Patients Undergoing Debridement for PN

	Group I 1993–2001 (*N*=59)	Group II 2002–2005 (*N*=43)	*p* Value
Age (year±SD)	53±16	54±16	0.76
Male gender (%)	31 (56)	28 (60)	0.74
Etiology of Pancreatitis			0.84
Biliary (%)	24 (44)	23 (49)	
Idiopathic (%)	16 (29)	14 (30)	
Alcohol (%)	10 (18)	5 (11)	
Hypertriglyceridemia (%)	3 (5)	2 (4)	
Post-ERCP (%)	2 (4)	3 (6)	
APACHE II scores (mean±SD)	11.5±7	9.8±6	0.20
APACHE II scores (range)	4–26	2–32	
Balthazar CT classification			<0.0001
B/C/D	35 (63%)	11 (23%)	
E	20 (37%)	36 (77%)	

ERCP=endoscopic retrograde cholangiopancreatography

Table 3 Indications for Debridement, Time to Debridement, Reoperation Rate, Morbidity, Mortality, and ICU and Hospital Length of Stays

	Group I 1993–2001 (N=59)	Group II 2002–2005 (N=43)	p Value
Indications for debridement			0.79
Infected necrosis (%)	42 (76)	34 (72)	
Symptomatic sterile necrosis (%)	11 (20)	12 (26)	
Progressive organ failure (%)	2 (4)	1 (2)	
Time to initial debridement (days±SD)	46±46	44±40	0.82
Reoperation rate (%)	37 (67)	32 (68)	0.93
Morbidity rate (%)	49 (89)	34 (72)	0.03
Pancreatic fistula rate (%)	27 (49)	28 (60)	0.29
Intensive care unit length of stay (days±SD)	13±25	9±13	0.33
Hospital length of stay (days±SD)	38±33	26±23	0.04
Mortality rate (%)	10 (18)	2 (4)	0.03

had similar ages, gender, and etiology of pancreatitis (Table 2). The primary etiology was biliary in both groups (46%), followed by idiopathic (29%), then alcohol (15%). On admission, patients had an overall average APACHE II score of 10.4, with means of 11.5 and 9.8 in groups I and II, respectively. Balthazar scoring based on contrast-enhanced CT showed that patients in group II had significantly worse imaging scores ($p<0.0001$) than patients in group I, with the vast majority of patients in group II having Balthazar grade E scans.

Indications for operation were infected necrosis in 75%, symptomatic sterile necrosis in 22%, and for deteriorating clinical course despite maximal medical therapy in only 3% of patients (Table 3). These indications remained consistent and did not differ significantly through both time periods. The time from the initial episode of SAP to surgical debridement averaged just over 6 weeks in both time periods without a significant difference between groups ($p=0.82$).

Infected necrosis was identified at operation in 76 and 72% of patients, respectively, in each time period, with no statistically significant differences in either the types of bacteria or numbers (monomicrobial vs polymicrobial) of organisms cultured (Table 4). In both groups, we identified a preponderance of gram-positive organisms (group I= 55%, group II=52%; $p=0.94$) and equally low incidences of both anaerobic (group I=7%, group II=9%; $p=1.00$) and fungal infections (group I=13%, group II=17%; $p=0.54$). *Staphylococcal* species were the dominant organism cultured in both time periods.

Postoperative morbidity rates were high in both groups (group I=89% vs group II=72%; $p=0.03$), with the major complication being pancreatic fistula, which occurred in 49 and 60% of patients, respectively. Infectious complications occurred in an additional 18 and 12% of patients, most presenting as intraabdominal fluid collections. There were four episodes (group I=2 [4%], group II=2 [4%]) of *early* postoperative bleeding (no pseudoaneurysms), all managed with prompt reoperation. Patients in both groups required almost 2 weeks of postoperative intensive care (ICU) (group I=13±25 days vs group II=9±13 days; $p=0.33$). Whereas the total length of hospital stay was protracted in both groups, group II patients had a statistically significant decrease in postoperative length of stay (group I=38± 33 days vs group II=26±23 days; $p=0.04$). Overall, 10 of 55 patients (18%) died in group I whereas only 2 of 47 patients (4%) died in group II, representing a significant decline in mortality rate ($p=0.03$). Two patients in group I died of postoperative hemorrhage, and eight died of sepsis with progressive multiple organ failure. Both patients in group II died of sepsis and multiple organ failure.

Table 4 Bacteriology of PN in 102 Patients who Underwent Debridement

	Group I 1993–2001 (N=59)	Group II 2002–2005 (N=43)	p Value
Sterile necrosis (%)	13 (23)	13 (28)	0.64
Infected necrosis (%)	42 (77)	34 (72)	
Monomicrobial (%)	19 (45)	20 (59)	0.24
Polymicrobial (%)	23 (55)	14 (41)	
Gram-positive organisms (%)	30 (55)	26 (55)	0.94
Staphylococcal species (%)	15 (27)	14 (30)	0.78
Streptococcal species (%)	11 (20)	9 (19)	0.91
Gram-negative organisms (%)	15 (27)	10 (21)	0.48
Anaerobic organisms (%)	4 (7)	4 (9)	1.00
Fungus (%)	7 (13)	8 (17)	0.54

Discussion

Severe acute pancreatitis was recognized to evolve over a period of time, involving two rather distinct phases.[14] During the initial phase (0–14 days), release of proinflammatory mediators causes a systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS).[15,16] The secondary phase (days–weeks) is characterized by one of three clinical courses: (1) resolution of inflammation with compartmentalization and organization of necrosis[17]; (2) secondary infection in pancreatic or peripancreatic necrosis accompanied by a late deterioration of organ function or generalized systemic illness (fever, tachycardia, and leukocytosis)[18,4]; or (3) plateau in clinical course without complete resolution resulting in persistent unwellness.[11]

Surgical intervention during the initial phases of this illness was shown in prospective clinical trials to carry an exceedingly high morbidity and mortality rate,[19] and pancreatic resection has no effect on shock, respiratory, or renal failure.[20] Early mortality (<7 days) in patients with SAP is related to MODS, and results predominately from pulmonary complications without an obvious infectious etiology.[16,21] The current concept of managing patients medically through this early SIRS phase before surgical intervention strives for two important goals. First, it provides the opportunity for some patients with PN to resolve their organ dysfunction, compartmentalize and organize their necrosis, and progress to resolution without the need for debridement.[17] Second, it allows time for the acute inflammatory process to subside and the necrotic process to mature, enhancing the demarcation of live from dead tissue, both of which facilitate the technical aspects of surgical debridement.[12] It is unknown how long after the initial episode of SAP one should wait before intervention in patients with symptomatic sterile necrosis, although recent analysis of a large surgical series using sequential group comparison showed no additional outcome advantage to delaying operation past 4 weeks.[22]

Since the introduction of routine prophylactic antibiotics in SAP, infection rates in PN declined from historical norms of 50–70% to 12–40% in several recent reports.[23-25] In this series, the incidence of infected necrosis in patients who required operation was 75% despite our routine use of prophylactic antibiotics. Possible explanations for this high incidence of infected necrosis include the fact that 77% of our patients were transferred to our facility after initial treatment at outside hospitals, and 32% of this group had undergone prior attempts at ineffective percutaneous drainage, an intervention known to cause secondary infection of PN.[5] In addition, the rate of infection in PN increases over time, progressing from 24% after the first week to 71% by the third week after SAP.[18] Whereas antibiotics have decreased the overall infection rates, their effect on this time-dependent infection risk is unknown. Our mean time to debridement in both groups was 46 and 44 days, respectively. This delay may have contributed to the high rate of infected necrosis in our series. Fine needle aspiration biopsy (FNAB) to define the bacteriologic status of necrosis was used in combination with a patient's clinical course, organ dysfunction, and CT imaging to guide therapeutic decision making and the need for surgical intervention. Infected necrosis was not used as our sole indication for surgical intervention in patients with PN.[23] Approximately one quarter of the patients in both periods underwent debridement for symptomatic sterile necrosis, a percentage similar to that reported in other series.[22,26] Debridement in sterile necrosis was only done in symptomatic patients, and only after at least 4 weeks of medical treatment. The mortality rate for patients with sterile necrosis was consistently low, averaging only 2% in both time periods analyzed.

Our overall mortality rate in this complex group of patients decreased from 18% in group I after the introduction of routine prophylactic antibiotics to only 4% in group II after the routine use of evidence-based guidelines for intervention from the IAP.[5] Multiple factors undoubtedly contributed to this decline in mortality rate. Some of the more conspicuous include delayed surgical intervention,[5,14,17,26,27] aggressive debridement for infected necrosis,[4,5,14,22,23,26] and centralization of surgical management.[5,14] Whereas the use of broad-spectrum prophylactic antibiotics in SAP remains a topic of considerable controversy and debate, they were used routinely at our institution during the years involved in this study (1993–2005) and are a component of the IAP guidelines for the surgical management of acute pancreatitis.[5] The potential exists that these data are unrelated to treatment changes and simply reflect a selection during the group II period where application of the IAP guidelines resulted in healthier patients undergoing pancreatic debride-

Table 5 Infected Necrosis Versus Sterile Necrosis

	Infected Necrosis (N=66)	Sterile Necrosis (N=23)	p Value
Age (years±SD)	54±16	49±15	0.25
Sex (% male)	42 (64)	11 (48)	0.18
Admission APACHE II score (median)	9	9	0.17
Balthazar score			0.44
B/C/D (%)	23 (40)	6 (26)	
E (%)	43 (60)	17 (74)	
Reoperation rate (%)	22 (33)	7 (30)	0.80
Morbidity (%)	57 (86)	18 (78)	0.36
Mortality (%)	10 (15)	2 (9)	0.72

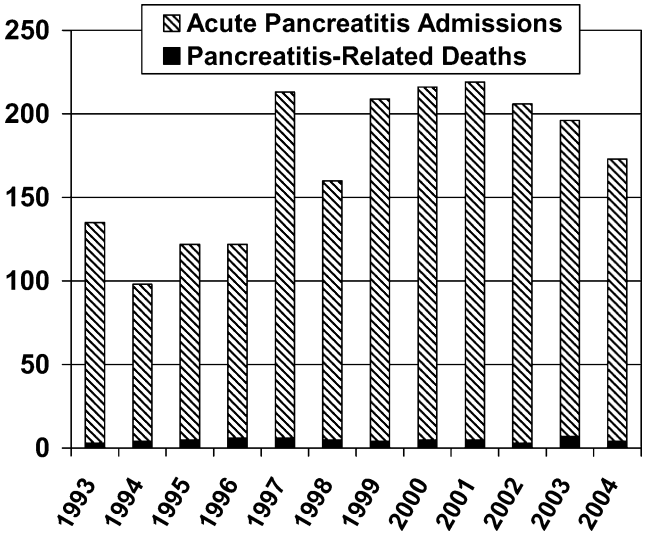

Figure 1 Statistics on the total number of hospital admissions to our hospital for acute pancreatitis and total number of pancreatitis-related deaths during the time period (1993–2004) covered by this study.

ment. The database query used in this study identified only patients who had debridement for PN and did not capture either patients with PN who died without operation or patients who were managed entirely medically and recovered without needing operative intervention. Both data sets are unavailable but would be essential to adequately address this issue of selection bias.

The bacteriology of secondary pancreatic infection in this series closely resembles that of our previous report,[6] which mirrors that of other groups[22,23] who use prophylactic antibiotics, showing a predominance of gram-positive organisms. We found no differences in mortality rate related to the type of bacteria cultured or whether fungus was identified in the necrosis (data not shown). Whereas secondary infection in PN is postulated to account for the majority of organ failure and death in some clinical series,[4,18,23] we found no association between the incidence of infected necrosis and the admission APACHE II score, postoperative morbidity rate, reoperation rate, length of ICU stay, length of hospital stay, or mortality rate (Table 5). Similar observations were made in other recent surgical series,[22,26] suggesting a complex relationship between necrosis, infection, organ failure, time to intervention, and mortality.[28] In all of the experiences where infected necrosis was found not to be associated with postoperative mortality, the time to surgical intervention was at least 3 weeks after the initial episode of SAP. This presumably allows time for the initial organ failure to stabilize or resolve and perhaps, just as importantly, allows time for the necrosis to mature before operative debridement.

Reoperation rates (67% in group I and 68% in group II patients) in our series are higher than the reported 25–49% in other surgical series,[12,22–24,26] but our data includes *all* subsequent reoperations including: tracheostomy for pulmonary insufficiency (N=8), elective ventral hernia repairs (N=10), fistula takedowns (N=8), and pancreatic pseudocyst drainage (n=6), which accounted for 46% of reoperations carried out on these patients. Of the remaining reoperations, 36% (N=25) were done to maintain adequate external control of a postoperative pancreatic fistula. In our experience, loss of control of a pancreatic fistula early in the postoperative period before a fistulous tract is established is the most common cause of recurrent intraabdominal sepsis and late postoperative organ failure particularly in patients with an adequate mechanical debridement. If we are unable to regain adequate fistula control via CT-guided percutaneous drainage (as evidenced by an improving clinical course), patients underwent reoperation and surgical drainage. We believe that this aggressive surgical posture has had a substantial impact on our decreasing mortality rate. Figure 1 shows the total hospital admissions (boxes) at our institution for patients with the diagnosis of acute pancreatitis (ICD-9=577.0) per year over the 12-year course of this study. The in-hospital mortality rate (black boxes) for acute pancreatitis is also shown. The overall mortality rate for all patients with the admission diagnosis of acute pancreatitis to our facility is low (from 1–5% per year), and these numbers have remained relatively consistent throughout the 12-year period of observation. Forty-one deaths occurred in 1,588 patients (2.6%) during the group I period, and 15 deaths occurred in 585 patients (2.6%) during the group II period. The majority of these deaths were from MODS early (<7 days after onset of SAP) and from sepsis and MODS later in the clinical course (>7 days after onset of SAP). Patients requiring surgical intervention had an incidence of death of 24% (10/41) in the group I period, but only 13% (2/15) in the group II period. These data reinforce the fact that SAP has an early mortality rate within the first week of hospitalization that is independent of surgical intervention.[16] Delayed surgical intervention in PN does not impact these early SIRS-mediated deaths, but attempts to improve the late mortality rate, which is commonly related to secondary bacterial or fungal infection of PN.

Conclusion

Current methods of surgical management utilizing IAP guidelines have resulted in a decreased operative morbidity, mortality, and hospital length of stay in patients with PN at our institution.

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References

1. Bradley, E. L. III (1990). A clinically based classification system for acute pancreatitis. *Archives of Surgery, 174*, 331–336.
2. Klar, E., Endrich, B., & Messmer, K. (1990). Microcirculation of the pancreas. A quantitative study of physiology and changes in pancreatitis. *International Journal of Microcirculation, Clinical and Experimental, 9*, 85–101.
3. Balthazar, E. J. (2002). Acute pancreatitis: Assessment of severity with clinical and CT evaluation. *Radiology, 223*, 603–613.
4. Isenmann, R., Rau, B., & Beger, H. (1999). Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. *British Journal of Surgery, 86*, 1020–1024.
5. Uhl, W., Warshaw, A., Imrie, C., Bassi, C., McKay, C. J., Lankisch, et al. (2002). IAP guidelines for the surgical management of acute pancreatitis. *Pancreatology, 2*, 565–573.
6. Howard, T. J., & Tempel, M. B. (2002). Prophylactic antibiotics alter the bacteriology of pancreatic necrosis in severe acute pancreatitis. *Journal of the American College of Surgeon, 195*, 759–776.
7. Howard, T. J., Wiebke, E. A., Mogavero, G., Kopecky, K., Baer, J. C., Sherman, S., et al. (1995). Classification and treatment of local septic complications in acute pancreatitis. *American Journal of Surgery, 170*, 44–50.
8. Larvin, M., & McMahon, M. J.(1989). APACHE-II score for assessment and monitoring of acute pancreatitis. *Lancet, 2*, 201–204.
9. Büchler, M., Malfertheiner, P., Friess, H., Isenmann, R., Vanek, E., Grimm, H., et al. (1992). Human pancreatic tissue concentration of bactericidal antibiotics. *Gastroenterology, 103*, 1902–1908.
10. Gerzof, S. G., Banks, P. A., Robbins, A. H., Johnson, W. C., Spechler, S. J., Wetzner, S. M., et al. (1987). Early diagnosis of pancreatic infection by computed tomography-guided aspiration. *Gastroenterology, 93*, 1315–1320.
11. Rattner, D. W., Legermate, D. A., Lee, M. J., Mueller, P. R., Warshaw, A. L. (1992). Early surgical débridement of symptomatic pancreatic necrosis is beneficial irrespective of infection. *American Journal Surgery, 163*, 105–110.
12. Howard, J. M. (1989). Delayed débridement and external drainage of massive pancreatic or peripancreatic necrosis. *Surgery, Gynecology & Obstetrics, 168*, 25–29.
13. Tann, M., Maglinte, D., Howard, T. J., Sherman, S., Fogel, E., Madura, J. A., et al. (2003). Disconnected duct syndrome (DPDS): Imaging findings and therapeutic implications in twenty-six surgically corrected patients. *Journal of the Centre for Advanced Television Studies, 27*, 577–582.
14. Werner, J., Feurerbach, S., Uhl, W., & Büchler, M. W. (2005). Management of acute pancreatitis: From surgery to interventional intensive care. *Gut, 54*, 426–436.
15. Werner, J., Z'Graggen, K., Fernandez-del Castillo, C., Lewandrowski, K. B., Compton, C. C., & Warshaw, A. L. (1999). Specific therapy of local and systemic complications of acute pancreatitis with monoclonal antibodies against ICAM-1. *Annals of Surgery, 229*, 834–840.
16. McKay, C. J., & Imrie, C. W. (2004). The continuing challenge of early mortality in acute pancreatitis. *British Journal of Surgery, 91*, 1243–1244.
17. Bradley, E. L., & Allen, K. (1991). A prospective longitudinal study of observation versus surgical intervention in the management of necrotizing pancreatitis. *American Journal Surgery, 161*, 19–24.
18. Beger, H. G., Bittner, R., Block, S., & Buchler, M. (1986). Bacterial contamination of pancreatic necrosis—a prospective clinical study. *Gastroenterology, 91*, 433–441.
19. Mier, J., Luque-de Leon, E., Castillo, A., Robledo, F., & Blanco, R. (1997). Early versus late necrosectomy in severe necrotizing pancreatitis. *American Journal Surgery, 173*, 71–75.
20. Teerenhovi, O., Norback, I., & Isolauri, J. (1988). Influence of pancreatic resection on systemic complications in acute necrotizing pancreatitis. *British Journal Surgery, 75*, 793–795.
21. Renner, I. G., Savage, W. T. III, Pantoja, J. L., Renner, V. J. (1985). Death due to acute pancreatitis: A retrospective analysis of 405 autopsy cases. *Digestive Diseases and Sciences, 30*, 1005–1018.
22. Fernández-del-Castillo, C., Rattner, D. W., Makary, M. A., Mostafavi, A., McGrath, D., & Warshaw, A. L. (1998). Débridement and closed packing for the treatment of necrotizing pancreatitis. *Annals of Surgery, 228*, 676–684.
23. Büchler, M. W., Gloor, B., Müller, C. A., Friess, H., Seiler, C. A., & Uhl, W. (2000). Acute necrotizing pancreatitis: Treatment strategy according to the status of infection. *Annals of Surgery, 232*, 619–626.
24. Pederzoli, P., Bassi, C., Vesentini, S., & Campedelli, A. (1993). A randomized multicenter clinical trial of antibiotic prophylaxis of septic complications in acute necrotizing pancreatitis with imipenem. *Surgery, Gynecology & Obstetrics, 176*, 480–483.
25. Ho, H. S., & Frey, C. F. (1993). The role of antibiotic prophylaxis for acute pancreatitis. *Archives of Surgery, 128*, 586–590.
26. Ashley, S. W., Perez, A., Peirce, E. A., Brooks, D. C., Moore, F. D. Jr., Whang, E. E., et al. (2001). Necrotizing pancreatitis: Contemporary analysis of 99 consecutive cases. *Annals of Surgery, 234*, 572–580.
27. Hartwig, W., Maksan, S.-M., Foitzik, T., Schmidt, J., Herfarth, C., & Klar, E. (2002). Reduction in mortality with delayed surgical therapy of severe pancreatitis. *Journal of Gastrointestinal Surgery, 6*, 481–487.
28. Tenner, S., Sica, G., Hughes, M., Noordhoek, E., Feng, S., Zinner, M., et al. (1997). Relationship of necrosis to organ failure in severe acute pancreatitis. *Gastroenterology, 113*, 899–903.

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Improved Outcomes in Postoperative and Pancreatitis-related Visceral Pseudoaneurysms

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Abstract Pseudoaneurysm (PSA) of the visceral arterial tree is an uncommon but highly lethal complication of pancreatic surgery and pancreatitis. Surgical and angiographic interventions are used in treatment; however, optimal therapy remains unclear. We hypothesized that the natural history of PSA is different in these discrete clinical settings. From 1995–2005, 37 patients with PSA were treated: 13 after pancreatic surgery and 24 in the setting of pancreatitis. Postoperative patients most frequently presented with bleeding (92%), either from the gastrointestinal (GI) tract or a surgical drain. In this group, the diagnosis was most commonly made by angiography (77%), and 62% had a pancreatic fistula. In patients with pancreatitis, abdominal pain was the only presenting symptom in 62%, and GI bleeding was present in 29%. Eighty-seven percent had an associated pseudocyst or fluid collection. Interventional radiologic therapy successfully arrested hemorrhage in all 35 patients in whom it was employed. There were four false negative angiograms, and two patients required repeated interventions for rebleeding. The overall mortality was 14%. Pseudoaneurysms present differently in these two clinical settings, but transcatheter intervention is the first treatment of choice in clinically stable patients. Early recognition and prompt angiographic occlusion leads to improved outcomes.

Keywords Pseudoaneurysm · Pancreatitis · Pancreatic surgery · Angiography

Introduction

Pseudoaneurysm (PSA) of the visceral arterial tree may arise both in the postoperative period after pancreatic surgery and in the setting of acute and chronic pancreatitis.[1,2] Although uncommon, massive hemorrhage from PSA has long been recognized as the most rapidly lethal complication in both of these clinical scenarios, with reported mortality rates ranging from 25 to 50%.[1,2] Most reports of PSA consist either of small case series or small subgroups of patients with bleeding complications reported in the context of larger series of pancreatic surgery. The rarity of PSA and heterogeneity of the associated inflammatory states, combined with the frequently urgent nature of its presentation, have made it difficult to define the optimal clinical management.

Recent advances in interventional radiology techniques have led to more widespread application of angiography and embolization for treatment of PSA. (Fig. 1) Although recent small series using transcatheter embolization have demonstrated good outcomes, some authorities continue to advocate surgical intervention.[3,4] Over the past decade at a tertiary pancreatic referral center, we have treated a large number of patients with PSA both after pancreatic surgery and in the setting of pancreatitis, increasingly by utilizing interventional radiology techniques. The purpose of this review was to compare the clinical presentation, diagnosis, and treatment of patients with visceral PSA in these two

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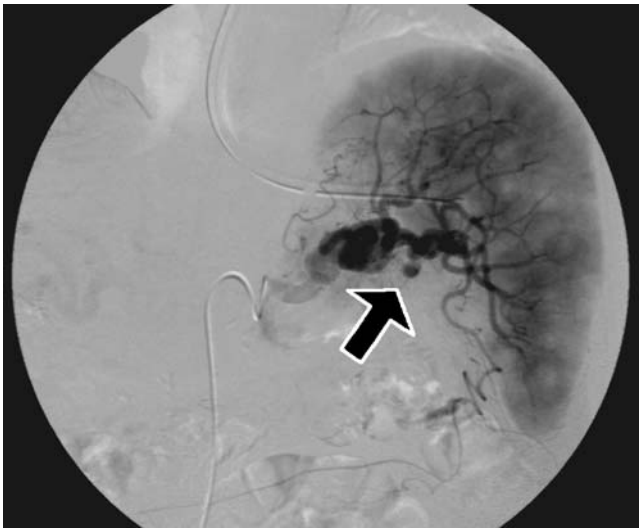

Figure 1 Angiogram demonstrating PSA of the splenic artery (arrow) in a patient with chronic pancreatitis and a pseudocyst. This patient presented with massive GI bleeding, and the initial angiogram failed to identify the PSA.

discrete settings. We hypothesized that the presentation and clinical course may be different in these two groups of patients. In addition, we sought to clarify the role of angiographic intervention in treatment of this potentially devastating condition.

Methods

This retrospective analysis was approved by the Indiana University institutional review board (study number 0405-55). The study time period was 1995–2005. Patients presenting to Indiana University with the diagnosis of PSA of the visceral arterial tree (ICD-9 codes 442.83 and 442.84) were identified from a discharge database and cross-validated against a separate, prospectively collected interventional radiology database (HI-IQ). Clinical factors were abstracted from review of patient charts. SAS version 9.0 (SAS Institute, Cary, NC) was used to perform all the statistical analysis. Pearson chi-square or Fisher's exact test was used as appropriate to compare categorical variables; Wilcoxon rank-sum test was used to compare median values of continuous data. A two-sided P value of less than 0.05 was considered significant.

Results

Thirty-seven patients with PSA were identified, 13 after pancreatic surgery (POSTOP) and 24 with PSA arising in the setting of pancreatitis (PANC). Indications and operations performed on patients in the POSTOP group are shown in Table 1; patient demographics and clinical variables are shown in Table 2. The mean age was younger in the PANC group (46 vs 62, $p<0.01$), and there were similar numbers of male and female patients in each group. Associated inflammatory states identified in both groups of patients were significantly different. In 8 of 13 (62%) patients in the POSTOP group, the clinical course was complicated by a pancreatic fistula, whereas no patient in the PANC group had a fistula. The median time until PSA presentation in the POSTOP group was 22 days (range 2–90 days). In contrast, 22 patients (92%) in the PANC group had recurrent episodes of acute pancreatitis (acute-on-chronic pancreatitis), whereas only two developed PSA during their first bout of pancreatitis. The principal etiology of pancreatitis in the PANC group was alcohol ($n=19$, 79%). Other causes of pancreatitis were pancreas divisum ($n=1$), gallstones ($n=1$), hypertriglyceridemia ($n=1$), post-endoscopic retrograde cholangiopancreatography (post-ERCP) ($n=1$), and idiopathic ($n=1$). Twenty-one patients (87%) had an associated pancreatic pseudocyst or fluid collection.

Clinical Presentation Twelve of 13 (93%) patients in the POSTOP group presented with bleeding—either from the gastrointestinal (GI) tract ($n=7$) or with visible blood in a surgically placed drain ($n=7$, Table 2). One patient had both GI bleeding and blood in the surgical drain, and one patient in this group presented with hypotension alone. In the PANC group, only seven (29%) patients presented with GI bleeding; the vast majority of these patients ($n=15$, 62%) presented with increasing abdominal pain. Two

Table 1 Indications and Operations Performed in Postoperative Group ($n=13$)

Indications and Operations
Diagnosis
Adenocarcinoma of pancreas ($n=3$)
Necrotizing pancreatitis ($n=2$)
Pancreatic fistula after debridement of necrotizing pancreatitis ($n=2$)
Periampullary adenocarcinoma
Cholangiocarcinoma
Renal cell carcinoma metastatic to pancreas
Adenocarcinoma of colon with coloduodenal fistula
Intraductal papillary mucinous neoplasm of pancreas
Chronic pancreatitis
Operation
Pylorus-preserving pancreaticoduodenectomy ($n=6$)
Necrosectomy ($n=2$)
Pancreaticoduodenectomy with portal vein resection
Pancreaticoduodenectomy with total abdominal colectomy
Duodenal-preserving pancreatic head resection
Pancreaticojejunostomy
Distal pancreatectomy/splenectomy

Table 2 Clinical Characteristics of Patients with Visceral Arterial PSA

	Postoperative (n=13)	Pancreatitis (n=24)	P Value
Mean age ± SD (years)	62±15	46±11	0.0007
Female, n (%)	6 (46)	10 (42)	
Male, n (%)	7 (54)	14 (58)	
Inflammatory states, n (%)			
Pancreatic fistula	8 (62)	0	<0.01
Pseudocyst/fluid collection	0	21 (87)	<0.01
Peripancreatic necrosis	0	2 (8)	<0.01
Clinical presentation, n (%)			
GI bleed	7 (54)	7 (29)	0.14
Blood in drain	7 (54)	0	<0.01
Abdominal pain	0	15 (62)	<0.01
Hypotension	1 (7)	2 (8)	1.00
Diagnosis, n (%)			
CT scan	2 (15)	16 (67)	0.005
Angiography	10 (77)	5 (21)	0.002
Operative exploration	1 (7)	0	0.35
Ultrasound	0	2 (8)	0.52
ERCP	0	1 (4)	1.00
Mortality	4 (31)	1 (4)	0.04

patients (8%) in the PANC group presented with hypotension alone.

Diagnosis In the POSTOP group, the first diagnostic test employed was endoscopy in four patients, angiography in four, abdominal computed tomography (CT) in two, operative exploration in two, and percutaneous transhepatic cholangiography in one. In the PANC group, the initial diagnostic test was abdominal CT in 18 and endoscopy in 5. The details of initial work-up before transfer to our hospital were unclear in one patient. In the POSTOP group, PSA was definitively diagnosed by abdominal CT in 2 patients (15%) and by angiography in 10 (77%). One patient in this group underwent emergent operation for refractory hypotension; the diagnosis of PSA was made intraoperatively. In the PANC group, the definitive diagnosis of PSA was made in 16 patients (67%) with abdominal CT scan and by angiography in 5 (21%). Two patients (8%) were diagnosed by ultrasound—one endoscopic and one transabdominal. One patient in the PANC group was diagnosed at the time of ERCP when the PSA was inadvertently lacerated during attempted endoscopic drainage of a pancreatic pseudocyst. The diagnosis of PSA was confirmed by angiography in 36 of 37 patients and by direct visual inspection at the time of operation in one.

Treatment Transcatheter interventional therapy was ultimately successful in controlling hemorrhage in all patients (35/35) in whom it was employed. (Table 3) Thirty-four patients had treatment of the PSA by coil embolization, and one patient's treatment was by exclusion of the PSA with a covered stent. One patient in each group required repeat embolization for recurrent hemorrhage (2 of 35, 6%). Three additional patients in the PANC group underwent repeated angiography without embolization for suspicion of continued hemorrhage. Two patients did not receive transcatheter treatment of PSA: one patient in the POSTOP group underwent immediate operation (without angiography) because of hemodynamic instability, and one patient in the PANC group underwent angiography identifying a PSA without embolization. Initial angiography was falsely negative in 4 of 35 patients (11%), 3 in the POSTOP group and 1 in the PANC group. The arteries involved by PSA are shown in Table 3. Complications of angiographically directed treatment occurred in 6 of 35 patients (17%), and included splenic abscess (n=2), rebleeding (n=2), hepatic abscess, and hemobilia. One patient with splenic abscess was initially treated with percutaneous drainage, however, subsequently underwent splenectomy. No other patient required operative treatment of interventional complications.

Outcomes The mean length of stay after definitive interventional treatment of PSA was 14 days (range 2–57) in the POSTOP group and 17 days (range 2–76) in the PANC group (p=0.79). Four patients in the POSTOP group died (31%), one of uncontrolled hemorrhage and three of sepsis and multiorgan system failure after successful angiographic control of PSA hemorrhage (Table 2). All four patients who died underwent operation: one for hemorrhage, one to

Table 3 Angiographic Data

	Postoperative, n (%)	Pancreatitis, n (%)	P value
Arteries involved, n	13	24	
Gastroduodenal	3 (23)	6 (24)	1.00
Splenic	5 (38)	9 (36)	0.95
Pancreaticoduodenal	1 (8)	5 (20)	0.39
Superior mesenteric branch	0	3 (12)	0.54
Dorsal pancreatic	0	1 (4)	1.00
Hepatic	4 (31)	1 (4)	0.04
Right gastric	0	1 (4)	1.00
Multiple visceral arteries	0	2 (8)	0.53
Angiogram result	12	24	
False negative	3 (25)	1 (4)	0.11
Need for repeat angiogram	4 (33)	4 (17)	0.40
Complication from angiogram	1 (8)	5 (22)	0.64

evacuate intraabdominal hematoma and relieve abdominal compartment syndrome, and two for debridement and control of enteric and pancreatic fistula.

Eight patients in the POSTOP group had pancreatic fistulas. Two of these patients died of multiorgan system failure. Two patients with necrotizing pancreatitis and disconnected pancreatic duct underwent distal pancreatectomy/splenectomy to achieve fistula control. One patient had a fistula after pancreaticoduodenectomy that had closed by the time of presentation with PSA. Three patients had active fistulas at the time of presentation with PSA. All three of these patients manifest their PSA approximately 3 weeks status/postpancreaticoduodenectomy, and all had controlled, low-output fistulas that eventually resolved with conservative management.

In the PANC group, 12 patients underwent surgery directed toward resolving the pancreatic inflammatory process during the same hospital admission as treatment of their PSA. These operations included distal pancreatectomy/splenectomy ($n=7$), pseudocystenterostomy ($n=2$), necrosectomy ($n=2$), and duodenal-preserving pancreatic head resection ($n=1$). Two additional patients in this group underwent operation during the same hospital admission as treatment of their PSA for complications unrelated to the pancreatic process (drainage of intraabdominal abscess and total abdominal colectomy for fulminant *Clostridium difficile* colitis). Ten patients were discharged from the hospital after transcatheter therapy for their PSA without definitive therapy for their pancreatitis-related inflammatory process. One patient died of cerebrovascular accident unrelated to angiography or PSA.

Discussion

This large contemporary review of patients with visceral arterial PSA arising in two discrete clinical situations highlights differences in clinical presentation and diagnosis between the two groups and emphasizes the utility of transcatheter therapy in successful treatment. Patients in the postoperative period more frequently presented with GI bleeding or blood visible in a surgical drain, an uncontrolled situation often associated with hypotension and active blood loss requiring prompt diagnosis and treatment. In contrast, patients with PSA arising in the setting of pancreatitis most commonly presented with increasing abdominal pain caused by bleeding within the confines of a thick-walled pseudocyst cavity, without associated hypotension of active blood loss. Given these differences in clinical presentation, it is not surprising to note that the most common method of diagnosis was by angiography in the POSTOP group and by abdominal CT in the PANC group.

Pseudoaneurysm was frequently associated with pancreatic fistula (62%) in POSTOP patients and with a pseudocyst or acute fluid collection (87%) in the PANC group. Identification of these associated inflammatory conditions in these two discrete clinical settings should alert treating physicians to the potential presence of underlying PSA and may allow early intervention. The most important finding of this study is the 100% success rate of angiographic intervention in controlling PSA hemorrhage. This success should not be considered absolute by any means, given the 11% false negative rate, 6% need for repeat angiographic intervention because of recurrent bleeding, and overall 14% mortality rate in this series. Nonetheless, when compared to the dismal outcomes of patients undergoing emergent attempts at operative control, both in this series and historically, angiographic intervention provides a far more effective treatment modality for PSA in patients who are clinically stable.

The incidence of major arterial hemorrhage in the postoperative setting after pancreatic surgery ranges from 2 to 5%.[5–7] Early postoperative bleeding (less than 24 h) is generally related to intraoperative technical factors, whereas major hemorrhage from PSA usually occurs several weeks postoperatively. The median time to PSA presentation of 22 days in the POSTOP group is in accordance with the median times of 18–27 days reported in the literature.[1,7] The precise incidence of PSA formation in the setting of pancreatitis is more difficult to estimate. Several relatively large series have suggested that this complication may occur in 10–17% of patients, which is perhaps more common than previously appreciated.[7–9] The outcome of patients suffering major hemorrhage in either of these clinical scenarios has historically been dismal. Mortality from postoperative hemorrhage ranges from 18–60%,[1,7,10,11] and mortality from PSA hemorrhage in the setting of pancreatitis is approximately 20%.[2,4,8,12] Notably, these data are from an era when angiographic embolization was infrequently applied, and operation was often the primary therapeutic intervention. The overall mortality of 14% in the current study represents a marked improvement compared to historical data and may be related to our aggressive use of angiography and embolization as primary therapy.

Early recognition of the clinical signs and symptoms associated with PSA allows prompt diagnosis and intervention. Bleeding, either from the GI tract or from surgically placed drains, has long been recognized as a harbinger of PSA in postoperative patients. The fact that 12 of 13 postoperative patients in this series presented with some form of bleeding reinforces this sign. Shankar and Russell[13] initially described the so-called “sentinel bleed,” the finding of a small amounts of blood in an operative drain or a small

hematemesis closely preceding a major hemorrhagic event. Sentinel bleeding has subsequently been reported with relative frequency in the presence of PSA.[1,7] Although the retrospective nature of this review did not allow us to clearly delineate the incidence of sentinel bleed in our POSTOP group, the presence of any form of bleeding in a postoperative patient clearly demands immediate attention and prompt investigation to rule out PSA.

In contrast to the bleeding almost always observed in POSTOP patients, only 29% of patients in the PANC group presented with bleeding, and 62% presented solely with increasing abdominal pain. Our observed frequency of pain as the only presenting symptom is quite similar to that reported in the literature.[4,8] The pain is often described as "crescendo" and different than the "usual" pain of pancreatitis.

The presence of an active inflammatory process in the retroperitoneum logically contributes to the formation of PSA. Sixty-two percent of patients in the POSTOP group had a pancreatic fistula, and 82% of patients in the PANC group had associated pseudocyst or acute fluid collection. Both fistula and pseudocyst/fluid collection were recognized as being frequently associated with PSA formation.[1,2,4,7,8,10] Thus, the presence of pancreatic fistula or pseudocyst should heighten the clinician's awareness to the potential for PSA formation.

Angiography proved the diagnosis of PSA in 77% of POSTOP patients, whereas more patients in the PANC group were diagnosed by abdominal CT. This difference is likely a reflection of the more urgent nature of presentation in POSTOP patients. In a clinically stable patient, it is certainly reasonable to obtain CT or endoscopy as an initial method of diagnosis; however, in the situation with a high degree of suspicion for PSA, angiography offers both diagnostic and therapeutic capability.

Transcatheter embolization has increasingly been used to treat PSA arising both postoperatively and in the setting of pancreatitis.[1,3,12,14,15] The accuracy of angiography in identifying the source of arterial hemorrhage is reported to be 94–100%, and the efficacy of embolization in arresting hemorrhage has ranged from 64–78%.[1,2,12,14] The 100% success in control of hemorrhage in this series highlights improvements in technique and experience and is likely to have significantly contributed to the decreased mortality we observed relative to historical data. The clinician must be aware of the real potential for false negative angiograms, which occurred in 11% of patients in this series and were far more frequent in POSTOP patients. This problem may, in part, be related to vasoconstriction in the setting of acute hemorrhage and highlights the need for meticulous angiographic evaluation particularly in the postoperative setting.

Angiography is an invasive and not completely benign procedure. Complications of angiography generally include bleeding, hematoma, femoral artery PSA, dissection, atheroembolism, thrombosis, contrast reaction, renal failure, and access site infection. Complications of embolization generally include abscess, organ failure, nontarget embolization with ischemia/infarction, procedural failure, and death.[2,14] Complications of angiography and embolization in this series included splenic and hepatic abscess and the need for repeated intervention for rebleeding. Nonetheless, when compared to the high morbidity and mortality associated with primary operative intervention for treatment of PSA, angiography and embolization clearly are the first choice for intervention in patients who are clinically stable.

Once control of bleeding is secured, attention must be directed toward the associated inflammatory condition, i.e., pancreatic fistula in the POSTOP patients and pancreatic pseudocyst in the PANC patients. The formation of PSA is related to the persistent inflammatory process, which weakens the arterial wall. In the setting of POSTOP patients, adequate external control of an associated pancreatic fistula is paramount to prevent episodes of rebleeding, continued intraabdominal sepsis, and death. Adequate control implies effective fistula drainage, which can generally be achieved by percutaneous methods but occasionally requires reoperation.

A more difficult question relates to the best clinical management of patients with pancreatitis and a pancreatic pseudocyst in whom bleeding from the PSA was angiographically controlled. Long-term data regarding the incidence of rebleeding after successful angiographic control are severely lacking. However, even in the short-term, rebleeding was documented to occur in 18 to 37% of patients.[2,12] Twenty-one (87%) patients in the current series developed PSA in the setting of a pseudocyst or acute fluid collection, and an additional two had acute pancreatic necrosis. Thus, a full 96% had an active inflammatory process in the retroperitoneum. Leaving this process in situ may perpetuate irritation of visceral arteries leading to enlargement of existing PSA or new PSA formation. On the other hand, in the setting of chronic pancreatitis, operation directed at the inflammatory focus (resection or drainage) can be problematic. Dense adhesions from repeated bouts of inflammation obliterate normal anatomy. In addition, splenic or portal vein thrombosis with either sinistral or portal hypertension, combined with frequently identified comorbidities such as hepatic cirrhosis and malnutrition, complicate the indications for and timing of definitive surgical treatment.

In this series, 10 patients with PSA arising in the context of pancreatitis were dismissed from the hospital without definitive treatment of their pancreatic disease; 2 underwent operation for a separate abdominal process and 12 underwent operation to address their primary pancreatic inflammatory process. Unfortunately, retrospective comparison of these subgroups of patients offers little guidance in deter-

mining the optimal management of this difficult clinical situation, principally because of unsatisfactory end points. Length-of-stay data are intrinsically biased because of operative intervention. The need for readmission or future operation may occur even after satisfactory treatment of the pseudocyst and simply be related to progression of this complex pathologic process. In addition, the strong possibility of selection bias exists, as common comorbidities such as hepatic cirrhosis may have precluded operation in some. The optimal approach for dealing with this challenging clinical scenario remains unclear at present, and the infrequency of this problem makes it unlikely that prospective evaluation will be undertaken. In the absence of better data, treatment of concomitant pancreatic inflammatory disease (i.e., pseudocyst) in a patient with an adequately treated PSA should be approached on a case-by-case basis. In a physiologically fit patient, we favor an aggressive operative approach to eliminate continuing retroperitoneal inflammation. In patients with multiple confounding medical conditions or ongoing physiologic or nutritional derangement, limited treatment by controlling the PSA would appear to be adequate.

Conclusions

PSA of the major visceral arteries is a potentially lethal condition afflicting patients in the postoperative period after pancreatic surgery and in the setting of pancreatitis. The presence of a postoperative pancreatic fistula or pseudocyst in the setting of pancreatitis is commonly associated with PSA formation and should elevate the clinician's level of suspicion. The occurrence of GI bleeding or blood in surgical drains in the postoperative patient or the acute onset of increasing pain or unexplained hypotension in the patient with pancreatitis should stimulate prompt investigation. Angiography with embolization is the preferred initial therapeutic modality as early angiographic intervention optimizes outcomes. Aggressive control of pancreatic fistulae in the postoperative patients with a PSA is mandatory although the best treatment of pancreatic pseudocysts after angiographic control of PSA is not completely clear; therapy in this setting should be individualized.

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References

1. Sato N, Yamaguchi K, Shimizu S, Morisaki T, Yokohata K, Chijiiwa K, et al. Coil embolization of bleeding visceral pseudoaneurysms following pancreatectomy: the importance of early angiography. Arch Surg 1998;133(10):1099–10102.
2. Balachandra S, Siriwardena AK. Systematic appraisal of the management of the major vascular complications of pancreatitis. Am J Surg 2005;190(3):489–495.
3. Beattie GC, Hardman JG, Redhead D, Siriwardena AK. Evidence for a central role for selective mesenteric angiography in the management of the major vascular complications of pancreatitis. Am J Surg 2003;185(2):96–102.
4. de Perrot M, Berney T, Buhler L, Delgadillo X, Mentha G, Morel P. Management of bleeding pseudoaneurysms in patients with pancreatitis. Br J Surg 1999;86(1):29–32.
5. Sohn TA, Yeo CJ, Cameron JL, Geschwind JF, Mitchell SE, Venbrux AC, et al. Pancreaticoduodenectomy: role of interventional radiologists in managing patients and complications. J Gastrointest Surg 2003;7(2):209–219.
6. Schmidt CM, Powell ES, Yiannoutsos CT, Howard TJ, Wiebke EA, Wiesenauer CA, et al. Pancreaticoduodenectomy: a 20-year experience in 516 patients. Arch Surg 2004;139(7):718–725; discussion 725–727.
7. de Castro SM, Kuhlmann KF, Busch OR, van Delden OM, Lameris JS, van Gulik TM, et al. Delayed massive hemorrhage after pancreatic and biliary surgery: embolization or surgery? Ann Surg 2005;241(1):85–91.
8. Bergert H, Hinterseher I, Kersting S, Leonhardt J, Bloomenthal A, Saeger HD. Management and outcome of hemorrhage due to arterial pseudoaneurysms in pancreatitis. Surgery 2005;137 (3):323–328.
9. Waltman AC, Luers PR, Athanasoulis CA, Warshaw AL. Massive arterial hemorrhage in patients with pancreatitis. Complementary roles of surgery and transcatheter occlusive techniques. Arch Surg 1986;121(4):439–443.
10. Choi SH, Moon HJ, Heo JS, Joh JW, Kim YI. Delayed hemorrhage after pancreaticoduodenectomy. J Am Coll Surg 2004;199(2):186–191.
11. Tien YW, Lee PH, Yang CY, Ho MC, Chiu YF. Risk factors of massive bleeding related to pancreatic leak after pancreaticoduodenectomy. J Am Coll Surg 2005;201(4):554–559.
12. Boudghene F, L'Hermine C, Bigot JM. Arterial complications of pancreatitis: diagnostic and therapeutic aspects in 104 cases. J Vasc Interv Radiol 1993;4(4):551–558.
13. Shankar S, Russell RC. Haemorrhage in pancreatic disease. Br J Surg 1989;76(8):863–866.
14. Gambiez LP, Ernst OJ, Merlier OA, Porte HL, Chambon JP, Quandalle PA. Arterial embolization for bleeding pseudocysts complicating chronic pancreatitis. Arch Surg 1997;132(9):1016–1021.
15. Shibata T, Sagoh T, Ametani F, Maetani Y, Itoh K, Konishi J. Transcatheter microcoil embolotherapy for ruptured pseudoaneurysm following pancreatic and biliary surgery. Cardiovasc Interv Radiol 2002;25(3):180–185.

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Long-term Results After Surgery for Autoimmune Sclerosing Pancreatitis

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Abstract Autoimmune sclerosing pancreatitis (ASP) is a recently recognized cause of chronic pancreatitis. The role of operative intervention in this disease is controversial. A single center experience with 161 consecutive pancreatic resections for chronic pancreatitis was retrospectively reviewed. Operative specimens were reanalyzed and assessed for histological features of ASP. Long-term outcome was assessed by patient survey. Eight patients were identified with histological changes consistent with ASP. The pancreatic anatomic configuration according to intraoperative findings and preoperative radiographic evaluation was categorized into (1) diffusely enlarged pancreas (n=4), (2) localized mass (n=2), or (3) refractory pancreatic duct disruption without pancreatic enlargement (n=2). Five patients underwent pancreaticoduodenectomy and three patients underwent distal pancreatectomy. Perioperative morbidity, operative time, and intraoperative estimated blood loss were similar to the same operation for other etiologies of chronic pancreatitis. Biliary obstruction occurred in two patients. Seven patients were alive 5±0.4 years after operation. Good quality of life measured by the SF-36 questionnaire was present in 4 of 7 patients surveyed. Good pain control was achieved with return to work in 5 of 7 patients. Two patients with poor pain control received glucocorticosteroids therapy without improvement in symptoms. Patients with ASP and a mass suspicious for malignancy or refractory duct disruption require operative intervention. Early postoperative outcome, long-term pain control, and improvement in quality of life appear to be good.

Keywords Chronic pancreatitis · Autoimmune · Pancreaticoduodenectomy · Distal pancreatectomy

Introduction

Autoimmune sclerosing pancreatitis (ASP) is a rare cause of chronic pancreatitis. Treatment is considered medical and predominantly involves the use of corticosteroids. If an adequate diagnosis is made clinically, the success rate with medical therapy is high.[2] Because typical clinical presentation can mimic that of pancreatic neoplasm, a frequent dilemma is making an adequate diagnosis without tissue examination. The role of operative intervention in management of ASP is controversial. Surgical intervention can be beneficial in providing a definite diagnosis with good symptom control and potential resolution of associated biliary strictures.[3,10] The aim of this study was to evaluate the long-term operative outcome for ASP.

Patients and Methods

The histological specimens of 161 consecutive patients who underwent pancreatic resection for chronic pancreatitis at the Department of Surgery, Medical University of South Carolina, from 1995 through 2002, were reanalyzed by a single pathologist. Eight patients were found to have histological changes consistent with ASP. This included

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five patients who underwent pancreaticoduodenectomy and three patients who underwent distal pancreatectomy. Clinical and operative experiences were retrospectively reviewed. The principal indications for operation were suspicion for a malignant pancreatic lesion or pancreatic duct disruption with pseudocyst or disconnected tail. Morbidity and mortality included complications during operation, hospitalization, or within 30 days of discharge after operation. Pancreatic fistula was defined as drainage more than 50 ml/day of amylase-rich fluid after postoperative day 6. Fluid was considered amylase-rich if the amylase level was greater than threefold the normal serum value. Delayed gastric emptying was defined as need for gastric decompression beyond postoperative day 10 or inability to tolerate regular diet after postoperative day 14. A diagnosis of an intraabdominal abscess required a fluid collection on computer tomography and positive cultures from the source. Long-term outcome was assessed by survey applying the SF-36v2 (QualityMetric, Inc., Lincoln, RI) quality of life questionnaire.

Data is reported as percentage or median ± SE unless otherwise specified. The chi-square contingency test and Student's *t* test were used to analyze the data. *P* values <0.05 were considered significant.

Results

Out of eight patients with ASP there were six men and two women with a mean age of 48 years (range 22–73 years). Abdominal pain was the most common symptom present in seven patients followed by jaundice in five patients; four patients had radiographic evidence of terminal biliary stenosis. Three patients were diabetic and two patients had steatorrhea. Nausea, vomiting, and anorexia were infrequent and only one patient was malnourished. Mean onset of symptoms was 3±4.2 months before operation, including two patients with a longstanding history of chronic pain. Associations with other autoimmune diseases were not present. None of the patients were diagnosed with ASP in the preoperative period. None of the patients received preoperative therapy with corticosteroids.

The pancreatic anatomic configuration according to intraoperative findings and preoperative radiographic evaluation utilizing computer tomography and endoscopic ultrasound can be categorized as follows. Four patients had a diffuse pancreatic enlargement with a solid mass in three patients and peripancreatic lymphadenopathy in two. Two patients had a localized mass either within the head or tail. Two patients presented with pancreatic duct disruption without pancreatic enlargement or mass (Table 1). Fine needle aspiration of the pancreas was performed in five patients and revealed benign glandular cells in four and epithelial cells with mucin and macrophages consistent with mucinous cystic neoplasm in one.

Table 1 Pancreatic Anatomic Configuration According to Intraoperative Findings and Preoperative Radiographic Evaluation

Pancreatic Anatomic Configuration
Autoimmune sclerosing pancreatitis with *pan-pancreatic* enlargement
Diffusely enlarged pancreas ("sausage-like pancreas") with mass in head ± lymphadenopathy
Treatment: pancreaticoduodenectomy (4 patients)
Autoimmune sclerosing pancreatitis with *loco-pancreatic* enlargement
Localized mass within head or tail ± duct disruption
Treatment: pancreaticoduodenectomy and distal pancreatectomy (2 patients)
Autoimmune sclerosing pancreatitis *without* pancreatic enlargement
Duct disruption with disconnected tail or refractory pseudocyst
Treatment: Distal pancreatectomy (2 patients)

Perioperative morbidity (pancreaticoduodenectomy: ASP 60% vs others 53%; distal pancreatectomy: ASP 33% vs others 29%; $p>0.05$), operative time (pancreaticoduodenectomy: ASP 402±29 min vs others 271±8 min; distal pancreatectomy: ASP 129±21 min vs others 155±6 min; $p>0.05$), and intraoperative estimated blood loss (pancreaticoduodenectomy: ASP 1,200±267 ml vs others 600±99 ml; distal pancreatectomy: ASP 500±367 ml vs others 1,000±126 ml; $p>0.05$) was not statistically different compared to patients who underwent the same operation for all other causes of chronic pancreatitis. One patient died 2 weeks after an initially uncomplicated course after pancreaticoduodenectomy. The patient had evidence of autoimmune sclerosing pancreatitis at the biliary margin. After hospital discharge the patient was readmitted with biliary sepsis and died because of a cardiac arrest.

Three out of the eight patients were diagnosed with autoimmune sclerosing pancreatitis at initial postoperative histological examination. The other five patients were diagnosed with chronic pancreatitis, which was not further specified and were found to have histological findings of autoimmune sclerosing pancreatitis on reexamination. All eight patients had typical histological findings with dense lymphoplasmacytic infiltration of the pancreas, interstitial fibrosis, periductal inflammation, and periphlebitis.

Seven patients were alive and available for patient survey 5±0.4 years after operation. All seven patients initially presented with pain. At follow-up two patients were pain-free and good pain control was achieved in three patients. All five patients considered their health status as good and returned to work. None of them received corticosteroid therapy. The two patients with poor pain control were started on a corticosteroid trial after identification of the etiology of the disease during this study. After a 2-month trial, both still had poor pain control.

Good quality of life was defined as Physical Component Score or Mental Component Score below 40 percentile on the norm-adjusted SF-36 questionnaire. Four of the seven patients surveyed had good quality of life. The average Physical Component Score was at the 55±5.1 percentile and the average Mental Component Score was at the 54±2.8 percentile. At follow-up the average patients' weight increased by 8.6±2.1 kg. Three patients developed new onset of diabetes mellitus. New onset of steatorrhea occurred in two patients. Recurrence of jaundice because of biliary obstruction occurred in two patients including the one patient who died in the immediate postoperative period. The other patient was diagnosed with primary sclerosing cholangitis 6 months after the operation.

Discussion

Autoimmune sclerosing pancreatitis is an unusual cause of chronic pancreatitis, which differs from other forms of chronic pancreatitis because it may respond to corticosteroid therapy. Nevertheless, a significant number of patients with autoimmune sclerosing pancreatitis receive operative treatment for an inflammatory mass suspicious for neoplasm or for pancreatic duct disruption refractory to endoscopic treatment. Operative long-term results are scarce in the literature.

In our institution 5% of all resections for chronic pancreatitis were performed for autoimmune sclerosing pancreatitis. In this study, pain control correlated with quality of life making pain control the most important end point in treatment of this benign disease. Because of the overall infrequency of autoimmune sclerosing pancreatitis, most studies lack a large cohort of patients. The long-term outcome of medical, interventional, and operative treatment modalities on pain control is unknown. Case series suggest very good success with normalization of radiographic findings, serologic markers, and disease-induced diabetes applying medical therapy alone.[2,4,6] The influence of corticosteroids on pain control however was not demonstrated. Operative treatment in this study showed improvement in 5 out of 7 patients (71%). These results reflect the medium-term pain control after pancreatic resection of 8 out of 9 (89%) and 1 out of 2 (50%) in patients with preoperative abdominal pain reported by others.[3,10] It is also consistent with the long-term pain control of 66 to 89% after pancreatic head resection[1,7,8] and 57 to 81% after distal pancreatectomy[5,9] reported for other etiologies of chronic pancreatitis. Like other reports, we found a relatively high incidence of biliary restenosis. The 29% biliary obstruction rate is similar to the reported 0 to 24% in the literature.[3,10] Overall, these results stress the validity of operative intervention for autoimmune sclerosing pancreatitis in selected cases.

Conclusion

Patients with autoimmune sclerosing pancreatitis and a mass suspicious for malignancy or refractory duct disruption require operative intervention. Perioperative morbidity is similar to patients undergoing pancreatic operations for other etiologies of chronic pancreatitis. Long-term pain control and improvement in quality of life with operative intervention alone appear to be good.

References

1. Beger, H. G., Schlosser, W., Friess, H. M., & Buchler, M. W. (1999). Duodenum-preserving head resection in chronic pancreatitis changes the natural course of the disease: A single-center 26-year experience. *Annals of Surgery, 230*, 512–519.
2. Gelrud, A., & Freedman, S. D. (2005). Autoimmune pancreatitis. *Journal of Gastrointestinal Surgery, 9*, 2–5.
3. Hardacre, J. M., Iacobuzio-Donahue, C. A., Sohn, T. A., Abraham, S. C., Yeo, C. J., Lillemoe, K. D., et al. (2003). Results of pancreaticoduodenectomy for lymphoplasmacytic sclerosing pancreatitis. *Annals of Surgery, 237*, 853–858.
4. Horiuchi, A., Kawa, S., Hamano, H., Hayama, M., Ota, H., & Kiyosawa, K. (2002). ERCP features in 27 patients with autoimmune pancreatitis. *Gastrointestinal Endoscopy, 55*, 494–499.
5. Hutchins, R. R., Hart, R. S., Pacifico, M., Bradley, N. J., & Williamson, R. C. (2002). Long-term results of distal pancreatectomy for chronic pancreatitis in 90 patients. *Annals of Surgery, 236*, 612–618.
6. Kamisawa, T., Yoshiike, M., Egawa, N., Nakajima, H., Tsuruta, K., & Okamoto, A. (2005) Treating patients with autoimmune pancreatitis: Results from a long-term follow-up study. *Pancreatology, 5*, 234–238.
7. Rumstadt, B., Forssmann, K., Singer, M. V., & Trede, M. (1997). The Whipple partial duodenopancreatectomy for the treatment of chronic pancreatitis. *Hepatogastroenterology, 44*, 1554–1559.
8. Sakorafas, G. H., Farnell, M. B., Nagorney, D. M., Sarr, M. G., & Rowland, C. M. (2000) Pancreatoduodenectomy for chronic pancreatitis: Long-term results in 105 patients. *Archives of Surgery, 135*, 517–523.
9. Sakorafas, G. H., Sarr, M. G., Rowland, C. M., & Farnell, M. B. (2001). Postobstructive chronic pancreatitis: Results with distal resection. *Archives of Surgery, 136*, 643–648.
10. Weber, S. M., Cubukcu-Dimopulo, O., Palesty, J. A., Suriawinata, A., Klimstra, D., Brennan, M. F., et al. (2003). Lymphoplasmacytic sclerosing pancreatitis: Inflammatory mimic of pancreatic carcinoma. *Journal of Gastrointestinal Surgery, 7*, 129–139.

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Absorbable Mesh Reinforcement of a Stapled Pancreatic Transection Line Reduces the Leak Rate with Distal Pancreatectomy

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Abstract Pancreatic leak remains a significant cause of morbidity after distal pancreatectomy. We report the use of an absorbable mesh to reinforce a stapled pancreatic transection line for distal pancreatectomy. Forty consecutive distal pancreatectomies (33 open and 7 laparoscopic) were performed since the introduction of mesh reinforcement. We utilized an inclusive definition of pancreatic leak to critically evaluate the staple line reinforcement material. In addition, we compared the pancreatic leak rate for this case series with the antecedent 40 cases where mesh reinforcement was not available. In the prospective series there was 1 leak in 29 cases (3.5%) in which mesh reinforcement was utilized, and 4 leaks in 11 cases (36%) when mesh was not utilized ($p<0.005$). The 12.5% leak rate for the 40 cases during the prospective period, compared favorably to the 27.5% leak rate for the 40 cases preceding the study period ($p=0.09$). Twenty-nine cases receiving mesh compared favorably to the 23 stapled cases in the control series, reducing leak rate from 22 to 3.5% ($p=0.04$). Mesh reinforcement of the stapled pancreatic transection line reduced the pancreatic leak rate after distal pancreatectomy. Mesh reinforcement was possible with open or laparoscopic resections. No complications were attributable to the use of absorbable mesh.

Keywords Distal pancreatectomy · Mesh reinforcement · SeamGuard · Pancreatic leak · Pancreatic fistula

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Introduction

Pancreatic leak after distal pancreatectomy remains a clinically significant problem. Historically, attempts to reduce the fistula rate have met with limited success. To examine this problem, we conducted a prospective non-randomized trial of mesh-reinforced stapled pancreatic transection. For the study period, participating surgeons agreed to utilize a reabsorbable polytrimethylene carbonate mesh to reinforce the stapled pancreatic transection line. To have a uniform test method, we selected a laparoscopic stapler and agreed to use a uniform staple size in combination with the mesh. An identical method was utilized for both the open and the laparoscopic cases. Furthermore, recognizing that there may be situations where the agreed upon approach was not technically possible or appropriate, we sought to elucidate such situations. The management of these situations was left to

the discretion of the treating physician. In this study, we report our experience with mesh-reinforced pancreatic transection in 40 consecutive patients over 14 months. We also describe the situations in which mesh-reinforced stapled transection was not possible. In addition, we compared the 40 cases of the prospective study period with the 40 consecutive cases before our initiation of this technique.

Materials and Methods

A prospective 14-month study (September 23, 2004 to November 22, 2005) was initiated for all distal pancreatectomies performed in the Section of HPB/GI Surgery at Washington University Medical Center/Barnes–Jewish Hospital. During the study period, all distal pancreatectomies suitable for stapling with the 4.8-mm endoscopic linear stapler (US Surgical, Norwalk, CT) had bioabsorbable mesh (SeamGuard, W.L. Gore, Flagstaff, AZ) placed over the stapler before firing (Fig. 1). The operative approach (laparoscopic or open), method of dissection, or diagnosis were not restricted by the study protocol. In Fig. 2, above and left of the surgeon's finger is the cut edge of the proximal pancreas, seen end on end between two layers of mesh. To the lower right is the mesh incorporated into the staple line, at the superior surface of the distal remnant before removal. The primary end point was failure of the occlusion (pancreatic leak) during the initial 60-day postoperative period. Additional information was obtained from the physician and hospital records and supplemented with interview of primary surgeon as needed. At the time of analysis a minimum of 60 days of follow-up was available for all patients. Outcomes analyzed included pancreatic leak rate, morbidity, and length of stay. For the purposes of this particular study, pancreatic leak was defined as any of the following: amylase-rich fluid obtained from the drain at the pancreatic bed at any time, or any intraabdominal fluid collection requiring a drain or antibiotics. This inclusive definition was utilized to capture as many leaks as possible regardless of clinical significance. All patients had drain amylase measured but the days chosen for sampling were left to the individual clinicians. Drain amylase was not sampled before day 4. In addition, the 40 cases during the prospective trial were compared to the 40 consecutive cases performed before the study period. Finally, we analyzed all groups for potential confounding variables, including age, sex, operative surgeon, operative approach, and extensive additional procedures. We define an extensive procedure as a partial or complete resection of a contiguous organ. This included gastrectomy, colectomy, hepatectomy, and nephrectomy. Splenectomy and extended lymphadenectomy were not counted as extensive procedures. Chi-square analyses were utilized for all comparisons. This protocol received the approval of the Washington University School of Medicine Human Studies Committee (WUMC HSC 05-0796).

Results

Prospective Trial of Mesh-Reinforced Stapled Transection of the Pancreas

During the 14-month investigational study, a total of 40 distal pancreatectomies were performed (33 open and 7 laparoscopic). There was 1 leak in 29 cases (3.5%) in which the mesh-reinforced stapled transection was performed and 4 leaks in 11 (36%) cases in which an alternative technique was performed ($p=0.005$). Patient

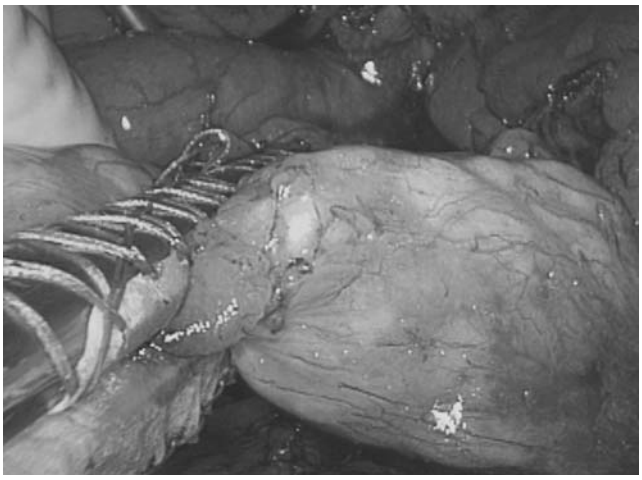

Figure 1 The endoscopic linear stapler is shown with the bioabsorbable SeamGuard mesh (W.L. Gore) over the anvil and jaw, with the distal pancreas ready to be transected.

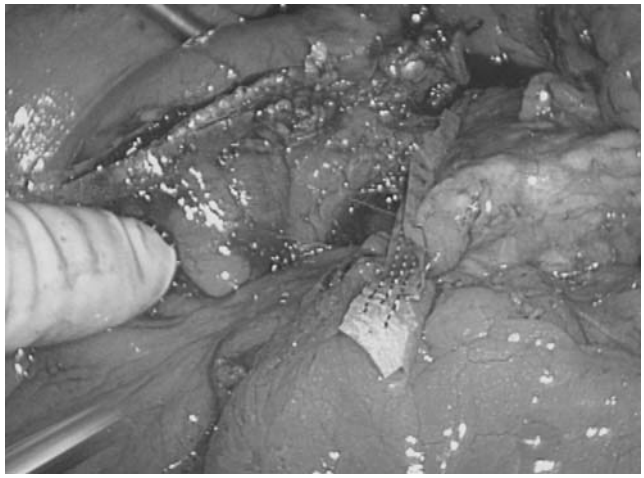

Figure 2 Above and left of the surgeon's finger is the cut edge of the proximal pancreas, seen end on end between two layers of mesh. To the lower right is the mesh incorporated into the staple line, at the superior surface of the distal remnant before removal.

characteristics between groups undergoing mesh-reinforced stapled transection or an alternative closure did not differ (Table 1). Eighty-three percent (n=33) of procedures were performed for neoplasia, including adenocarcinoma, neuroendocrine tumors, and cystic neoplasms: five for benign disease and two for late sequelae of trauma.

In the one instance in which there was a postoperative leak, the mesh-reinforced transection was performed using an open technique after conversion from laparoscopic resection because of venous bleeding. A drain was left and the fistula was noted in the early postoperative course. The fistula completely resolved after 10 weeks and there were no long-term sequelae.

Eleven cases during the investigational period did not receive the mesh-reinforced stapled transection and there were four pancreatic leaks noted in this group (36% leak rate). There were three resections with the protocol stapler but without mesh because of inconsistent availability of the mesh in the initial 3 months of the study period, resulting in one leak (33% leak rate).

In the eight cases during the prospective study when a surgeon chose to deviate from the study protocol, the techniques used for pancreatic transection and closure were handsewn closure (n=5) and an alternate stapler (n=3). In five cases of handsewn reinforcement, two leaks were noted (40% leak rate). In one handsewn case, an extremely friable pancreas was noted with areas of gross necrosis. The surgeon elected no closure other than oversewing of the main pancreatic duct in the face of potential infection. In the other handsewn closure resulting in leak, the surgeon could not apply the 4.8-mm endoscopic linear stapler because of the thickness of the pancreas. In an additional three patients in whom the pancreas was too thick to accommodate the 4.8-mm endoscopic linear stapler and an alternative TA stapler was utilized, there was one leak (leak rate 33%).

Table 1 Patient Characteristics for the Prospective Series

	Mesh-reinforced Stapled Transection (n=29)	Alternative Closure (n=11)
Mean age (year)	59 (34–78)	57 (31–76)
Gender distribution	16 F/13 M	5 F/6 M
Neoplastic lesion (%)	24/29 (83)	10/11 (91)
Laparoscopic approach (%)	6/29 (21)	1/11 (9.1)
Complex/extensive operation (%)	10/29 (34)	6/11 (55)
Postoperative pancreatic leak[a] (%)	1/29 (3.5)	4/11 (36)
Median length of stay (days±SD)	7±6.2	8±2.5
60-Day mortality	0	0

[a] Only use of mesh correlated with pancreatic leak rate (p=0.005)

We analyzed our prospective series for other potentially confounding variables. Development of pancreatic leak did not correlate with preoperative variables, including age of patient, sex of patient, etiology of pancreatic lesion, or clinical presentation. Development of pancreatic leak did not correlate with any intraoperative variable, other than the use of mesh reinforcement. Intraoperative variables analyzed included operative surgeon, operative approach, and extensive surgical procedure at time of distal pancreatectomy. A large proportion of procedures were complex and included resection of adjacent organs, which did not differ between comparison groups. Ten of 29 cases with mesh and 6 of 11 cases without mesh were extensive procedures. Operative approach did not correlate with pancreatic leak rate, with 1 of 6 laparoscopic (16.7%) and 4 of 29 open cases (13.8%) developing postoperative leak.

In summary, pancreatic leak correlated only with use of mesh, with 3.5% of cases with mesh-reinforced stapled transection developing a leak and 36% of cases without mesh reinforcement developing leaks. There were no mortalities during the study period. In this study, pancreatic leak was not associated with an increase in the length of stay. We also did not detect any complications related to utilization of the mesh, and complications other than pancreatic leak did not differ between comparison groups.

Comparison of the Prospective Case Series with a Control Series

We compared the overall leak rate for the 40 cases of the prospective trial (14 months, September 23, 2004 to November 22, 2005), with the 40 consecutive distal pancreatectomies immediately proceeding the study period (20 months, January 14, 2003 to September 22, 2004). The 12.5% overall leak rate for the 40 cases during the prospective period, compared favorably to the 27.5% leak rate for the 40 control cases (p=0.09) (Table 2). In an effort to isolate the effect of the absorbable mesh on leak rate, we performed subset analysis comparing stapled distal pancreatectomies receiving mesh in the prospective series to stapled cases performed during the control series. The 3.5% leak rate (1/29 leaks) for meshed-reinforced cases compared favorably to the 22% leak rate (5/23 leaks) for stapled pancreatectomies in the control series (p=0.04) (Table 2). With the exception of operative surgeon, no preoperative, intraoperative, or postoperative variable differed between the prospective series where mesh-reinforced pancreatic transection was utilized and the control series where mesh was not available. One surgeon left the division and two surgeons were added to the division during the study period. Operative surgeon did not affect leak rate in either

Table 2 Patient Characteristics Comparing the Prospective Series with a Control Series

	Prospective Series (n=40)	Control Series (n=40)	Total Experience (N=80)
Mean age (year)	58 (31–78)	59 (26–87)	58.7 (26–87)
Gender distribution	21 F/19 M	28 F/12 M	49 F/31 M
Neoplastic lesion, n (%)	34/40 (85)	32/40 (80)	66/80 (83)
Laparoscopic approach, n (%)	7/40 (18)	3/40 (7.5)	10/80 (13)
Complex/extensive operation, n (%)	16/40 (40)	12/40 (30)	28/80 (35)
Postoperative pancreatic leak[a], n (%)	5/40 (12.5)	11/40 (27.5)	16/80 (20)
Stapled cases, pancreatic leak, n (%)	3/35 (8.6)	5/23 (22)	8/58 (14)
Stapled cases w/mesh, leak[b], n (%)	1/29 (3.5)	0	1/29 (3.5)
Median length of stay (days±SD)	7±5.5	7±5.0	7±5.3
60-Day mortality	0	0	0

[a] Utilization of mesh reinforcement reduced postoperative leak rate by more than 50% (p=0.09).

[b] Utilization of mesh-reduced leak rate by more than 84% when comparing the subset of cases receiving mesh to stapled cases in the control series (3.5 vs 22% leak rate) (p=0.04).

of the case series, or in an analysis of the entire study period (80 patients).

In summary, there was a 55% reduction in the number of leaks from 27.5 to 12.5% when the prospectively collected series of 40 patients was compared to the control series of 40 patients, with a trend toward statistical significance. When cases reinforced with mesh in the prospective series were compared only to stapled cases from the control series, pancreatic leak rate was reduced by 84%.

Discussion

Distal pancreatectomy is commonly performed for neoplastic and benign lesions located in the body or tail of the pancreas. Distal pancreatectomy may also be performed for the sequelae of pancreatitis or traumatic injury.[1,2] In a prospective series the overall morbidity after distal pancreatectomy was reported to be as high as 47%.[3] Whereas referral centers continue to report a high morbidity for distal pancreatectomy, perioperative mortality has declined over time and is less than 6%.[1,3] Pancreatic leak after a pancreatic resection remains the single most significant technically correctable reason for postoperative morbidity.[4,5] Fortunately, the majority of fistulae that follow a pancreatectomy are self-limited and have few long-term sequela.[1,6–8] On occasion, a pancreatic leak can have more serious consequences. These collections often become secondarily infected and retroperitoneal or intraabdominal abscess formation, wound infection, dehiscence, ascites, and effusions are some of the more common clinical manifestations. In some instances, pancreatic duct leaks or the secondary infections may initiate serious systemic effects and/or clinical sepsis. This in turn may result in systemic inflammatory response syndrome with resulting pulmonary failure, and or renal failure, and occasionally death.[7,9,10]

Definition of pancreatic fistula and severity grading remain controversial. A recent consensus conference classified pancreatic fistula into three categories based on severity.[11] Grade A fistulae are biochemical without sequelae, grade B require therapeutic intervention, and grade C has severe clinical manifestations. In this study, there were no grade C fistulas. The costs associated with caring for patients with grade B and C fistulae are substantial, with grade C resulting in total costs in excess of $100,000.[8,11]

Despite the clinical importance of this problem, only a handful of studies comparing techniques were prospective, or have employed control groups for comparison.[3] These studies vary greatly in their definition of pancreatic leak, patient population, and surgical approach. Thus, the reported rates of pancreatic leak are highly variable.[12] In fact, incident rates range from 0 to as high as 61%.[1,3,7,9,10,13–16]

The use of a stapler may confer a benefit over handsewn methods, but this was not shown conclusively. The only randomized clinical trial of stapling vs hand sewing showed a nonsignificant advantage to stapling (14 vs 33% incidence of fistula).[3,6] A leak rate of 23% for stapled closure after distal pancreatectomy was derived from meta-analysis and is slightly lower than that for handsewn closures.[3] Since this publication, some centers have demonstrated that handsewn closure is at least as good as stapled transection and may even result in lower fistula incidence based on a retrospective review of their experience.[3,6] We commonly, although not exclusively, employ stapling for distal pancreatectomy. We believe stapling is the likely equivalent with regard to preventing pancreatic leaks and offers a significant advantage with regard to operative efficiency.

In our institution, as in other specialized centers, distal pancreatectomy is increasingly being performed laparoscopically.[1,16–18] We perform our laparoscopic transections using an endoscopic linear stapler in almost all instances. With the rapidly increasing number of laparoscopic

resections, we sought an improved method of closure that would not only reduce the leak rate but could be utilized for minimally invasive resections from the outset.

There were many previous single institution attempts to diminish the pancreatic fistula rates, including standardized methods for oversewing the pancreatic remnant, use of various surgical staplers, fibrin glue, handsewn patches, stenting of the pancreatic duct, and ablative dissection techniques to seal small ducts.[1,2,4,5,7,9,10,13–21] Several systemic efforts were made to diminish leak rates in the postoperative period, including the use of octreotide.[22] Even the necessity of drain placement after pancreatic resection was questioned.[23]

To our knowledge, this is the first investigation of mesh reinforcement of stapled closure in pancreatic tissue in humans. A porcine model was used to assess the effect of mesh reinforcement in laparoscopic distal pancreatectomy. In this study, (published only in abstract form) pancreatic fistula, perioperative bleeding, and mortalities were quantitatively reduced (p values not cited) in the mesh-reinforced group.[24] Mesh reinforcement or buttressing of the staple line has demonstrated clinical utility in other organ sites, including gastric resection for prevention of bleeding, leakage, and anastomotic disruption.[25,26] Mesh reinforcement was also reported with pneumonectomy where the primary goal is prevention of air leaks.[27,28] Most recently, the SeamGuard bioabsorbable mesh was used in a series of 30 colorectal cases with hepatic resection without reported complications.[29,30] Because of its ease of use and ready availability, SeamGuard mesh was chosen for reinforcement and incorporation into the stapled pancreatic transection line for this study. This polyglyconate polymer is familiar to most surgeons as surgical suture. The polymer has a random array porous structure, which is composed solely of polyglycolic acid and trimethylene carbonate in a 2:1 ratio. It is thought to maintain its strength for 4–6 weeks, and is completely absorbed by 4–6 months.[31] It may be ideal for the short time period after pancreatic resection, when pancreatic leak or fistulas are likely to develop.

There are two mechanisms by which the mesh reinforcement is thought to benefit the resection line. First, the array of mesh fibers may more evenly distribute tension at the resection margin, limiting ischemia or erosion because of pressure. Second, the material may act as a mechanical barrier to small lacerations and gaps in the staple line, preventing leakage or bleeding.[19,27,28,31] Compared to other reported materials, this absorbable mesh may have the theoretical benefit of decreased antigenicity and dissolution of the material after its period of usefulness. This avoids long-term foreign body complications such as infection, migration, erosion, or hindrance to future resection.[19,25–29]

We compared mesh-reinforced stapling to other closure methods during a prospective series of 40 cases, and to a control series of 40 distal pancreatectomies before our use of mesh reinforcement. For the comparison, we selected an inclusive definition of pancreatic leak. In contrast to other studies, we did not arbitrarily exclude leaks of short duration, or with limited systemic consequence. We think that this definition allowed us to identify the largest number of events (leaks) and thus permitted the best chance to detect a difference between our treatment groups. Similarly, we did not limit the preoperative diagnosis nor exclude cases not amenable to our reinforced stapling technique to prevent us from describing a result that would ultimately prove to be a consequence of patient selection.

During the 14-month investigational study period, there was 1 leak in 29 cases (3.5%) with mesh-reinforced stapling, and 4 leaks in 11 cases (36%) without mesh ($p=0.005$). In interpreting our results, we cannot exclude the possibility that the 36% leak rate (4/11 cases) in cases without mesh reinforcement, selected not only for situations where stapling was not practical, but also for situations with a higher risk for leak. The factors that could either preclude stapling or promote leak included a thick or steep triangular shape to the pancreas, excessively hard pancreatic tissue, and a far right resection.

This caveat may also apply to our subset analysis of stapled pancreatectomies receiving mesh to stapled pancreatectomies in the control series. Whereas the dramatic reduction in leak rate from 22 to 3.5% should be interpreted with caution, this comparison may most accurately isolate the effect of mesh on leak rate by excluding handsewn cases.

In summary, the 12.5% overall leak rate for the 40 cases compares favorably to the 27.5% leak rate in the 40 control cases and to historical controls. The 55% reduction in our leak rate compares favorably to published series of patients where technical methods of fistula reduction were attempted and to the meta-analysis of studies using only stapled closures. Subset analysis comparing only stapled cases demonstrated a reduction in leak rate of 84% for cases receiving mesh per protocol compared to stapled control series cases. To isolate the effect of mesh on pancreatic fistula, we plan a randomized clinical trial of identical methods of stapled closures, differing only in use of mesh.

Conclusions

Use of bioabsorbable mesh to reinforce the staple line for distal pancreatectomy lowered our pancreatic leak rate during the period of mesh implementation, and was not associated with complications. Comparison to a case series immediately before our implementation of this technique demonstrated a 55% reduction in the leak rate, which trended toward significance. Subset analysis comparing only stapled cases receiving mesh during the prospective

series to stapled cases in the control series demonstrated an 84% reduction in pancreatic leak rate.

Cases during the prospective study period that were not resected with mesh-reinforced stapling had a significantly higher pancreatic leak rate. They include cases with a far right dissection, and cases with a markedly thick pancreas, precluding the use of sheathed stapler. These cases are instructive as to situations that preclude reinforced stapling but we cannot exclude that these factors might also promote pancreatic leak.

We conclude that incorporation of mesh into the stapled transection line is safe and holds considerable promise as a method to reduce the pancreatic leak rate after open and laparoscopic distal pancreatectomy. We plan a prospective randomized clinical trial to formally test this methodology.

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References

1. Balcom JH, 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 2001;136(4):391–398.
2. Brennan MF, Moccia RD, Klimstra D. Management of adenocarcinoma of the body and tail of the pancreas. Ann Surg 1996;223 (5):506–511.
3. Knaebel HP, Diener MK, Wente MN, Buchler MW, Seiler CM. Systematic review and meta-analysis of technique for closure of the pancreatic remnant after distal pancreatectomy. Br J Surg 2005;92(5):539–546.
4. Mori T, Abe N, Sugiyama M, Atomi Y. Laparoscopic hepatobiliary and pancreatic surgery: An overview. J Hepatobiliary Pancreat Surg 2002;9(6):710–722.
5. Sperti C, Pasquali C, Liessi G, Pinciroli L, Decet G, Pedrazzoli S. Pancreatic resection for metastatic tumors to the pancreas. J Surg Oncol 2003;83(3):161–166.
6. Bassi C, Butturini G, Molinari E, Mascetta G, Salvia R, Falconi M, Gumbs A, Pederzoli P. Pancreatic fistula rate after pancreatic resection. The importance of definitions. Dig Surg 2004;21 (1):54–59.
7. Fahy BN, Frey CF, Ho HS, Beckett L, Bold RJ. Morbidity, mortality, and technical factors of distal pancreatectomy. Am J Surg 2002;183(3):237–241.
8. Pratt W, Maithel S, Vanounou T, Huang Z, Callery M, Vollmer C. Clinical and economic validation of the International Study Group of Pancreatic Fistula (ISPGF) classification scheme. HPB 2006;8 (Suppl 1):24.
9. Farkas G, Leindler L, Farkas G, Jr. Safe closure technique for distal pancreatic resection. Langenbecks Arch Surg 2005;390 (1):29–31.
10. Fernandez-del Castillo C, Rattner DW, Warshaw AL. Standards for pancreatic resection in the 1990s. Arch Surg 1995;130 (3):295–299.
11. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J. et al. Postoperative pancreatic fistula: An International Study Group (ISGPF) Definition. Surgery 2005;138(1):8–13.
12. Bruce J, Krukowski ZH, Al Khairy G, Russell EM, Park KG. Systematic review of the definition and measurement of anastomotic leak after gastrointestinal surgery. Br J Surg 2001;88 (9):1157–1168.
13. Bilimoria MM, Cormier JN, Mun Y, Lee JE, Evans DB, Pisters PW. Pancreatic leak after left pancreatectomy is reduced following main pancreatic duct ligation. Br J Surg 2003;90 (2):190–196.
14. Lillemoe KD, Kaushal S, Cameron JL, Sohn TA, Pitt HA, Yeo CJ. Distal pancreatectomy: Indications and outcomes in 235 patients. Ann Surg 1999;229(5):693–698.
15. Suzuki Y, Fujino Y, Tanioka Y, Hori Y, Ueda T, Takeyama Y, Tominaga M, Ku Y, Yamamoto YM, Kuroda Y. Randomized clinical trial of ultrasonic dissector or conventional division in distal pancreatectomy for non-fibrotic pancreas. Br J Surg 1999;86(5):608–611.
16. Wagner M, Dikopoulos N, Kulli C, Friess H, Buchler MW. Standard surgical treatment in pancreatic cancer. Ann Oncol 1999;10(Suppl 4):247–251.
17. Lansing PB, Browder IW, Harkness SO, Kitahama A. Staple closure of the pancreas. Am Surg 1983;49(4):214–217.
18. Pachter HL, Pennington R, Chassin J, Spencer F. Simplified distal pancreatectomy with the auto suture stapler: Preliminary clinical observations. Surgery 1979;85(2):166–170.
19. Gyurko G, Czehelnik R. Closure of wounds of the stomach and pancreas with tissue adhesive and autoplastic peritoneum patch: An experimental study. Am Surg 1971;37(12)761–764.
20. Kajiyama Y, Tsurumaru M, Udagawa H, Tsutsumi K, Kinoshita Y, Akiyama H. Quick and simple distal pancreatectomy using the GIA stapler: Report of 35 cases. Br J Surg 1996;83(12):1711.
21. Ohwada S, Ogawa T, Tanahashi Y, Nakamura S, Takeyoshi I, Ohya T, Ikeya T, Kawashima K, Kawashima Y, Morishita Y. Fibrin glue sandwich prevents pancreatic fistula following distal pancreatectomy. World J Surg 1998;22(5):494–498.
22. Yeo CJ, Cameron JL, Lillemoe KD, Sauter PK, Coleman J, Sohn TA, Campbell KA, Choti MA. 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(3):419–429.
23. Conlon KC, Labow D, Leung D, Smith A, Jarnagin W, Coit DG, Merchant N. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. Ann Surg 2001;234(4):487–493.
24. Consten E, Gagner M, Milone L, Bardaro S. Reducing pancreatic duck leak and hemorrhage during laparoscopic distal pancreatectomy and partial splenectomy using staple line reinforcement with an absorbable polymer membrane. HPB 2006;6(Suppl 1):34.
25. Consten EC, Gagner M, Pomp A, Inabnet WB. Decreased bleeding after laparoscopic sleeve gastrectomy with or without duodenal switch for morbid obesity using a stapled buttressed absorbable polymer membrane. Obes Surg 2004;14(10):1360–1366.
26. De la Torre RA, Scott JS. Laparoscopic Roux-en-Y gastric bypass: A totally intra-abdominal approach—technique and preliminary report. Obes Surg 1999;9(5):492–498.
27. Roberson LD, Netherland DE, Dhillon R, Heath BJ. Air leaks after surgical stapling in lung resection: A comparison between stapling alone and stapling with staple-line reinforcement materials in a canine model. J Thorac Cardiovasc Surg 1998;116 (2):353–354.
28. Vaughn CC, Wolner E, Dahan M, Grunenwald D, Vaughn CC, III, Klepetko W, Klepetko W, Filaire M, Vaughn PL, Baratz RA. Prevention of air leaks after pulmonary wedge resection. Ann Thorac Surg 1997;63(3):864–866.

29. Consten EC, Gagner M. Perioperative outcome of laparoscopic left lateral liver resection is improved by using staple line reinforcement technique: A case report. J Gastrointest Gurg 2005;9(3):360–364.
30. Franklin ME, Jr, Berghoff KE, Arellano PP, Trevino JM, Abrego-Medina D. Safety and efficacy of the use of bioabsorbable SeamGuard in colorectal surgery at the Texas Endosurgery Institute. Surg Laparosc Endosc Percutan Tech 2005;15 (1):9–13.
31. Katz AR, Mukherjee DP, Kaganov AL, Gordon S. A new synthetic monofilament absorbable suture made from polytrimethylene carbonate. Surg Gynecol Obstet 1985;161(3):213–222.

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Resection of Hepatic Colorectal Metastases Involving the Caudate Lobe: Perioperative Outcome and Survival

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Abstract
Purpose: To examine clinical features and outcome of patients who underwent hepatic resection for colorectal liver metastases (LM) involving the caudate lobe.
Patients and Methods: Consecutive patients who underwent hepatic resection for LM from May 1990 to September 2004 were analyzed from a multicenter database. Demographics, operative data, pathologic margin status, recurrence, and survival were analyzed.
Results: Of 580 patients, 40 (7%) had LM involving the caudate. Six had isolated caudate LM and 34 had LM involving the caudate plus one or more other hepatic segments. Patients with caudate LM were more likely to have synchronous primary colorectal cancer (63% vs. 36%; $P=0.01$), multiple LM (70% vs. 51%; $P=0.02$) and required extended hepatic resection more often than patients with non-caudate LM (60% vs. 18%; $P<0.001$). Only four patients with caudate LM underwent a vascular resection; three at first operation, one after recurrence of a resected caudate tumor. All had primary repair (vena cava, $n=3$; portal vein, $n=1$). Perioperative complications (43% vs. 28%) and 60-day operative mortality (0% vs. 1%) were similar (caudate vs. non-caudate LM, both $P>0.05$). Pathological margins were positive in 15 (38%) patients with caudate LM and in 43 (8%) with non-caudate LM ($P<0.001$). At a median follow-up of 40 months, 25 (64%) patients with caudate LM recurred compared with 219 (40%) patients with non-caudate LM ($P=0.01$). Patients with caudate LM were more likely to have intrahepatic disease as a component of recurrence (caudate: 51% vs. non-caudate: 25%; $P=0.001$). No patient recurred on the vena cava or portal vein. Patients with caudate LM had shorter 5-year disease-free and overall survival than patients with non-caudate LM (disease-free: 24% vs. 44%; $P=0.02$; overall: 41% vs. 58%; $P=0.02$).
Conclusions: Patients who undergo hepatic resection for caudate LM often present with multiple hepatic tumors and tumors in proximity to the major hepatic veins. Extended hepatectomy is required in the majority, although vascular resection is not frequently necessary; when performed, primary repair is usually possible. Despite resection in this population of patients with multiple and bilateral tumors, and despite close-margin and positive-margin resection in a significant proportion, recurrence on the portal vein or vena cava was not observed, and long-term survival is accomplished (41% 5-year overall survival).

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Introduction

Despite the steady expansion of indications for resection of colorectal liver metastases (LM), such as in patients with extensive disease, including large and bilateral tumors,[1] 5-year survival after hepatic resection has improved to 58%.[2–5] Survival following hepatic resection in patients

with solitary colorectal LM is even more impressive—5-year overall and disease-free survival reported to be 72% and 50%, respectively.[6] Such improvements are likely the result of many factors, including better staging, systemic chemotherapy, patient selection, and resection techniques.[1]

Caudate tumors frequently lie in contact with the inferior vena cava (IVC), major hepatic veins or the portal venous bifurcation. Clearer understanding of the relevant surgical anatomy of the caudate lobe[7–9] and progressive improvement in surgical technique have contributed to advancing efforts to safely resect isolated caudate tumors and tumors involving the caudate liver.[10–13] Variable definitions of the "caudate" in series reporting on caudate LM and series focused on resection of other tumor types make analysis of the existing data on resection of caudate LM difficult. Realization that the width of the negative hepatic transection margin does not impact recurrence and survival has led to more aggressive surgical approaches to extirpating hepatic metastatic disease, including tumors in difficult anatomic locations. This study was designed to examine the clinical characteristics, recurrence patterns, and outcome for resection of colorectal LM involving the caudate liver.

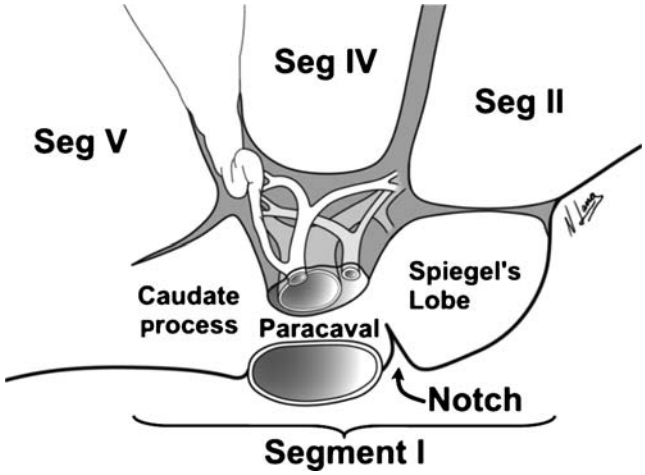

Figure 1 En-face anatomy of the caudate lobe. The *en-face* view of the caudate emphasizes the external anatomy of the lobe. A significant proportion of patients have an external "notch" described by Kogure et al.,[8] which defines the internal subsegmental plane between the Spiegel lobe and the paracaval portion of the caudate lobe. This view emphasizes the intimate contact of the paracaval portion with the vena cava, just behind the hilum, and shows the lack of a defined border between the right and often the anterior border of the caudate process and the main right liver. Seg=segment. Reprinted from: Abdalla EK, Vauthey JN, Couinaud C. The caudate lobe of the liver: implications of embryology and anatomy for surgery. Surg Oncol Clin N Am 2002;11:835–848, with permission from the Society for Surgery of the Alimentary Tract.

Patients and Methods

A retrospective review of patients who underwent hepatic surgery for colorectal liver metastases with curative intent at the University of Texas M. D. Anderson Cancer Center, Institute of Research and Cure of Cancer, Candiolo, Italy, and the University Hospital, Geneva, Switzerland between May 1990 and September 2004 was undertaken. Patients were identified from the prospective database of each institution, which records tumor location including segment I. Patients were divided into two groups: those with tumors involving the caudate liver (caudate LM group, 40 patients) and those without caudate involvement (non-caudate LM group, 540 patients). Caudate anatomy was defined as previously described[9] and lesion location reported according to the position within the caudate liver (caudate process, paracaval caudate, or Spiegel lobe) (Fig. 1).

Analysis focused on the group with caudate LM. Data were reviewed on all patients including demographics, details of the resection, characteristics of resected tumors, and pathologic margin status. Patterns of recurrence and survival were analyzed. Outcomes for patients with caudate LM and non-caudate LM were compared.

Preoperative imaging included chest radiograph or chest computed tomography when indicated, as well as abdominopelvic imaging with computed tomography or magnetic resonance imaging in all patients. Clinical criteria such as tumor number, tumor size, preoperative CEA, or primary tumor characteristics were not used to select patients for hepatic resection; rather, the anticipated ability to achieve a complete resection of all tumor-bearing liver leaving an adequate liver remnant (approximately 20% of the standardized total liver volume)[14] was used to define resectability. CT volumetry, using our previously described technique, was performed in patients selected for an extended right hepatectomy or in those for whom the future liver remnant was deemed small, according to the attending surgeons' judgment.[14,15] Patients with encasement of hepatic veins and significant abutment of the IVC were included (Fig. 2). No patient studied underwent prior surgical treatment for LM (hepatic resection or tumor ablation).

All patients were treated at open laparotomy. Intraoperative ultrasound was used to determine the presence of additional lesions not visualized on preoperative imaging studies, to determine the tumor association with intrahepatic vascular structures and to determine the appropriate parenchymal transection plane in all patients. Positive margins were defined as previously described[5] to include patients with pathologic evidence of tumor at the inked parenchymal transection margin and those with tumor <1 mm of the inked margin. Hepatic resections were defined as hemihepatectomy, extended hepatectomy, segmentectomy, and wedge resections according to the Brisbane terminology.[16,17] All patients had pathologic confirmation of colorectal liver metastasis.

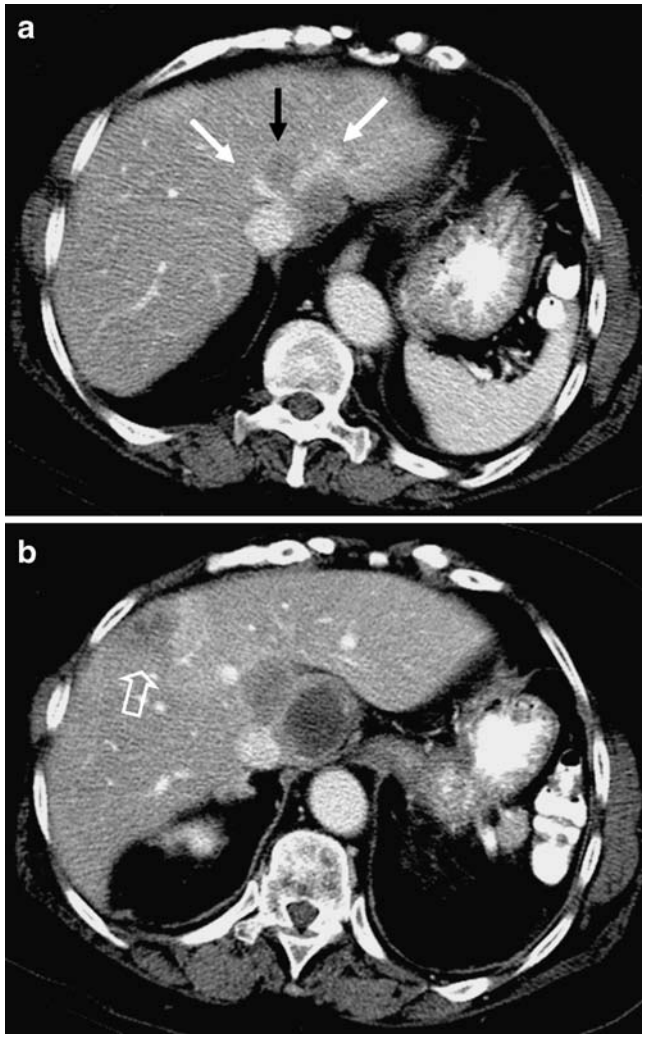

Figure 2 Patient with caudate liver metastasis. A: The upper panel demonstrates the caudate tumor (black arrow), which occupies the entire Spiegel lobe and much of the paracaval portion, encasing the left and abutting the middle hepatic veins (white arrows) and abutting the vena cava. B: The lower panel demonstrates a second metastasis in segment V anteriorly (open arrow). This patient underwent an extended left hepatectomy with en bloc caudate lobectomy (resection of segments I–V and VIII) without vascular resection.

Summary statistics were obtained using established methods. Survival was estimated using Kaplan–Meier analysis; differences in survival were analyzed using the log-rank test. Differences in tumor recurrence rates between groups were analyzed using the Fischer's exact and two-sided Chi-square tests. Differences were considered to be statistically significant when the P value was <0.05.

Results

A total of 580 patients were studied. Forty (7%) with caudate liver metastases comprised the primary study group: there were 17 male and 23 female with a median age of 61 years (range 33–76). Most (63%) of patients with caudate LM presented with synchronous LM (defined as LM diagnosed within 1 year of diagnosis of primary colorectal tumor), 70% presented with multiple hepatic tumors (median number of tumors 2, range 1–16), and 35% presented with disease considered initially unresectable, thus received downsizing chemotherapy before hepatic resection. All patients who received downsizing chemotherapy were treated with fluoropyrimidine-based regimens (except one who received gemcitabine). Two patients received fluorouracil (FU) alone, whereas a total of 11 patients received oxaliplatin (six oxaliplatin plus FU, two oxaliplatin and irinotecan plus FU, and three oxaliplatin plus bevacizumab). Liver surgery was performed as soon as tumor downsizing was sufficient to permit complete resection. Median preoperative CEA was 16 ng/mL (range 1.2–1060). Pathologic analysis of the resected specimen revealed the median size of the resected largest tumor to be 4.0 cm (range 0.8–17). Four patients with caudate LM underwent preoperative portal vein embolization.

Patients who presented with initially unresectable disease (14 patients) were so designated because of extensive metastatic disease in the liver (11 patients) such that complete resection preserving an adequate liver remnant was not possible. Three additional patients were deemed unresectable at presentation because of unresectable extrahepatic disease.

Six (15%) patients had tumors confined to the caudate, whereas 34 (85%) had tumors involving the caudate liver and at least one other Couinaud segment either contiguously or by other tumors elsewhere in the liver. Caudate tumor locations were confined to the caudate process in six, involving both the caudate process and paracaval caudate in one, confined to the paracaval caudate in six, involving both the paracaval caudate and Spiegel lobe in six, involving the Spiegel lobe only in 16; in one patient, two separate tumors were located in the caudate (one in the caudate process, one in the Spiegel lobe).

Surgical Procedures

The majority of patients (24, 60%) underwent extended hepatectomy with en-bloc caudate resection. Among these, 15 underwent extended right hepatectomy (of which three underwent additional wedge resection of another lesion or lesions in the lateral liver), and nine underwent extended left hepatectomy with caudate resection. Sixteen (40%) patients underwent segmental or wedge resection of the caudate (six patients underwent resection of the caudate only, including one isolated total caudate resection, one paracaval caudate plus Spiegel lobe resection and four Spiegel lobe only resection, whereas 10 patients underwent segmental or wedge resection of the caudate plus additional segmental or wedge resection). No patient underwent ablation as a part of their surgical procedure.

Three patients (8%) required vascular resection to enable complete resection of the caudate lesion. One underwent extended right hepatectomy with portal vein resection; one underwent caudate resection with the IVC, and one a resection of segments II/III, VII and caudate with the IVC. Primary repair of the involved vessel was accomplished in all three cases. In addition, one patient who recurred at the parenchymal transection margin after resection of a tumor involving the caudate process underwent re-resection of the paracaval caudate and Spiegel lobe with IVC resection. Primary repair of the IVC was accomplished in this case as well. Pringle clamping was used in all patients, and only one patient required total vascular exclusion.

Complications occurred in 17 (43%) patients. Complications were liver-related in eight patients (bile leak, two; abscess requiring percutaneous drainage, two; transient jaundice, one; bleeding requiring transfusion, two; bleeding requiring transfusion and reoperation, one). Other complications occurred in nine (ileus, two; respiratory, five; central venous catheter infection, one; one recorded complication, type not defined). The median duration of hospitalization was 10 days (range 5–46). No 60-day mortality occurred.

Pathologic assessment of margins of resection is presented in Fig. 3 as previously reported.[5] Six patients (15%) had liver transection margins pathologically involved by tumor, and nine (23%) additional patients had margins <1 mm; thus, a total of 38% of patients were defined as having positive margins. Eighteen patients (45%) had margins ≥1 but less than 5 mm, four patients (10%) 5 to 9 mm, and only three patients (8%) had margins ≥10 mm.

Chemotherapy was used as postoperative adjuvant treatment in 26 patients. All were treated with fluoropyrimidine-based regimens (12 FU alone, eight oxaliplatin plus FU, two irinotecan plus FU, two oxaliplatin and irinotecan plus FU, and one locoregional floxuridine infusion).

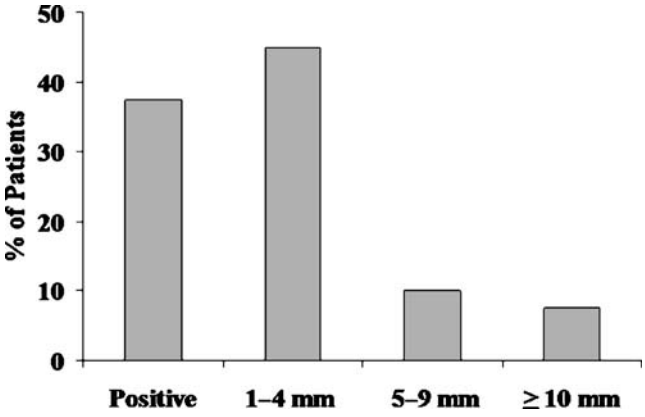

Figure 3 Resection margins. Distribution of patients stratified by the pathologic width of the hepatic parenchymal resection margin. Margins were defined as positive if tumor was present at or <1 mm of the inked margin.

Recurrence

The majority of patients with caudate LM recurred during the follow-up period (25 of 39 patients with complete recurrence data, 64%). Among these, 11 recurred in the liver only, nine recurred in the liver plus at least one extrahepatic site, five at an extrahepatic site only. Thus, in 20 of 39 (51%) patients, the liver was a site of recurrence.

Four patients (10%) recurred at the parenchymal transection margin. All four with marginal recurrence also recurred at an extrahepatic site. One patient with recurrence at the transection margin underwent reoperation with IVC resection as indicated above. All four patients with marginal recurrence are currently alive with disease at 12, 17, 24, and 42 months.

There were no recurrences on IVC or PV in any patient including those who underwent vascular resection.

No difference was observed in the recurrence rate between patients who underwent postoperative chemotherapy (66%) vs. those who did not (55%) (P=0.31), nor between those considered initially unresectable (40%) vs. those considered resectable at initial evaluation (31%) (P=0.42).

Comparison of Caudate LM with Non-caudate LM

Prognostic factors were compared between groups (caudate LM vs. non-caudate LM, Table 1). Patients with caudate LM had a higher incidence of presentation with synchronous (63% vs. 36%; P=0.01), and multiple (70% vs. 51%; P=0.02) tumors. Other prognostic factors such as largest tumor size >5 cm and pre-hepatectomy CEA were similar between groups. Extended hepatic resection was utilized three times more often for caudate LM than for non-caudate LM (60% vs. 18%; P<0.001). There was no significant difference in complications between groups, but the median hospital stay was 2 days longer for caudate LM (10 vs. 8 days for non-caudate LM; P<0.001). There was no difference in 60-day mortality between groups (caudate LM: 0% vs. non-caudate LM: 1%; P>0.05).

Use of preoperative chemotherapy was not significantly different between groups with (63%) or without (60%) caudate LM. Use of modern therapy with either oxaliplatin or irinotecan was also similar (33% vs. 34%, respectively).

Overall recurrence (64% vs. 40%; P=0.01) and liver recurrence (51% vs. 25%; P=0.001) were more common in the caudate LM group than the non-caudate LM group. The rate of positive margin resection was higher in patients with caudate LM than non-caudate LM (38% vs. 8%; P<0.001);

Table 1 Comparison of Patients with Caudate Versus Non-caudate Liver Metastases

	Caudate	Non-caudate	*P* value
Synchronous presentation	63%	36%	0.01
Multiple tumors	70%	51%	0.02
Extended hepatectomy	60%	18%	<0.001
Largest tumor >5 cm	40%	31%	NS
CEA prehepatectomy (ng/ml)	13	8	NS
Complications	43%	28%	NS
Hospital stay (median, days)	10	8	<0.001
60-day mortality	0%	1%	NS
Any recurrence	64%	40%	0.01
Liver recurrence	51%	25%	0.001
Surgical margin recurrence	10%	3.7%	NS
Positive resection margin	38%	8%	<0.001
Preoperative chemotherapy	63%	60%	NS
Preoperative chemotherapy with oxaliplatin or irinotecan	33%	34%	NS

CEA=carcinoembryonic antigen, synchronous=diagnosis of liver metastases within 1 year of diagnosis of primary colorectal cancer.

however, the surgical margin recurrence rate was not statistically different (10% vs. 3.7%; $P>0.05$).

Survival

At a median follow-up of 40 months, 5-year overall survival was significantly shorter in patients with caudate LM (41%, median 49 months) than in patients without caudate LM, (58%, median 74 months) ($P=0.02$) (Fig. 4A). Five-year recurrence-free survival was also shorter in patients with caudate LM (24%, median 20 months) than in patients without caudate LM (44%, median 42 months) ($P=0.02$) (Fig. 4B).

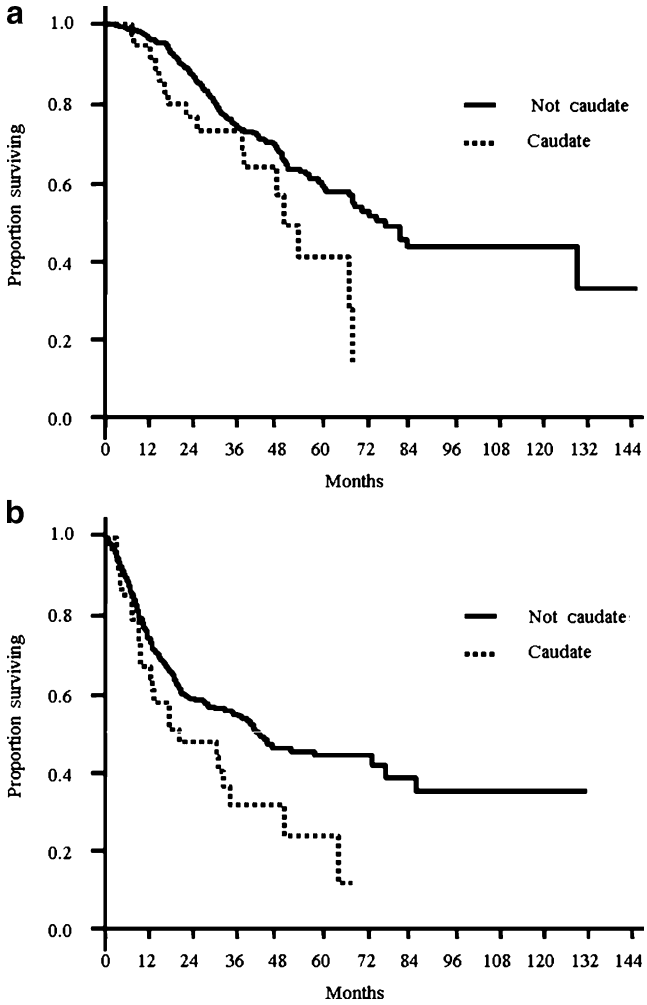

Figure 4 Overall and recurrence-free survival for caudate LM vs. non-caudate LM groups. A: Five-year overall survival was longer for non-caudate (58%) vs. caudate (41%) LM (median overall survival 74 vs. 49 months, respectively; $P=0.02$). B: Five-year recurrence-free survival was longer for non-caudate (44%) vs. caudate (24%) LM (median recurrence-free survival 42 vs. 20 months, respectively; $P=0.02$). Median follow-up for the entire group was 40 months.

Discussion

Several reports suggest that resection of caudate LM is worthwhile, but that recurrence is common. The first report on caudate resection for LM included nine patients of which nine underwent surgery for recurrent LM.[18] In that report, 67% of patients underwent major hepatectomy, 22% with vascular resection, and 56% recurred. Other small series found similar major hepatectomy rates (43–57%) but reported variable vascular resection rates (0–57%) with similar recurrence rates (71–85%).[19,20] One larger series was reported; however, the anatomical portions of the caudate resected, patient and tumor characteristics, and the proportion of re-resections in the series were not presented.[21] Recently, Tanaka reported on resection of five patients with solitary caudate LM in which four underwent major hepatectomy, and though three patients recurred, 40% were alive at 3 years.[22] Although analysis of patient and tumor characteristics is not possible from these studies, findings suggest the need for major hepatectomy in the majority of patients, significant need for vascular resection and a median survival of approximately 3 years for patients with resected caudate LM.[18–22]

Yamamoto's recent report on seven patients with caudate LM stimulates further discussion of the surgical approach to caudate LM.[20] The authors performed isolated resection of the caudate preserving the hepatic veins in several cases, using vascular resection in 57% of cases. The recurrence

rate was high (86%). Although isolated caudate resection has been shown to be an acceptable treatment for patients with benign tumors and for patients with hepatocellular carcinoma in cirrhotic patients in whom parenchymal preservation is needed to minimize the risk of post-hepatectomy liver insufficiency,[10,23–26] this parenchyma-preserving approach may not be warranted in many patients with colorectal LM as most patients have no chronic liver disease. Use of extended hepatectomy to include resection of hepatic veins in proximity to the tumor might be considered as an alternative to local resection as a strategy to reduce the probability of local tumor recurrence. Certainly, the surgical procedure to resect caudate tumors must be tailored to the specific patient, particularly in the setting of recurrence after prior hepatectomy or in patients with liver damaged by extensive chemotherapy,[27] but extended hepatectomy can be performed with very low mortality (0% in the present series, < 1% in large series of extended hepatectomies).[28] Thus, when tumors abut hepatic veins, we have taken the approach of extended hepatectomy with en-bloc resection of the caudate and involved hepatic veins rather than attempting to preserve parenchyma at the cost of a positive parenchymal transection margin. As a result, vascular resection was not necessary in most cases—total vascular exclusion was used in only one case.

Specifically regarding the abutment of tumor against the vena cava, the proposal to "peel the tumor" off the IVC[29] may be described more accurately as dissection of the plane often present between the tumor and the cava. We found this approach to be possible in the majority of cases. The absence of recurrences on the IVC in our series despite dissection of tumors off the IVC suggests that this anatomic location may be analogous to the liver capsule, and may not represent an oncologically significant margin of resection when a dissection plane can be identified. When tethered to the IVC or portal vein, resection was possible (three primary operations, one after recurrence) with primary repair in all cases. No recurrences at the venous resection sites were found. Although caval resection with graft reconstruction has been performed,[30] the mortality appears to be high and the oncologic outcome poor when this is necessary, possibly because patients with such extensive disease have metastases, which are not limited to the liver.

A significant proportion of patients in this study were reported to have positive parenchymal transection margins (38%). Despite this finding, only 10% recurred at the margin, and none recurred on the IVC or portal vein. The retrospective nature of this study does not permit differentiation between involvement of the cut surface of the liver vs. involvement of the exposed interface between the liver and the IVC or portal vein. The relatively low local recurrence rate suggests that the oncologic significance of tumor abutting the major vascular structures may be different than oncologic significance of tumor at the parenchymal transection margin. In a detailed analysis of recurrence patterns and survival after hepatic resection for colorectal LM, we previously showed that the width of a negative surgical margin (1–4 mm vs. 5–9 mm vs. ≥10 mm) does not affect survival, recurrence risk, or site of recurrence after resection of hepatic colorectal metastases.[5] The present study confirms these findings and supports an aggressive surgical approach to patients with multiple metastases and tumors in difficult anatomic locations such as the caudate lobe, and supports the contention that selected patients with adverse prognostic indicators should be treated with curative intent. Complete resection in the studied cohort was associated with 41% 5-year survival, significantly superior to the best results after modern chemotherapy in unresected patients (median survival 20–21 months)[31] or treatments using resection plus radiofrequency ablation or ablation alone (21 months).[3] These findings support the utilization of strategies designed to increase resectability and safety of resection including two-stage hepatectomy, extended hepatectomy, preoperative portal vein embolization, and downsizing chemotherapy.

Summary

Overall 5-year survival following hepatic resection for colorectal liver metastases involving the caudate liver is 41%. Major resections are generally required, whereas vascular resection is infrequently necessary. Despite minimal margin resection in patients with extensive hepatic disease, long-term survival can be achieved. Whether outcome for treatment of patients with caudate LM reflects a biologically aggressive phenotype (synchronous, multiple, initially unresectable tumors) remains to be clarified.

References

1. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. Improving resectability of hepatic colorectal metastases: Expert Consensus Statement. Ann Surg Oncol 2006 13(10), 1271–1280.
2 Choti MA, Sitzmann JV, Tiburi MF, Sumetchotimetha W, Rangsin R, Schulick RD, Lillemoe KD, Yeo CJ, Cameron JL. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg 2002;235:759–766.
3. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR, Hess K, Curley SA. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004;239:818–25; discussion 825–827.
4. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg 2004;240:438–47; discussion 447–450.
5. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, Curley SA, Loyer EM, Muratore A, Mentha G, Capussotti L,

Vauthey JN. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg 2005;241:715–722.
6. Aloia TA, Vauthey JN, Loyer EM, Ribero D, Ahrar K, Pawlik TM, Zorzi D, Abdalla EK. Solitary colorectal liver metastasis: resection determines outcome. Arch Surg 2006;141:460–467.
7. Kumon M. Anatomy of the caudate lobe with special reference to portal vein and bile duct. Acta Hepatol Jpn 1985;26:1193–1199.
8. Kogure K, Kuwano H, Fujimaki N, Makuuchi M. Relation among portal segmentation, proper hepatic vein, and external notch of the caudate lobe in the human liver. Ann Surg 2000;231:223–228.
9. Abdalla EK, Vauthey JN, Couinaud C. The caudate lobe of the liver: implications of embryology and anatomy for surgery. Surg Oncol Clin N Am 2002;11:835–848.
10. Yanaga K, Matsumata T, Hayashi H, Shimada M, Urata K, Sugimachi K. Isolated hepatic caudate lobectomy. Surgery 1994;115:757–761.
11. Bartlett D, Fong Y, Blumgart LH. Complete resection of the caudate lobe of the liver: technique and results. Br J Surg 1996;83:1076–1081.
12. Sasada A, Ataka K, Tsuchiya K, Yamagishi H, Maeda H, Okada M. Complete caudate lobectomy: its definition, indications, and surgical approaches. HPB Surg 1998;11:87–93.
13. Fan J, Wu ZQ, Tang ZY, Zhou J, Qiu SJ, Ma ZC, Zhou XD, Yu YQ. Complete resection of the caudate lobe of the liver with tumor: technique and experience. Hepato-Gastroenterology 2001;48:808–811.
14. Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg 2002;137:675-680; discussion 680–681.
15. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C, Hicks M, Alsfasser G, Lauwers G, Hawkins IF, Caridi J. Standardized measurement of the future liver remnant prior to extended liver resection: Methodology and clinical associations. Surgery 2000;127:512–519.
16. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. J Hepatobiliary Pancreat Surg 2005;12:351–355.
17. Strasberg SM. International Hepato-Pancreato-Biliary Association Terminology Committee Survey: the Brisbane 2000 Terminology of Liver Anatomy and Resections. HPB 2000;2:333–339.
18. Elias D, Lasser PH, Desruennes E, Mankarios H, Detroz B. Surgical approaches to segment I for malignant tumors (20 cases). J Chir (Paris) 1993;130:335–342.
19. Morise Z, Yamafuji K, Asami A, Takeshima K, Hayashi N, Baba H, Endo T, Hattori T, Ito Y, Tokura Y. Hepatectomy following transarterial chemotherapy for a metastasis in the caudate lobe. Hepato-Gastroenterology 2004;51:583–585.
20. Yamamoto H, Nagino M, Kamiya J, Hayakawa N, Nimura Y. Surgical treatment for colorectal liver metastases involving the paracaval portion of the caudate lobe. Surgery 2005;137:26–32.
21. Hawkins WG, DeMatteo RP, Cohen MS, Jarnagin WR, Fong Y, D'Angelica M, Gonen M, Blumgart LH. Caudate hepatectomy for cancer: a single institution experience with 150 patients. J Am Coll Surg 2005;200:345–352.
22. Tanaka K, Shimada H, Matsuo K, Nagano Y, Togo S. Surgical outcome of solitary colorectal metastasis to the hepatic caudate lobe. Br J Surg. 2005;92:847–848.
23. Kosuge T, Yamamoto J, Takayama T, Shimada K, Yamasaki S, Makuuchi M, Hasegawa H. An isolated, complete resection of the caudate lobe, including the paracaval portion, for hepatocellular carcinoma. Arch Surg 1994;129:280–284.
24. Asahara T, Dohi K, Hino H, Nakahara H, Katayama K, Itamoto T, E. O, Moriwaki K, Yuge O, Nakanishi T, Kitamoto M. Isolated caudate lobectomy by anterior approach for hepatocellular carcinoma originating in the paracaval portion of the caudate lobe. J Hepatobiliary Pancreat Surg 1998;5:416–421.
25. Yamamoto J, Kosuge T, Shimada K, Yamasaki S, Takayama T, Makuuchi M. Anterior transhepatic approach for isolated resection of the caudate lobe of the liver. World J Surg 1999;23:97–101.
26. Sarmiento JM, Que FG, Nagorney DM. Surgical outcomes of isolated caudate lobe resection: a single series of 19 patients. Surgery 2002;132:697–708; discussion 708–709.
27. Vauthey JN, Pawlik TM, Ribero D, Wu T, Zorzi D, Hoff PM, Xiong HQ, Eng C, Lauwers GY, Mino-Kenudson M, Risio M, Muratore A, Capussotti L, Curley SA, Abdalla EK. Chemotherapy regimen predicts steatohepatitis and an increase in 90-Day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006;24:2065–2072.
28. Vauthey JN, Pawlik TM, Abdalla EK, Arens JF, Nemr RA, Wei SH, Kennamer DL, Ellis LM, Curley SA. Is extended hepatectomy for hepatobiliary malignancy justified? Ann Surg 2004;239:722–730; discussion 730–732.
29. Okada Y, Nagino M, Kamiya J, Yamamoto H, Hayakawa N, Nimura Y. Diagnosis and treatment of inferior vena caval invasion by hepatic cancer. World J Surg 2003;27:689–694.
30. Nardo B, Ercolani G, Montalti R, Bertelli R, Gardini A, Beltempo P, Puviani L, Pacile V, Vivarelli M, Cavallari A. Hepatic resection for primary or secondary malignancies with involvement of the inferior vena cava: is this operation safe or hazardous? J Am Coll Surg 2005;201:671–679.
31. Venook A. Critical evaluation of current treatments in metastatic colorectal cancer. Oncologist 2005;10:250–261.

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Undifferentiated Embryonal Sarcoma of the Liver Successfully Treated With Chemotherapy and Liver Resection

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Abstract Undifferentiated embryonal sarcoma is the third most common malignant tumor of the liver in children, accounting for 13% of hepatic malignancies in this age group. It has been considered an aggressive neoplasm with very poor prognosis until the late 1980s, when long-term survivors were reported after multiagent chemotherapy followed by resection. We, herein, report two pediatric cases of undifferentiated embryonal sarcoma treated successfully with surgical resection after neoadjuvant chemotherapy based on therapy used in childhood soft tissue sarcomas and in childhood hepatic malignancies. The first patient also had a concurrent cerebellar tumor (pilocytic astrocytoma), for which he first underwent craniotomy and resection, delaying the liver tumor resection by 10 weeks. They are alive and tumor free at 48 months (case no. 1) and 18 months (case no. 2) following neoadjuvant chemotherapy and liver resection.

Keywords Malignant liver tumor · Chemotherapy · Cerebellar tumor · Liver resection

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Introduction

Undifferentiated embryonal sarcoma (UES), first described by Stocker and Ishak in 1978, is the third most common malignant tumor of the liver in children, accounting for about 13% of hepatic malignancies[1,2]. It is most commonly seen in children between 6 and 10 years of age, and about 88% occur in children less than 15 years of age. The tumor is located in the right lobe of the liver in the majority of the patients, and it rarely involves both lobes. The main presenting symptoms are typically an abdominal mass and right upper quadrant or epigastric pain of few weeks or months duration. Complaints such as nausea, anorexia, intermittent fever or headache may also be present. Children have usually been otherwise healthy before diagnosis.

This tumor was considered an aggressive neoplasm with very poor prognosis[3] until the late 1980s, when long-term survivors were reported following multiagent chemotherapy before liver resection[4,5]. Complete surgical resection with neoadjuvant chemotherapy offers the best long-term results and possibility of cure[3,6–8].

We herein report two pediatric cases of UES successfully treated with surgical resection and neoadjuvant chemother-

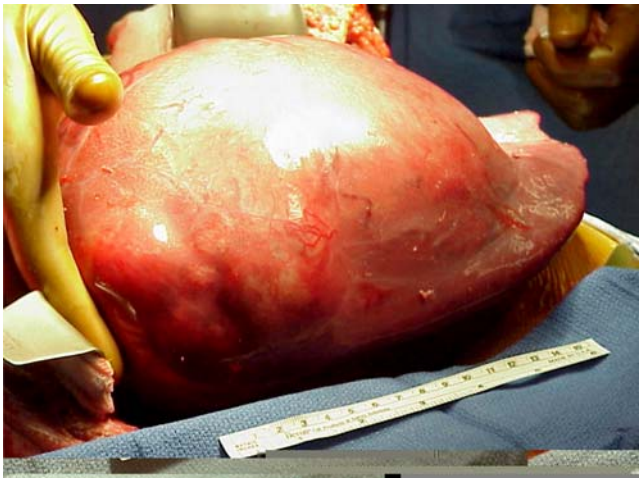

Figure 1 Undifferentiated embryonal sarcoma of the liver, in situ (case no. 1).

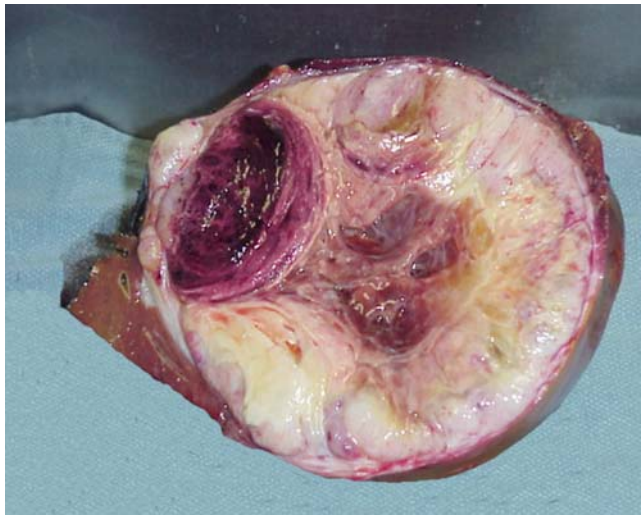

Figure 2 Cross-section of resected undifferentiated embryonal sarcoma of the liver, showing areas of cystic degeneration and hemorrhage (case no. 1).

apy, including a unique case of UES of the liver associated with pilocytic astrocytoma of the cerebellum.

Case 1

This 13-year-old previously healthy Caucasian male developed intermittent headache, high fever, sore throat, cough and rhinorrhea 3 months before presentation. A large epigastric nontender mass was found on physical examination. An extensive oncologic work-up revealed a large mass (20×14 cm) occupying the majority of the right lobe of the liver, with mild displacement of the inferior vena cava and the right kidney. A 2.9-cm tumor was also noted in the posterior cranial fossa at the level of the fourth ventricle. Resection of the cerebellar mass demonstrated pilocytic astrocytoma, but was complicated by intraventricular hemorrhage and subsequent hydrocephalus, treated with frontal ventriculostomy. His postoperative course was complicated by deep coma and respirator dependency for several weeks. After 10 weeks of slow postoperative improvement, he underwent a successful right hepatic trisegmentectomy. A histopathologic examination demonstrated a large undifferentiated embryonal sarcoma of the liver (3 kg, 25 cm in diameter), with tumor-free surgical margins. He received a total of six cycles of chemotherapy, all postoperatively, alternating a combination of cisplatin and adriamycin with vincristine, ifosfamide, and etoposide (VIE). Computed tomography (CT) scans of the abdomen and pelvis, 3 and 6 months after surgical resection, showed no evidence of recurrent liver tumor and showed almost complete regeneration of the right lobe of the liver. The child continues his neurologic rehabilitation, but is currently tumor-free, 48 months after surgical resection and neoadjuvant chemotherapy.

Case 2

This 11-year old boy developed fatigue, decreased appetite, and weight loss. His work-up revealed anemia and a large liver mass (12×8 cm) localized in the anterior segment of the right lobe (segments 5 and 8) and the medial segment of the left lobe of the liver (segment 4B). He underwent a needle biopsy of the tumor, which showed features typical of undifferentiated embryonal sarcoma. His metastatic work-up was negative. He underwent four courses of neoadjuvant chemotherapy, alternating cycles of cyclophos-

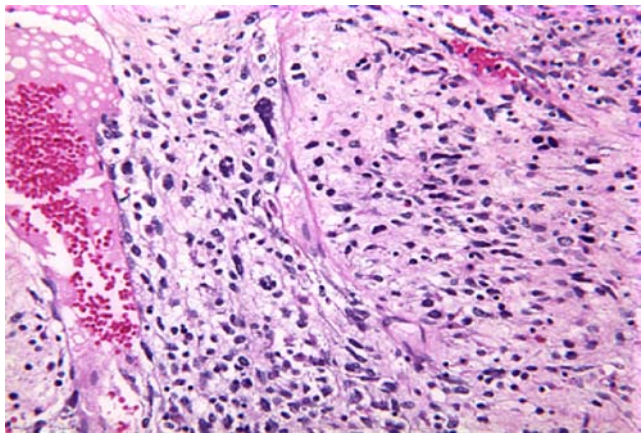

Figure 3 Microscopic appearance typical of undifferentiated embryonal sarcoma, with nondescript malignant spindled stromal cells and occasional intermixed large pleomorphic tumor giant cells. The tumor lacks any evidence of more specific differentiation as seen in the other more common malignant tumors of the pediatric liver, namely, muscle differentiation typical of biliary rhabdomyosarcoma or immature hepatocytes typical of hepatoblastoma. (hematoxylin–eosin stain, case no. 1).

phamide, mesna, vincristine, and actinomycin, with cycles of ifosfamide and VP-16. He responded very well, and his liver mass decreased in size by approximately 40%. Two weeks after chemotherapy, he underwent extended right lobectomy without complications. The surgical specimen revealed minimal residual viable tumor (less than 1%) with significant tumor necrosis and tumor-free surgical margins. He received two additional courses of chemotherapy after liver resection without complications. He is tumor free and doing well 18 months after surgical resection and neoadjuvant chemotherapy.

Discussion

UES is the third most common malignant tumor of the liver in children, after hepatoblastoma and hepatocellular carcinoma. It most commonly occurs between 6 and 10 years of age, in contrast to hepatoblastoma, which is most commonly seen in children under 5 years of age, and hepatocellular carcinoma which is more frequent in patients more than 10 years old. UES is rare in adults and is slightly more frequent in boys[9]. The tumor usually presents as a large abdominal mass, with or without pain or fever, as in our cases. The majority of the reported cases have not had liver function abnormalities despite massive tumor size.

Useful imaging studies include initial ultrasonography with Doppler examination, followed by CT or magnetic resonance imaging (MRI) to better characterize the tumor and assist in surgical planning. Tumor markers are typically not present in the serum of these patients. In one adult case, CA-125 was found elevated in the tumor itself[10].

These tumors are typically large and difficult to resect (Fig. 1), but distant metastasis is rare. The tumor rarely involves both lobes, but this was not the case in our experience. The characteristic gross appearance is that of a large intraparenchymal heterogeneous mass with solid and cystic areas, the latter often containing necrotic material and hemorrhage (Fig. 2). The tumor has a variable but distinctively sarcomatous appearance under the microscope, with the tumor cells showing variable morphology, but typically spindle-shaped or pleomorphic (Fig. 3), and often with relatively frequent tumor giant cells. Immunohistochemistry typically shows divergent staining, including variable expression of histiocytic, muscle and epithelial markers, suggesting origin from primitive stem cells.

One of our cases appears to be unique by virtue of its association with a low-grade cerebellar pilocytic astrocytoma. It raises the question as to whether this patient may have had some type of unrecognized underlying genetic disorder, which might have predisposed the development of these tumors. However, clinically, there was no recognized genetic or syndromic abnormality.

The prognosis of UES has been very poor until recently when aggressive chemotherapy similar to that used for rhabdomyosarcoma has come into use preoperatively, which more often permits complete tumor resection of initially unresectable tumors. Bisogno et al. reported 12 of 17 patients who were alive after a 20-year follow-up[11]. The use of a similar combination chemotherapy in our patients allowed us to achieve complete resection and tumor-free survival to date. Radiotherapy has not been considered helpful in patients with UES so far.

In conclusion, we report two pediatric cases of UES treated with neoadjuvant chemotherapy and liver resection that are tumor-free at 48 months (case no. 1) and 18 months (case no. 2) following resection. We also describe a unique case of UES associated with a low-grade pilocytic astrocytoma of the cerebellum.

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References

1. Weinberg AG, Finegold MJ. Primary hepatic tumors of childhood. Hum Pathol 1983;14(6):512.
2. Stocker JT, Ishak KG. Undifferentiated (embryonal) sarcoma of the liver: report of 31 cases. Cancer 1978;42(1):336.
3. Horowitz ME, Etcubanas E, Webber BL, et al. Hepatic undifferentiated (embryonal) sarcoma and rhabdomyosarcoma in children. Results of therapy. Cancer 1987;59(3):396.
4. Babin-Boilletot A, Flamant F, Terrier-Lacombe MJ, et al. Primitive malignant nonepithelial hepatic tumors in children. Med Pediatr Oncol 1993;21(9):634.
5. Kadomatsu K, Nakagawara A, Zaizen Y, et al. Undifferentiated (embryonal) sarcoma of the liver: report of three cases. Surg Today 1992;22(5):451.
6. Urban CE, Mache CJ, Schwinger W, et al. Undifferentiated (embryonal) sarcoma of the liver in childhood. Successful combined-modality therapy in four patients. Cancer 1993;72(8):2511.
7. Smithson WA, Telander RL, Carney JA. Mesenchymoma of the liver in childhood: five-year survival after combined-modality treatment. J Pediatr Surg 1982;17(1):70.
8. Ware R, Friedman HS, Filston HC, et al. Childhood hepatic mesenchymoma: successful treatment with surgery and multiple-agent chemotherapy. Med Pediatr Oncol 1988;16(1):62.
9. Leuschner I, Schmidt D, Harms D. Undifferentiated sarcoma of the liver in childhood: morphology, flow cytometry, and literature review. Hum Pathol 1990;21(1):68.
10. Houry S, Gharbi L, Huguier M, Callard P, Andre T. Undifferentiated embryonal sarcoma in the liver of adults. Presse Méd 1998;27(11):518.
11. Bisogno G, Pilz T, Perilongo G, et al. Undifferentiated sarcoma of the liver in childhood: a curable disease. Cancer 2002;94(1):252.

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Referrals for Surgical Therapy in Patients with Hepatocellular Carcinoma: A Community Experience

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Abstract The treatment of hepatocellular carcinoma (HCC) is notoriously difficult. Either because of oncogenic behavior or the frequent association of cirrhosis, successful therapy is elusive, particularly in cirrhotic patients. Surgical removal has been the only modality that has produced long-term, disease-free survival. In a large series of patients from specialty institutions, median survival in those who underwent resection of HCC lesions has ranged from 30 to 70 months. Similarly, liver transplantation has been shown to be an effective treatment when HCC is favorable (limited in size and number), producing long-term survival in greater than 70% of patients. However, less information is known about community-based treatment of HCC. Reports from referral centers may not accurately reflect the community experience. We have retrospectively reviewed patients with HCC seen in surgical referral from three teaching hospitals in a medium-size urban community from 1995 to 2004 who were not felt to be candidates for liver transplantation and who were not sent to referral centers. We sought to examine their suitability for operation and resection. The study group comprised 61 patients, whose ages ranged from 35 to 83 years old. There were 44 patients (72%) with cirrhosis (Childs A, B, and C in 27, 15, and 2 patients, respectively), 21 from hepatitic C virus (HCV) infection. Three recognized staging systems were used that incorporated the estimation of hepatic reserve and tumor burden. Seven patients (11%) were deemed nonoperable (five advanced disease by imaging, two comorbidities). Of the 54 patients who underwent surgical procedures, 32 underwent resection (28 patients) or cryoablation (4 patients). The reasons for unresectability were unrecognized multifocality (ten patients), poor risk for major hepatectomy (five patients), portal vein/hepatic vein involvement (three patients), metastatic disease (two patients), and excessive blood loss prior to hepatectomy (two patients). Eleven of 17 (65%) noncirrhotic patients and 21 of 44 (48%) cirrhotic patients were resectable or ablatable. There were ten postoperative deaths: six following resection, two following cryoablation, and two following exploratory celiotomy. All deaths were in cirrhotic patients (Childs A in four patients, B in five patients, and C in one patient), 10 of 44 patients (23%); 3 of 11 (27%) patients died following segmentectomy and 3 of 9 (33%) following major hepatectomy. Seven deaths that occurred were in patients with HCV; (P=NS). From this series, the difficulty in surgically treating cirrhotic patients in an urban practice is evident. From 39 to 73% of patients had advanced local disease. Less than half were resectable and, for cirrhotic patients, the postoperative mortality was high, even after "minor" hepatectomies. Noncirrhotic patients fared somewhat better. While HCC in community practice can be treated surgically in the majority of noncirrhotic patients, cirrhotic patients are less likely candidates, and surgical treatment is associated with significant postoperative mortality. This frequently reflected advanced disease and HCV but may be associated with access to preventative and surveillance measures. Only those with optimum hepatic reserve and small tumor burden should be considered for surgical resection.

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Introduction

While almost endemic in certain parts of the world, such as Southeast Asia, the incidence of hepatocellular carcinoma (HCC) is increasing in the United States. The incidence has more than doubled, from 1.4/100,000 population from 1975

to 1977 to 3.0/100,000 population from 1996 to 1998[1]. It is thought that hepatitic C virus infection (HCV) is largely responsible for this rise. Treatment has been particularly challenging because of the frequent presence of chronic liver disease (cirrhosis) and the advanced stage of disease at the time of diagnosis. Mainstays of treatment have been hepatic resection and liver transplantation (for cirrhotic patients). Perioperative mortality and long-term survival are comparable with either modality in selected patients[2]. The advantage of liver transplantation, of course, is that it affords a solution to two problems: the underlying liver disease and HCC. However, access to transplant centers is not uniform. Studies have shown that geographic location, age, gender, and payor status influence access to liver transplantation[3,4]. Furthermore, so-called high-volume centers for hepatic resection (more than 25 cases per year) are few and far between, and access—particularly for the under insured—could be difficult[5]. For these reasons, there are many patients appearing with HCC who will need treatment and who will not or cannot access national "centers of excellence."

We have reviewed our community experience, as an observational study, over a 10-year period (1995 through 2004) with HCC in patients who were not judged as candidates for liver transplantation and who elected to receive treatment locally. All were referred for consideration for surgery. The patients were evaluated and treated at one of three hospitals in the Kansas City, MO, metropolitan area: a city/county hospital, a tertiary referral hospital, and a Veterans Administration hospital, all part of a university training system [University of Missouri-Kansas City School of Medicine (UMKC)]. The UMKC system had only a pediatric liver transplant program—all potential adult candidates were referred to other transplant centers. Our primary aim in this study was to review, in an urban community population, suitability for resection and postoperative outcome compared to published outcomes from larger referral centers.

Materials and Methods

All patients seen by the senior author (T.S.H.) at one of three teaching hospitals in the UMKC system in consultation for surgical therapy for HCC over a 10-year period from 1995 through 2004 were concurrently entered into a database and are the subject of this review. Patients were evaluated for suitability for liver resection based on comorbid conditions, hepatic reserve, and number and location of hepatic tumors. Hepatic reserve was estimated using the Childs–Pugh scoring system[6]. Three HCC staging systems were used: the American Joint Committee on Cancer, 6th edition[7], the Okuda classification[8], and the Barcelona Clinic Liver Cancer (BCLC) Group classification[9]. Referral for transplantation was done for those with cirrhosis and who were appropriate for age and tumor burden. Such patients, entered into this database, were not considered transplant candidates by the referral centers based on age, tumor burden, or reimbursement and/or compliance issues. Surgical therapy was directed at patients with liver-only disease to produce "R0" resections (resection for cure). Conservation of liver tissue was stressed for all patients with compromised liver function from cirrhosis. In some patients judged to be at higher risk, ablative therapy was used (cryoablation). All operations were done in one of the three UMKC teaching hospitals. The numbers of liver resections performed by the senior author at these institutions over the 3 years 2004, 2003, and 2002 were 15, 29, and 26, respectively (average 23), with most of the resections (59/70) performed at one hospital. Intraoperative assessment for resectability included visual, manual, and histologic examination and the routine use of liver ultrasound. Postoperative death included any death within 30 days of operation or during the same hospitalization. Outcome measures included suitability for operation, suitability for resection, and postoperative mortality. Statistical analysis was by way of chi-square with a p value less than 0.05 set for significance. All patient information in the database was deidentified so as to conform to the Health Insurance Portability and Accountability Act.

Results

A total of 61 patients participated in the study group. There were 45 men and 16 women. Ages ranged from 35 to 83 years. Nineteen patients (31%) were 70 years of age or older. There were 44 patients (72%) with cirrhosis, 21 with HCV infection. At least four of the cirrhotic patients with HCV also had a history of alcohol use, but it was difficult in many cases to establish whether this was excessive and a cofactor in their chronic liver disease. By Childs–Pugh scoring, 27 patients were "A," 15 were "B," and 2 were "C." Staging of HCC in all patients is depicted in Table 1. Using the TMN classification, over half the patients had advanced-stage tumors, either large, multifocal, or exhibiting venous or lymphatic invasion. By the BCLC criteria, only ten patients (eight with cirrhosis) had a solitary tumor, good hepatic reserve (Childs–Pugh A), and no evidence of portal hypertension. Fifteen of the 17 patients without cirrhosis had large tumors greater than 5 cm, and only three patients had tumors of 3 cm or less. Overall, seven patients (11%) were deemed nonoperable, five with advanced disease determined by preoperative imaging and two with prohibitive comorbidities. Of the 54 patients who underwent surgical procedures, 32 (59%) underwent resection (28 patients) or cryoablation (four patients). Twenty-four of 28 resections were performed at one hospital. Resection

Table 1 Staging of HCC in Patients Referred for Surgical Treatment

Staging system	Distribution
TNM[7]	T1=29, T2=8, T3=23, T4=1, N1=5
Okuda et al.[8]	1=36, 2=24, 3=1
BCLC[9]	A1=10, A2=4, A4=2, B=30, C=12, D=3

TNM=tumor–node–metastases

was not possible in 22 patients because of unrecognized multifocality (ten patients), poor risk for major hepatectomy (five patients), portal vein/hepatic vein involvement (three patients), metastatic disease (two patients), and excess blood loss prior to hepatectomy (two patients). Eleven of 17 noncirrhotic patients (65%) and 21 of 44 cirrhotic patients (48%) were resectable or ablatable.

There were ten postoperative deaths. Six patients died following resection, two following ablation, and two following exploratory celiotomy. All the deaths were of cirrhotic patients; four in Childs–Pugh A, five in Childs–Pugh B, and one in Childs–Pugh C. In the eight cirrhotic patients considered to have optimum liver staging using the BCLC criteria (solitary, <5 cm, good hepatic reserve), there were two deaths (25%), one in the immediate postoperative period and one at 2 months. In the cirrhotic patients, 11 underwent hepatic segmentectomy, and three died (27%); nine underwent a major hepatectomy, and three (33%) died. All deaths were due to postoperative liver failure, occurring from 4 days to 2 months after operation. Seven deaths were in HCV-positive patients (P=NS). In noncirrhotic patients, seven underwent a major hepatectomy and four patients had segmentectomies.

Discussion

In this series of patients referred from an urban community for surgical treatment of HCC, most had advanced disease at the time of presentation. Many cirrhotic patients had less than optimal hepatic reserve, and only eight patients were judged ideal surgical candidates (BCLC class A1), that is, solitary tumor, good hepatic reserve, and no portal hypertension. Only a little over one half 52%, of all patients could be resected or ablated. Less than one half, 48%, of cirrhotic patients could be surgically treated. In those operated but not resectable, most had unrecognized advanced disease. While those patients without cirrhosis tolerated resection well, cirrhotic patients faired poorly. Almost 50% of cirrhotic patients died postoperatively, including two of eight patients with early (BCLC) stage HCC and optimum liver function, and all deaths were due to inadequate hepatic reserve and subsequent liver failure, even after relatively straightforward segmental resections.

These results stand in stark contrast to many published reports, at least for cirrhotic patients. Fong and coauthors[10] from the Memorial Sloan–Kettering Cancer Center described 412 cases of HCC referred to their center. While the percent of patients resected who were explored (66%) was not too dissimilar from our results, postoperative mortality in cirrhotic patients was 5%, significantly less than observed in this series (38%, $p<0.001$). Centers in Villejuif, France[11]; Tokyo, Japan[12]; and the Mayo Clinic[13] have reported overall mortality following resection, including cirrhotic and noncirrhotic patients, ranging from 9 to 14%. In fact, more recent work from Torzilli et al. at the University of Tokyo[14] has described no 30-day mortality in 64 cirrhotic patients with limited numbers of small HCC, and generally, good hepatic reserve.

There is little doubt that patient selection is important. Pooled data from four major hepatobiliary centers identified tumor number (solitary vs. multiple), vascular invasion, fibrosis/cirrhosis scoring, Childs–Pugh score, and the degree of tumor differentiation (Edmondson–Steiner grade) as statistically related to better outcomes[15]. In fact, 80% of patients in these series were scored as Childs–Pugh A, and almost 70% had solitary tumors. Similarly, Rene Adams and his group from Villejuif, France[16], reported that patients with poorer hepatic reserve and larger tumor burden were more likely to benefit from primary transplantation compared to better-risk patients who had fewer (one or two) tumors, good hepatic function, and absence of macrovascular invasion at the time of operation, and could be treated by primary resection. The Barcelona group[17] has advocated resection only for those patients with small (<2 cm), solitary tumors and good hepatic reserve (Childs–Pugh A) and normal portal pressures. In our series, those types of patients (good hepatic reserve and small, solitary tumors) comprised no more than 7% of patients (3 of 44 cirrhotic patients). More recently, investigators from the Mayo Clinic demonstrated the usefulness of the model for end-stage liver disease (MELD) score in predicting mortality from hepatic resection for HCC in patients with cirrhosis[18]. The MELD score is a compilation of weighted natural logarithms of serum creatinine, serum bilirubin, and international normalized ratio, and, as such, represents fairly standard tests of liver function. In their updated series, 80 of 82 patients were scored Childs–Pugh A. Within this historically favorable group, those with a MELD score of ≥9 had a significantly higher mortality (29%) than those with a score less than 9 (0%).

Nevertheless, according to the published literature, patients that are considered less than ideal candidates may still benefit from liver resection. Forty-eight percent of cirrhotic patients who underwent resection in the Milan series were scored as Childs–Pugh B or C and suffered only a 4.5% operative mortality[19]. Okuda and colleagues[8] reported a

median survival of 12.2 months for stage 2 patients compared to 3.5 months for those medically treated. From the Far East, cirrhotic patients have undergone successful extended hepatic resection[20], resection of large HCCs[21], and resection of bilobar tumors[22]. Multicenter information, some of which is from five centers, has indicated successful resection of HCC in patients with portal or hepatic vein invasion[23], considered by some to be a contraindication to resection or transplantation[17].

Does this mean that our results reflect substandard care? We think not. Clearly, there are proponents for referral of these patients to high-volume centers. Fong and coauthors[5] concluded that "superior long-term (and perioperative) survival is associated with complex visceral (liver, pancreatic) resections for cancer at high-volume centers." High-volume centers were defined as performing more than 25 cases per year—of which there were ten identified by the National Medicare database (none of the three UMKC hospitals qualified as high-volume centers). The relative risk of death following liver resection was 1.8 at low-volume centers. Similarly, Dimick and colleagues[24], examining the State of Maryland discharge database, found a relative risk of mortality of 3.1 at low-volume centers (<12 liver resections per year) compared to high-volume centers (12 or more liver resections per year). In this regard, the senior (T. S.H.) author has averaged 23 liver resections over the most recent 3 years. Although this number was distributed over three hospitals in the UMKC system, one hospital accounted for the bulk (24/28) of the liver resections performed. In the senior author's personal series, the published results have been in line with other reported series[25]. Moreover, the perioperative outcome in noncirrhotic patients in this series was quite different and mirrors other collected reports[26]. While quality of surgical care need not be wedded to volume, our present experience would not be viewed as occurring in a low-volume environment.

Instead, we feel that the poorer outcome for cirrhotic patients in our series may be more related to the type of patient referred. While tumor burden may have been larger than desired, our selection of patients with what is generally considered good hepatic reserve (Childs–Pugh A) did not differ from that of other centers. However, almost all of our cirrhotic patients were on some form of medical assistance or were indigent. Many had been seen and rejected at transplant centers. Could socioeconomic factors play a role? Such information from the United States on HCC is scarce, but a prevalent cause of chronic liver disease is alcoholism or a combination of alcoholism and HCV, comprising 45% of referred patients in one series[27], with the driving force in mortality seemingly due to ongoing excessive alcohol use. One study from the Veterans Affairs population indicated that patients with chronic liver disease have a greater likelihood of suffering from HCV and previous alcohol abuse[28]. Reports from Japan and South Africa indicate that rural or homeless individuals very often presented with advanced HCC[29,30]. Less than 10% were surgically curable. A major cause was likely a lack of surveillance, as others have demonstrated a survival advantage to those with semiannual or even annual follow-up[31].

Do the socioeconomically disadvantaged fare worse with surgery? Some contend they do. While we cannot provide direct evidence, and information specifically concerning HCC is lacking, Mahomed and coauthors[32], examining Medicare claims over a 1-year period for primary and revisional hip replacement, found that low income (Medicaid supplementation) increased the relative risk of death within 90 days (1.7), and wound infection (1.9) after risk adjustment using the Charlson comorbidity index. Others[33] have found an increase in mortality (relative risk 1.57) and postoperative complications (relative risk 1.22) in patients without private insurance, following surgery for colorectal carcinoma. In addition, risk-adjusted mortality after elective and emergent abdominal aortic aneurysm repair was significantly higher among those without insurance or with Michigan Medicaid coverage[34]. Why such a discrepancy exists is not readily apparent. Some have suggested that failure to access care due to lack of insurance coverage or nuances associated with utilization of city/county health care facilities, such as not having a primary care physician or readily available specialists, may dispose patients to poorer health management[34,35]. The combined effects of HCV and continued alcohol abuse have recognizable consequences on liver histology and seem to have a synergistic impact on liver injury[36,37], perhaps impairing the ability of the liver to recover from surgical attack and resection. Accordingly, steatohepatitis has been cited as a risk factor for liver failure following hepatectomy for HCC[38,39]. Lastly, with respect to liver transplantation, Yoo and Thuluvath[40] have reported that patients with Medicare and Medicaid had lower posttransplant survival compared to those with private insurance, which could be a disincentive for transplant programs to accept these types of patients.

With respect to cirrhotic patients, it is likely, then, that our experience reflects an urban population, many of whom are socioeconomically deprived and may have ongoing issues with substance abuse. Many have advanced disease at the time of diagnosis, perhaps from lack of proper surveillance or failure to access appropriate medical care. For a combination of reasons, including lack of insurance, difficult access to public health facilities, and poor overall health maintenance, outcome from surgical therapy in this group is discouraging. Transplantation is often not a realistic goal because of large tumor burden, inadequate coverage, or poor compliance. Surgical therapy cannot be aggressive, and optimum hepatic reserve must be established beforehand if postoperative mortality is to be minimized. Resection should

be confined to those patients with small tumor burden and who are amendable to segmental removal, ideally patients classified as A1 in the BCLC system. For others, even Childs–Pugh A patients, risks of liver resection should be carefully discussed and nonoperative treatment presented. Because alcohol use seems common in the setting of cirrhosis and can contribute to active hepatitis, it is imperative that surgical candidates abstain for at least 1 month prior to their operation. Noncirrhotic patients with otherwise healthy livers fair much better, and in this group, traditional determinants for resection can be used.

References

1. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continued increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139:817–823.
2. Farmer DG, Rosove MH, Shaked A, Busuttil RW. Current treatment modalities for hepatocellular carcinoma. Ann Surg 1994;219:236–247.
3. Tuttle-Newhall JE, Rutledge R, Johnson M, Fair J. A statewide, population-based, time series analysis of access to liver transplantation. Transplantation 1997;63:255–262.
4. McCormick PA, O'Rourke M, Carey D, Laffey M. Ability to pay and geographical proximity influence access to liver transplantation even in a system with universal access. Liver Transpl 2004;10:1422–1427.
5. Fong Y, Gonen M, Rubin D, Radzyner M, Brennan MF. Long-term survival is superior after resection for cancer in high-volume centers. Ann Surg 2005;242:540–547.
6. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the esophagus for bleeding esophageal varices. Br J Surg 1973;60:646–654.
7. Green FL, Page DL, Fleming ID, et al., eds. AJCC Cancer Staging Manual, 6th ed. Berlin Heidelberg New York: Springer, 2002.
8. Okuda K, Ohtsuki T, Obata H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer 1985;56:918–928.
9. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–338.
10. Fong Y, Sun RL, Jamagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a western center. Ann Surg 1999;229:790–800.
11. Bismuth H, Houssin D, Ornowski J, Meriggi F. Liver resections in cirrhotic patients: a western experience. World J Surg 1986;10:311–317.
12. Nagao T, Inoue S, Goto S, et al. Hepatic resection for hepatocellular carcinoma: clinical features and long-term prognosis. Ann Surg 1987;205:33–40.
13. Nagorney DM, van Heerden JA, Ilstrup DM, Adson MA. Primary hepatic malignancy: Surgical management and determinants of survival. Surgery 1989;106:740–749.
14. Torzilli G, Makuuchi M, Inoue K, et al. No-mortality liver resection for hepatocellular carcinoma in cirrhotic and noncirrhotic patients: is there a way? A prospective analysis of our approach. Arch Surg 1999;134:984–992.
15. Wayne JD, Lauwers GY, Ikai I, et al. Preoperative predictors of survival after resection of small hepatocellular carcinomas. Ann Surg 2002;235:722–731.
16. Adams R, Azoulay D, Castaing D, et al. Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy? Ann Surg 2003;238:508–519.
17. Llovet JM, Fuster J, Bruix J. The Barcelona approach: diagnosis, staging, and treatment of hepatocellular carcinoma. Liver Transpl 2004;10:S115–S120.
18. Teh SH, Christein J, Donohue J, et al. Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: model of end-stage liver disease (MELD) score predicts perioperative mortality. J Gastrointest Surg 2005;9:1207–1215.
19. De Carlis L, Giacomoni A, Pirotta V, et al. Surgical treatment of hepatocellular cancer in the era of hepatic transplantation. J Am Coll Surg 2003;196:887–897.
20. Poon RT, Fan ST, Lo CM, et al. Extended hepatic resection for hepatocellular carcinoma in patients with cirrhosis: is it justified? Ann Surg 2002;236:602–611.
21. Mok K-T, Wang B-W, Lo G-H, et al. Multimodality management of hepatocellular carcinoma larger than 10 cm. J Am Coll Surg 2003;197:730–738.
22. Liu CL, Fan ST, Lo CM, Ng IO, Poon RT, Wong J. Hepatic resection for bilobar hepatocellular carcinoma: is it justified? Arch Surg 2003;138:100–104.
23. Pawlik TM, Poon RT, Abdallah EK, et al. Hepatectomy for hepatocellular carcinoma with major portal or hepatic vein invasion: results of a multicenter study. Surgery 2005;137:403–410.
24. Dimick JB, Pronovost PJ, Cowan JA Jr, Lipsett PA. Postoperative complication rates after hepatic resection in Maryland hospitals. Arch Surg 2003;138:41–46.
25. Helling TS. Ruminations of an ordinary hepatic surgeon: a journey through the pitfalls of major liver resection. J Gastrointest Surg 2002;6:625–629.
26. Laurent C, Blanc JF, Nobili S, et al. Prognostic factors and longterm survival after hepatic resection for hepatocellular carcinoma originating from noncirrhotic liver. J Am Coll Surg 2005;201:656–662.
27. Said A, Williams J, Holden J, Remington P, Musat A, Lucey MR. The prevalence of alcohol-induced liver disease and hepatitis C and their interaction in a tertiary care setting. Clin Gastroenterol Hepatol 2004;2:928–934.
28. Chapman WC, Wright JK, Awad JA, et al. Nashville experience with liver transplantation in Veterans Administration patients. J Surg Res 1997;67:79–83.
29. Sakai Y, Seki S, Nishiguchi S, et al. Homeless patients with hepatocellular carcinoma in Osaka City, Japan. Hepatogastroenterology 1999;46:1106–1110.
30. Maraj R, Kew MC, Hyslop RJ. Resectability rate of hepatocellular carcinoma in rural southern Africans. Br J Surg 1988;75:335–338.
31. Trevisani F, De NS, Rapaccini G, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 2002;97:734–744.
32. Mahomed NN, Barrett JA, Katz JN, et al. Rates and outcomes of primary and revision total hip replacement in the United States Medicare population. J Bone Joint Surg Am 2003;85-A:27–32.
33. Kelz RR, Gimotty PA, Polsky D, Norman S, Fraker D, DeMichele A. Morbidity and mortality of colorectal carcinoma surgery differs by insurance status. Cancer 2004;101:2187–2194.
34. Boxer LK, Dimick JB, Wainess RM, et al. Payer status is related to differences in access and outcomes of abdominal aortic aneurysm repair in the United States. Surgery 2003;134:142–145.
35. Braveman P, Schaaf VM, Egerter S, Bennett T, Schecter W. Insurance-related differences in the risk of ruptured appendix. N Engl J Med 1994;331:444–449.
36. Anderson S, Nevins CL, Green LK, El-Zimaity H, Anand BS. Assessment of liver histology in chronic alcoholics with and without hepatitis C virus infection. Dig Dis Sci 2001;46:1393–1398.

37. Gao B. Interaction of alcohol and hepatitis viral proteins: implications in synergistic effect of alcohol drinking and viral hepatitis on liver injury. Alcohol 2002;27:69–72.
38. Farges O, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg 1999;229:210–221.
39. Eguchi H, Umeshita K, Sakon M, et al. Presence of active hepatitis associated with liver cirrhosis is a risk factor for mortality caused by posthepatectomy liver failure. Dig Dis Sci 2000;45:1383–1388.
40. Yoo HY, Thuluvath PJ. Outcome of liver transplantation in adult recipients: influence of neighborhood income, education, and insurance. Liver Transpl 2004;10:235–243.

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Temporal Trends in Early Clinical Outcomes and Health Care Resource Utilization for Liver Transplantation in the United States

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Abstract
Introduction Procedures such as liver transplantation, which entail large costs while benefiting only a small percentage of the population, are being increasingly scrutinized by third-party payors. The purpose of our study was to conduct a longitudinal analysis of the early clinical outcomes and health care resource utilization for liver transplantation in the United States.
Methods The Nationwide Inpatient Sample database was used to conduct a longitudinal analysis of the clinical outcome and resource utilization data for liver transplantation procedures in adult recipients performed in the United States over three time periods (Period I: 1988–1993; Period II: 1994–1998: Period III: 1999–2003).
Results Compared to Period I, adult liver transplant recipients were more likely to be male, older, and non-White in Period III. Recipients were more likely to have at least one major comorbidity preoperatively than in Period I. The in-hospital mortality rate after liver transplantation decreased significantly from Period I to Period III, but the major intraoperative and postoperative complication rates increased over the same time period. Mean length of hospital stay decreased over the 15-year period, but the percentage of patients with a non-routine discharge status increased.
Conclusion Our findings indicate that the rate of postoperative complications and non-routine discharges after liver transplantation is increasing. However, these negative changes in the cost–outcomes relationship for liver transplantation are balanced by improving postoperative survival rates and reductions in the length of hospital stay.

Keywords Liver transplantation · Outcome assessment · Longitudinal analysis · Health care resource utilization

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Introduction

Orthotopic liver transplantation is one of the costliest medical procedures available in the United States, ostensibly providing potential benefit to just a small percentage of the nation's population.[1] Because of this discrepancy between degree of health care resource utilization and extent of social utility, there has been significant pressure by both private and public health care payors to justify the continued widespread availability of liver transplantation.[2] The most effective way to provide such justification would be to show that the cost–outcome relationship in liver

transplantation is being maximized, meaning that the clinical outcomes after the procedure are improving, whereas the costs associated with the procedure are decreasing. Considerable effort has been devoted by the scientific community to improving clinical outcomes after liver transplantation. Similarly, a number of investigators have sought to determine the cost components of the procedure in an effort to identify areas of economic excess or inefficiency. [3–18] To our knowledge, however, no study has yet been published, which examines the longitudinal relationship between the level of health care resource utilization for liver transplantation procedures and the clinical outcomes of these procedures. The objective of our study was, therefore, to assess the trends in the relationship between early clinical outcomes and health care resource utilization for liver transplantation in the United States over the past 15 years.

Methods

Database Description

The Nationwide Inpatient Sample (NIS) databases for the years 1988 thorough 2003 were used for our study.[19] The NIS is a part of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest all-payor inpatient care database that is publicly available in the United States and contains approximately 5 to 8 million records of inpatient stays per year from about 1,000 hospitals, which represent a 20% stratified sample of community hospitals in the United States.[20] To ensure maximal representation of the US hospitals, the following sampling strata, based on five important hospital characteristics, were used for the creation of the NIS: geographic region (Northeast, North Central, West, and South), ownership (public, private not for profit, and private investor-owned), location (urban and rural), teaching status (teaching hospital and nonteaching hospital), and bed size (small, medium, and large).

NIS data sets provide the following information: a unique patient visit identifier, patient demographics, and procedure and diagnostic codes classified according to the *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM).[21] The HCUP has assigned validation and quality assessment of these data sets to an independent contractor.[22] The validation was performed by reviewing univariate statistics for all numeric data elements, determining the frequency distributions for all categorical and some continuous data elements, checking ranges against standard norms, and performing edit checks that identify inconsistencies between related data elements. The NIS has also been extensively validated against the National Hospital Discharge Survey and confirmed to perform very well for many estimates.[23]

Sample Selection

Records with valid ICD-9-CM procedure code 50.50 for liver transplant were extracted from the NIS data sets for the years 1998 to 2003. Each record in the data sets represented a single-patient encounter and has a unique identification number. Patients with a secondary procedure code of pancreatic transplant (52.80) or kidney transplant (55.60) were excluded from the analysis to impart homogeneity to our study population. To confine our study to adult transplant recipients only, we also excluded patients who were under 18 years of age. There were a total of 8,054 liver transplant procedures that were captured by the NIS from 1988 to 2003 after these exclusion criteria were applied.

Outcome Measures

The outcome variables of interest were as follows: (1) age, (2) race, (3) sex, (4) comorbidity index (the Charlson Index [24] as modified by Deyo et al.[25] measures comorbidity by assigning a score of 1, 2, 3, or 6 to each of the comorbid conditions present in a patient; these scores are then added to a single index score, which measured the overall comorbidity of the patient), (5) length of hospital stay, (6) percentage of patient discharges that were non-routine (i.e., the patient was discharged to a nursing home, rehabilitation facility, or intermediate care facility rather than to home), (7) in-hospital postoperative mortality, (8) major intraoperative complications, and (9) major postoperative complications. The major intraoperative and postoperative complications were identified using ICD-9-CM diagnostic code. We included any complication contained within the ICD-9-CM that might significantly affect the early perioperative outcome of liver transplant patients. The major intraoperative complications assessed included injury to adjacent structures (998.2), retained foreign body (998.4), and hemorrhage complicating a procedure (998.11).

Major postoperative complications that were assessed included primary liver allograft nonfunction or hyperacute rejection (996.8), septic or hypovolemic shock (998.0), mechanical wound disruption (998.3), postoperative infection including intra-abdominal abscesses, wound infection, or septicemia (998.5), systemic inflammatory release syndrome (995.9), hepatic arterial thrombosis (444.9), portal vein thrombosis (452), complications of biliary anastomosis (997.4), pneumonia (997.3), pulmonary embolism (415.1), adult respiratory distress syndrome (518.5), pulmonary edema (518.4), acute respiratory failure (518.81), myocardial ischemia (410), heart failure (428), acute renal failure (639.3), and gastrointestinal (GI) bleed

(578.9). Because the ICD-9-CM coding system does not include transplant-specific codes for many of the postoperative variables that are of particular interest, the best available ICD codes were used. For example, to identify any reported hepatic arterial thromboses, the code for "thrombosis of unspecified artery" was used. The decision as to which major complications to track was made based on both ICD code availability, and on the likely potential impact that such complications would have on health care resource utilization.

Primary Predictor Variables

The primary predictor variable was year of transplantation. The study period of 15 years from 1988 through 2003, was divided into three different time periods: Period I=1988-1993, Period II=1994-1998, Period III=1999-2003. We selected these time periods at random and without specific consideration to advances in immunosuppression therapy or organ allocation policies.

Covariates

Age, sex, race, and comorbidity index for each patient were used as confounders in the logistic regression models of non-demographic outcome variables. To assess the impact of the missing values for the variable race (2,111, 26.2%), logistic regressions were performed separately with and without race as a confounder. The results were then compared for consistency.

Statistical Analysis

Bivariate analyses were performed to assess the unadjusted association between the time period of transplantation and the respective outcome variables. Multivariable regression analyses were used to examine the risk-adjusted associations between time period of transplantation and the non-demographic outcome variables. All multivariable analyses were adjusted for the following potential confounders: age, race, and patient comorbidity. Multivariable regression analyses allow the assessment of the risk-adjusted (independent of other potential confounders) impact of the time period of transplantation on the outcomes. Differences between the potential confounders are thus decreased using this method. Risk-adjusted odds ratios with 95% confidence intervals (CI) and p values were used to assess the strength of the association between year of transplantation and outcomes. Adjusted estimates were calculated for length of stay using liner regression.

Statistical analyses were conducted using Intercooled STATA for Windows (version 7.0) (Stata Corporation, College Station, TX) and SAS for Windows (version 8.02) (SAS Institute, Cary, NC).

Results

Table 1 displays the temporal trends in demographic variables for patients undergoing orthotopic liver transplantation in the United States from 1988 to 2003. The mean age of transplant recipients has increased significantly from Period I to Period III. The percentage of adult recipients under the age of 43 years has decreased 51.23% ($p<0.001$), whereas the percentage of recipients who are greater than or equal to 57 years of age has increased by 15% ($p=0.006$). A larger proportion of adult recipients are of male gender (55.07% in Period I versus 64.36% in Period III, $p<0.001$), and the racial mix of the recipient population has diversified over time, with significantly lower proportion

Table 1 Temporal Trends in Demographic Characteristics of Patients Undergoing Orthotopic Liver Transplantation in the United States From 1988 to 2003

Demographic Variable		Period I 1988–1993 (n=1,834) (%)	Period II 1994–1998 (n=2,488) (%)	Period III 1999–2003 (n=3,732) (%)	Δ from I to III (%)	P Value
Age (years)	18–42	34.90	26.49	17.02	−51.23	<0.001
	43–49	20.34	26.05	24.57	+20.80	0.001
	50–56	19.52	22.75	29.37	+50.46	<0.001
	≥ 57	25.25	24.72	29.05	+15.05	0.006
Gender	Male	55.07	60.61	64.36	+16.87	<0.001
	Female	44.93	39.39	35.64	−20.68	<0.001
Race	White	82.55	77.51	71.75	−13.08	<0.001
	Black	5.94	6.92	5.55	−6.56	0.318
	Hispanic	5.58	10.26	13.73	+146.1	<0.001
	Other	5.94	5.31	8.96	+50.84	0.012
Charlson Score	0	14.39	8.56	9.86	−31.48	0.036
	1	32.17	29.42	32.32	+0.47	0.917
	>1	53.44	62.02	57.82	+8.20	0.118

of Caucasians making up the recipient population and a significantly higher proportion of Hispanics and patients with race designated as "other." The proportion of the recipients who are black has not changed over time, remaining at approximately 5% of the total recipient population.

The in-hospital postoperative mortality and major morbidity rates are shown in Table 2. The in-hospital mortality rate after liver transplantation has decreased significantly from 16.09% in Period I to 7.58% in Period III ($p<0.001$). The major intraoperative and postoperative complication rates, however, have increased significantly from Period I to Period III, although most of this change appears to have occurred between Periods I and II, with the major complication rates between Periods II and III appearing relatively stable.

Table 2 also shows the changes in perioperative length of hospital stay. Length of stay decreased significantly from Period I to Period III, with mean length of stay in the latter period being approximately half the number of days as during the earlier period (15.74 days in Period III versus 29.06 days in Period I, $p<0.001$). The percentage of patients who were discharged postoperatively to a facility other than home (i.e., nonroutine discharge status) increased significantly from Period I (14.56%) to Period III (32.37%, $p<0.001$).

Discussion

In the present study, we conducted an analysis of all liver transplant procedures captured by the Nationwide Inpatient Samples (NIS) database from 1988 through 2003. The NIS is the largest all-payor inpatient database publicly available in the United States. Use of the NIS permits the longitudinal analysis of both clinical outcomes and level of health care resource utilization using the same data source. From a demographic perspective, we have found that the mean age of the adult liver transplant recipients has increased significantly over time, with the greatest increase occurring in the 50–56-year-old age group. We have also found a trend toward sicker adult recipients, with the percentage of patients with few comorbidities (as represented by a Charlson index of zero) decreasing significantly from Period I to Period III. Thus, we conclude that the typical adult liver recipient in the United States has become progressively older and has more comorbid conditions.

We also found that the in-hospital mortality rate after liver transplantation has decreased by approximately 50% over the past 15 years, decreasing from 16.09% in Period I (1988–1993) to 7.58% in Period III (1999–2003, $p<0.001$). Over the same time period, however, we found that the rate of major intraoperative and postoperative complications has increased significantly. We interpret these results to indicate that, whereas more patients are surviving the initial postoperative period after liver transplantation, those patients are experiencing a higher incidence of major complications.

We have also shown in this study that the mean length of hospitalization for a patient undergoing liver transplantation has decreased significantly over the past 15 years, from a mean of 29.1 days in Period I to a mean of 15.7 days in Period III. Over the same time period, however, the percentage of patients who are discharged postoperatively to an intermediate care facility rather than to home has increased significantly, from 14.6% of patients in Period I to 32.4% of patients in Period III. Thus, whereas the average length of hospital stay for patients undergoing liver transplantation has been reduced by almost half, the percentage of patients who are requiring rehabilitative or skilled nursing care upon discharge has approximately doubled. Taken together, these results suggest that, whereas the costs associated with postoperative complications and non-hospital postoperative care may be increasing as more patients survive liver transplantation, such cost increases have been balanced by both reductions in early postoperative mortality as well as costs associated with perioperative hospitalization for liver transplantation. Thus, although the overall costs associated with liver transplan-

Table 2 Temporal Trends in In-hospital Mortality, Major Morbidity Rates, and Resource Utilization after Liver Transplantation in the United States From 1988 to 2003

Outcome	Period I 1988–1993 (n=1,834)	Period II 1994–1998 (n=2,488) (%)	Period III 1999–2003 (n=3,732) (%)	Δ From I to III	P Value
In-Hospital Mortality Rate	16.09%	9.32%	7.58%	−52.89%	<0.001
Major Intraoperative Complication Rate	1.42%	6.43%	7.61%	+435.9%	<0.001
Major Postoperative Complication Rate	15.10%	24.60%	23.93%	58.48%	<0.001
Length of Hospital Stay in Days (Standard Deviation)	29.06 (2.29)	19.26 (2.25)	15.74 (2.22)	−45.84%	<0.001
Percentage of Patients with Non Routine Discharge Status	14.56%	25.88%	32.37%	+122.3%	<0.001

tation may not be decreasing, the reason appears to be that more patients are surviving the procedure and being discharged from the hospital postoperatively.

Several other groups have analyzed temporal changes in clinical outcomes associated with liver transplantation, reporting findings that are similar to ours. The two centers in the United States with the largest experiences in this procedure have recently published their cumulative results. In an analysis of 4,000 liver transplant procedures at the University of Pittsburgh, Jain et al reported significant improvement over the past two decades in patient survival after liver transplantation.[26] In 2005, Busuttil and colleagues at the University of California at Los Angeles (UCLA) published a retrospective analysis of 3,200 consecutive liver transplantations performed at their center.[27] In this analysis, they divided the procedures into two groups: those performed from 1984 through 1991 (Era I) and those performed from 1992 through 2001 (Era II).

They found that patient survival rates were significantly greater in Era II than in Era I despite the fact that the mean recipient age, the number of transplantations that were performed urgently, and the mean donor age were all greater in the later Era. These investigators concluded that survival after liver transplantation has increased significantly over the past two decades, despite an older and more challenging donor and recipient population. This same group also found that the incidence of both biliary and infectious complications after liver transplantation has increased in the more recent era of liver transplantation, mirroring our finding of increased major postoperative complication rates over time. Finally, a recent report of the national Organ Procurement and Transplantation Network also appears to validate our outcome findings by showing improved recipient survival rates over the past 10 years of liver transplantation despite an increase in the incidence of renal dysfunction after transplantation.[28] The most recent 2005 report of the OPTN further validates our study with respect to temporal trends in the male/female ratio, age distribution, and ethnic profile of adult liver transplant recipients.[29]

There are only a few studies published that address the temporal trends in the length of hospitalization after liver transplantation. This and other resource utilization variables are not tracked by the national transplant database maintained by OPTN, and are not reported in the larger retrospective series of liver transplant procedures such as those from the University of Pittsburgh and UCLA. The only data that have been published on trends in resource use in liver transplantation come from single center experiences. In an analysis of 500 liver transplant recipients at the University of Alabama at Birmingham from 1989 to 1998, Eckhoff et al. compared resource use for that center's first 100 recipients against use for the most recent 100 recipients. They found that the median perioperative hospital stay decreased from 20.2 days for the early group of patients to 10.9 days for the later group. A temporal decrease in hospital charges was also reported in this study.[30]

Other centers also reported a decrease in the length of hospital stay for liver transplant recipients as their experience with the procedure has increased.[31–32] To our knowledge, no study has yet been published that examines the temporal trends in the postoperative discharge status of liver transplant recipients. In the present study, we show that, whereas the length of hospital stay associated with the procedure has decreased significantly over the past 15 years, the percentage of patients who are discharged to an intermediate care facility instead of home has more than doubled over the same time period. Thus, whereas patients are being discharged from the hospital sooner, an increasing percentage of those discharged patients are requiring rehabilitation or skilled nursing assistance. Potential reasons for this increase in nonroutine patient discharges is that patients are achieving medical stability sooner after the transplant procedure, but due to their deconditioned preoperative state and further deconditioning from the operation and its associated complications, they are requiring longer periods of nonacute rehabilitative services.[33]

The major limitations of our analysis are similar to those of any other study that relies on administrative data sources such as the NIS. For example, we were unable to assess more specific markers of healthcare resource utilization such as hospital charges or cost. Also, we were unable to track many of the complications that are relatively specific to organ allograft recipients, such as acute rejection or immunosuppressant toxicity, because these type of complications are not identified by specific ICD codes and therefore cannot be tracked using the NIS database. Furthermore, the reliability of our findings with respect to postoperative morbidity is necessarily dependent on the accuracy with which such data were reported to the NIS, which we did not independently verify. Additionally, we are unable to separate the index hospitalization into preoperative and postoperative periods. Thus, we have assumed but cannot prove that most of the major complications and the majority of hospital days that we report occur postoperatively instead of before the transplant procedure. Finally, our study includes only those deaths and major complications that occur during the index hospitalization. Commonly used outcome indicators for transplantation, such as 1-year patient and graft survival rates, cannot be tracked using the NIS database.

Despite these limitations, our use of the NIS database also lends some strength to our findings. Whereas we do not provide specific information about hospital charges or costs, we believe that our use of length of stay as a surrogate for health care resource utilization is valid. Investigators who

have itemized and ranked the different cost components have consistently identified the length of inpatient hospital stay as the largest single contributor to the cost of liver transplantation.[34–35] The national database of transplant procedures maintained by OPTN does not track early postoperative mortality rates, contains relatively little information on postoperative complication rates, and has no information at all available for postoperative health care resource utilization. As mentioned previously, large retrospective analyses from single centers have also failed to report resource utilization variables. Thus, to our knowledge, this study represents the only published longitudinal analysis of early clinical outcomes and health care resource utilization for liver transplantation on a national level and using a single database.

Conclusion

Whereas in-hospital mortality rates and the length of hospital stay have decreased for liver transplantation over the past 15 years, other markers of clinical outcomes and resource use, such as major postoperative complications and the percentage of nonrouting patient discharges, have increased over the same time period. Therefore, trends toward increased health care utilization for postoperative complications appear to be accompanied by improved perioperative survival and reductions in the length of hospitalization. Future attempts to improve the cost–outcomes relationship for liver transplantation might be focused on the prevention and management of postoperative complications. Such improvement will be necessary if the transplant community is to be able to continue to justify liver transplantation as a financially feasible treatment option for patients with end-stage liver disease or other indications for the procedure. To help correlate clinical outcomes with costs in the future, and to assist in identifying specific potential targets for cost reduction, national transplant databases such as that maintained by the OPTN should begin including variables that reflect health care resource utilization.

References

1. Evans RW, Manninen DL, Dong FB. An economic analysis of liver transplantation: costs, insurance coverage, and reimbursement. Gastroenterol Clin North Amer 1993;22(2): 451-473.
2. Englehardt HT. Shattuck Lecture – Allocating scarce medical resources and the availability of organ transplantation. New Engl J Med 1984;311(1): 66-71.
3. Filipponi F, Pisati R, Cavicchini G, et al. Cost and outcome analysis and cost determinants of liver transplantation in a European National Health Service hospital. Transplantaion 2003;75(10): 1731-1736.
4. Gilbert JR, Pascual M, Schoenfeld DA, et al. Evolving trends in liver transplantation: an outcome and charge analysis. Transplantation 1999;67(2): 246-253.
5. Kim WR, Therneau TM, Dickson ER, Evans RW. Preoperative predictors of resource utilization in liver transplantation. Clinical Transplants 1995:315-322.
6. Showstack J, Katz PP, Lake JR, et al. Resource utilization in liver transplantation. J Am Med Assoc 1999;281(15):1381-1386.
7. Markmann JF, Markmann JW, Markmann DA, et al. Preoperative factors associated with outcome and their impact on resources in 1148 consecutive primary liver transplants. Transplantation 2001; 72:1113-1122.
8. Brown RS, Lake JR, Ascher NL, Emond JC, Roberts JP. Predictors of the cost of liver transplantation. Liver Transpl Surg 1998;4:170-176.
9. Hosein Shokouh-Amiri M, Osama Gaber A, Bagous WA, et al. Choice of surgical technique influences perioperative outcomes in liver transplantation. Ann Surg 2000;231(6):814-823.
10. Kim WR, Badley AD, Wiesner RH, et al. The economic impact of cytomegalovirus infection after liver transplantation. Transplantation 2000;69(3):357-361.
11. Falagas ME, Arbo M, Ruthazer R, et al. Cytomegalovirus disease is associated with increased cost and hospital length of stay among orthotopic liver transplant recipients. Transplantation 1997; 63:1595.
12. Hollenbeak CS, Alfrey EJ, Souba WW. The effect of surgical site infections on outcomes and resource utilization after liver transplantation. Surgery 2001;130(2):388-395.
13. Brown RS, Ascher NL, Lake JR, et al. The impact of surgical complications after liver transplantation on resource utilization. Arch Surg 1997;132(10):1098-1103.
14. Spanier TB, Klein RD, Nasraway SA, et al. Multiple organ failure after liver transplantation. Crit Care Med 1995;23(3):466-473.
15. Quiroga M, Rodriguez MG, Montalvan C, et al. Trends in mechanical ventilation and immediate extubation after liver transplantation in a single center in Chile. Transplantation Proceedings 2004;36(6):1683-1684.
16. Hemming AW, Caltral MS, Greig PD, et al. A pharmacoeconomic analysis of neural without intravenous cyclosporine in liver transplantation in Canada. Clinical Transplantation 1998;12(5): 425-429.
17. Merion RM. Prostaglandins in liver transplantation. Adv Exper Med Biol 1997;433:13-18.
18. Lake JR, Gorman KJ, Esquivel CO, et al. The impact of immunosuppressive regimens on the cost of liver transplantation: results from the United States FK506 multicenter trial. Transplantation 1995;60:1089.
19. NIS Technical Documentation. Agency for Healthcare Research and Quality, Rockville, MD. Available from: URL: http://www.ahrq.gov/data/hcup/nis.htm. Accessed September 2005.
20. Overview of the HCUP Nationwide Inpatient Sample (NIS). Agency for Healthcare Research and Quality, Rockville, MD. Available from: URL: http://www.ahcpr.gov/data/hcup/nisdoc00/Overview_of_NIS_2000.pdf. Accessed September 2005.
21. International Classification of Diseases, Ninth Revision, Clinical Modification. Los Angeles: Practice Management Information Corporation, 2002.
22. HCUP quality control procedures. Agency for Healthcare Research and Quality, Rockville, MD. Available from: URL: http://www.ahrq.gov/data/hcup/sasddocu/techsupp2.pdf. Accessed September 2005.
23. Comparative Analysis of HCUP and NHDS Inpatient Discharge Data. Technical Supplement 13, NIS Release 5. Rockville, MD: Agency for Health Care Policy and Research. Available from: URL: http://www.ahrq.gov/data/hcup/niscomp.htm. Accessed September 2005.

24. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-383.
25. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-619.
26. Jain A, Reyes J, Kashyap R, et al. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg 2000;232(4):490-500.
27. Busuttil RW, Yersiz H, Hiatt JR, et al. Analysis of long-term outcomes of 3200 liver transplantation over two decades: a single-center experience. Ann Surg 2005;241:905-916.
28. Brown RS, Rush SH, Rosen HR, et al. Liver and intestine transplantation. Am J Transplant 2004;4(Suppl 9): 81-92.
29. Organ Procurement and Transplantation Network 2005 Annual Report, http://www.optn.org/AR2005, accessed March 4, 2006.
30. Eckhoff DE, McGuire BM, Young L, et al. Liver transplantation in the era of cost constraints. Southern Med J 2000;93(4):392-396.
31. Harrison DM, Stewart AS, Koneru B, Holman MJ. Reduction in hospital stay after liver transplantation. Transplantation Proceed 1996;28(2):896.
32. Payne JL, McCarty KR, Drougas JG, et al. Outcomes analysis for 50 liver recipients: the Vanderbilt experience. Am Surg 1996;62:320-325.
33. Cortazzo MH, Helkowski W, Pippin B, Boninger ML, Zafonte R. Acute inpatient rehabilitation of 55 patients after liver transplantation. Am J Physical Med Rehab 2005;84(11):880-884.
34. Oostenbrink JB, Kok ET, Verheol RM. A comparative study of resource use and costs of renal, liver, and heart transplantation. Transplant International 2005;18(4):437-443.
35. Kankaanpaa J. Cost-effectiveness of liver transplantation – How to apply the results in resource allocation. Preventive Medicine 1990;19:700.

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Conventional Predictors of Survival Poorly Predict and Significantly Underpredict Survival after H-graft Portacaval Shunts

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Abstract
Objective This study was undertaken to evaluate the ability to predict survival after 8 mm prosthetic H-graft portacaval shunts (HGPCS).
Methods Since 1988, 170 patients have been prospectively followed after HGPCS. Using preshunt data, predictors of survival after shunting [MELD Score, Emory Score, Child Pugh Score, Discriminant Function (DF), and Child Class] were determined and related to actual survival.
Results Child Class was: (a) 10%, (b) 28%, and (c) 62%. Actual 5- and 10-year survival by Child Class was: (a) 67% and 33%, (b) 49% and 16%, (c) 29% and 7%. Survival correlated with all predictors of survival ($p<0.01$ for each). Actual survival was better than predicted by MELD ($p<0.001$). By Multiple Variable Regression Analysis—Computed Model, explained variation in survival was greatest for Child Class (18%), followed by MELD (14%), with DF, Emory Score, and Child Pugh Score not significantly contributing.
Conclusions After HGPCS, actual survival is better than predicted by MELD. Child Class explains only a minor variation in survival, although it better explains survival than MELD, Emory Score, Child Pugh Score, or DF. Conventional predictors of survival poorly and underpredict survival after HGPCS and should be used with caution.

Keywords Portacaval shunt · Portal hypertension · H-Graft · MELD · Child pugh score

Introduction

Chronic liver failure or cirrhosis secondary to viral etiologies or alcoholism is common in the United States. Hepatitis C (HCV) infection is reaching epidemic proportions with up to 4 million Americans believed to be infected and 2.7 million chronically infected with HCV, excluding homeless and incarcerated populations.[1] Of those infected with the virus, 20% will develop cirrhosis. Alcohol abuse is pandemic in the United States, affecting up to 14 million Americans.[2,3] In autopsy studies, 10 to 15% of alcoholics have cirrhosis. Cirrhosis leads to portal hypertension as progressive distortion of hepatic architecture impedes portal blood flow through the liver. Portal hypertension can lead to a host of complications, such as variceal bleeding and ascites. Treatment of portal hypertension can require expensive hospital stays, estimated at $18,000 for each episode of care.[4,5] Cirrhosis with sequelae of portal hypertension is cured by orthotopic liver transplantation, but unfortunately, demand for liver transplants far outweighs supply, and a minority of patients with complicated cirrhosis meet the criteria for transplantation.

Alcoholic patients who present with complications of portal hypertension do not have the requisite abstinence record required by transplantation protocols. In addition, these patients may not have the socioeconomic buffer available to allow for orthotopic liver transplantation.

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Currently, it is estimated that 17,000 people in the United States are awaiting liver transplantation, while only 5,600 liver transplants were undertaken in 2003.[6] Given the limited applicability of hepatic transplantation, there remains a role for portal decompression to palliate portal hypertension.

There are many ways to achieve portal decompression. Transjugular intrahepatic portasystemic shunts (TIPS) is currently the approach most often applied. TIPS relative efficacy in palliating variceal bleeding due to portal hypertension was validated in a trial comparing TIPS to distal splenorenal shunts, but patients with splenorenal shunts had lower recurrence of variceal bleeding, encephalopathy, and shunt occlusion.[7] Small-diameter H-graft portacaval shunts (HGPCS) have been proven to be more durable, efficacious and provide better survival for patients than TIPS when studied in a randomized controlled study.[8] While studies support the relative roles for various shunting procedures, application of shunting, and thereby, the various shunting procedures, is often based on models that predict survival. Several predominate models are widely used such as Child Class and Child-Pugh Score, but have been criticized for use of subjective criteria or factors which allow for tremendous variability.[9–11] While these scoring systems and classifications were designed to predict survival after generic portal venous decompression, the model for end-stage liver disease (MELD) and the Emory Score were specifically designed to predict survival after TIPS.[12] These scoring systems and classifications have not been comparatively studied for their relative ability to predict outcome after operative portal decompression. The objective of this study was to evaluate the ability to predict survival after H-graft portacaval shunt (HGPCS) for portal hypertension using five different models—MELD, Child Class, Child-Pugh Score, Emory Score, and Discriminant Function. Our hypothesis was that conventional predictors of liver function would, to varying degrees, accurately predict survival after H-graft portacaval shunts.

Materials and Methods

Since 1988, 170 patients have been prospectively followed after HGPCS. This population includes patients with cirrhosis, portal hypertension, and variceal hemorrhage. Shunting was undertaken as definitive therapy, never as a "bridge" to transplantation. Using preshunt data, predictors of survival after shunting (MELD Score, Emory Score, Child Pugh Score, Discriminant Function, and Child Class) were determined and related to actual survival.

Child classification parameters included serum bilirubin, albumin, encephalopathy, ascites, and nutrition.[13] Pugh modified the Child classification to include prothrombin time (PT) and cause of cirrhosis.[14] Through standard preoperative testing, both Child and Child-Pugh Score was calculated and assigned using the appropriate criteria. Encephalopathy and ascites were characterized as previously reported.[15] Briefly, encephalopathy was determined as none, mild (controlled at home with a protein-restricted diet and lactulose), or severe (hospital admissions required despite therapy). Ascites was graded as absent, moderate (clinically evident, but well controlled with fluid restriction and oral diuretics), or severe (abdominal distention refractory to fluid restriction and maximal diuretic therapy, often requiring large-volume paracentesis or placement of a peritoneovenous shunt).

MELD scores were calculated as follows: MELD score $= 3.8 \times \log_e(\text{total bilirubin, mg/dL}) + 11.2 \times \log_e(\text{INR}) + 9.6 \times \log_e(\text{creatinine, mg/dL})$. MELD score was used to predict survival by calculating a risk score $(S(t) = S_0(t)^{\exp(R-R_0)}$ where R_0 was the average risk score of the patient in the series.[12] Discriminant function was calculated as follows: Discriminant function (DF)=4.6×[patient's PT−control PT]+total bilirubin (mg/dL).[16]

The Emory Score was based on four parameters: bilirubin >3 mg/dL, ALT level >100 U/L, and presence of encephalopathy pre-shunt placement are weighed with one point; the need for emergency intervention is scored as two points. The sum of these points generates an individual risk score for each patient. Patients with four to five points are considered at high risk to die; those with one to three points at moderate risk, and those with zero points are at low risk of death.[17] Circumstances of shunting were defined as elective, urgent, (within 24 hours of patient presentation), or emergency (as soon as possible or within 8 hours of patient presentation).

Our technique in constructing a small diameter 8-mm prosthetic HGPCS has been previously described.[18] The prosthetic HGPCS is constructed from ring-enforced PTFE. Grafts are 3 cm from toe to toe and 1.5 cm from heel to heel. Portal vein pressures and inferior vena cava pressures are measured before and after shunting. Necessary components of a successful shunt include decrease in portal pressure of more than 10 mmHg, a decrease in portal vein to inferior vena cava pressure gradient of more than 10 mmHg, a post-shunt portal vein to inferior vena cava pressure gradient of less than 10 mmHg, and a thrill in the inferior vena cava cephalad to the shunt–cava anastomosis.[19] If necessary, a portion of the caudate lobe is excised to facilitate graft placement.

Shunt patency is confirmed before discharge from the hospital with a transfemoral cannulation of the shunt. Per protocol, after discharge, patients underwent transfemoral cannulation of their shunts at 1, 3, 5, and 10 years. In the event of onset of complications associated with cirrhosis, portal hypertension or varices, shunts are studied. Data are

Table 1 Demographic Data

Etiology of Cirrhosis	Percentage (%)
Ethanol	56
Hepatitis C	10
Ethanol + hepatitis C	11
Methotrexate	1
Cryptogenic	12
Other	9
Location of varices	
Esophageal	44
Gastric	10
Both	45
Timing of shunting	
Elective	72
Urgent	10
Emergent	18
Age: 54 years; median: 55±13	
Gender	
Male: 52 years, 53±13	68
Female: 60 years, 57±14	32

presented as median, mean ± standard deviation (SD) when appropriate. All data are stored in a file-based registry (Excel, Microsoft, Redmond, Washington). Comparisons were undertaken utilizing True Epistat (Epistat Services, Richardson, TX). Statistical significance is accepted with 95% confidence.

Results

One hundred and seventy patients underwent H-graft portacaval shunts. One hundred and fifteen (68%) were males and 55 were females (32%). Median age of patients undergoing H-graft portacaval shunts was 54 years (55±13) (Table 1). The majority of patients in this population developed cirrhosis secondary to alcohol abuse (67%). The etiology of cirrhosis in the remainder of the population was hepatitis C (21%), methotrexate, autoimmune, hepatitis B, hemochromotosis, and cryptogenic (Table 1). Seventy-five patients (44%) had esophageal varices, 77 patients (45%) had a combination of both gastric and esophageal varices, and the remaining 18 patients (11%) had gastric varices alone. (Table 1). One hundred and twenty-three (72%) of the patients underwent elective H-graft portacaval shunts, with 17 patients (10%) undergoing urgent procedures and the remaining 30 (18%) requiring emergency decompression (Table 1).

Preshunt scores were determined, preoperatively. One-hundred and six (62%) of the patients undergoing small-diameter H-graft portacaval shunt were Child class C, 47 (28%) were of Child class B, and 17 (10%) were of Child class A. Median Child-Pugh Score was 8 (8.2±2.2). Median MELD score was 13 (14±5.5). Median Emory Score was 0 (0.7±1.1). Median Discriminant Function was calculated to be 68, 70±10.4. Overall survival of this population is shown in Fig. 1. Actual 5- and 10-year

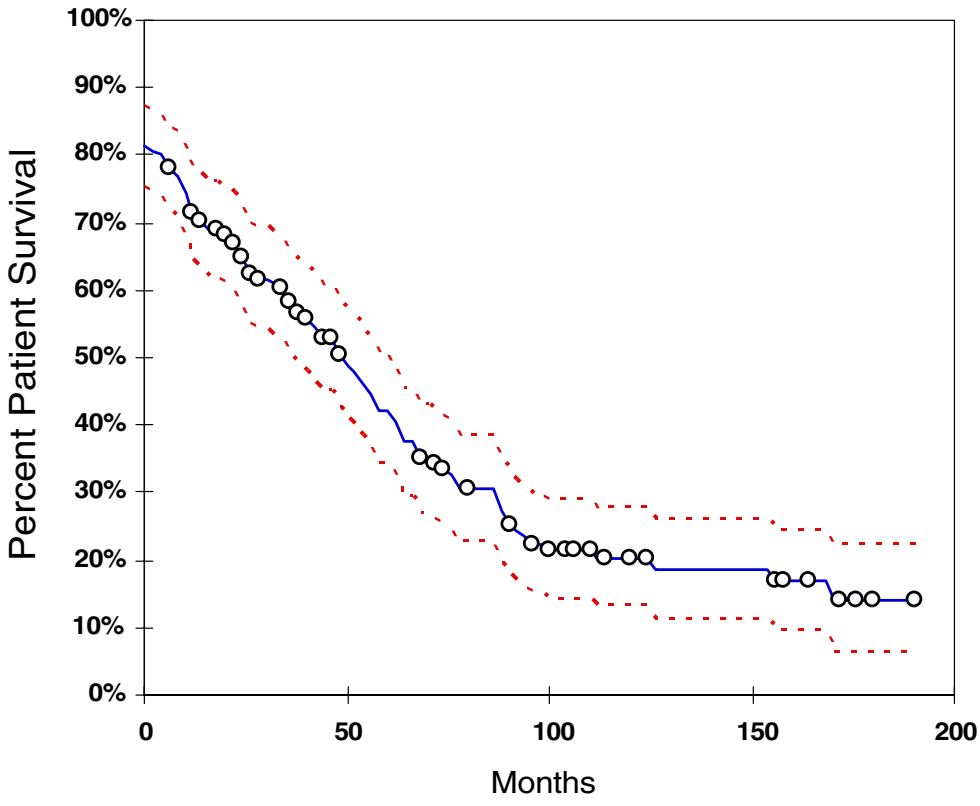

Figure 1 Actual survival after HGPCS.

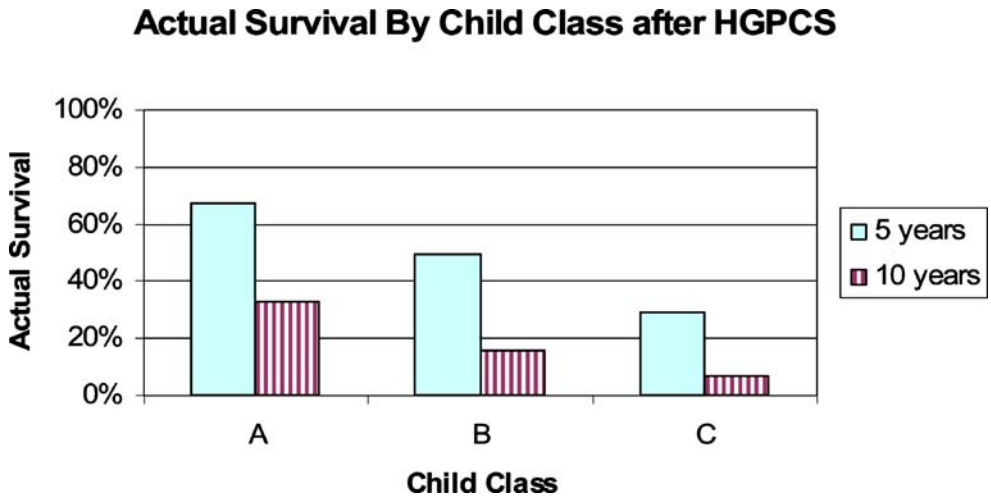

Figure 2 Actual survival by Child Class after HGPCS.

survival by Child Class was: (a) 67% and 33%, (b) 49% and 16%, and (c) 29% and 7% (Fig. 2). By regression analysis, survival correlated with all predictors of survival ($p<0.01$ for each). Actual survival was better than predicted by MELD [$p<0.001$, Mantel–Haenszel chi-square (Fig. 3)]. By Multiple Variable Regression Analysis—Computed Model, explained variation in survival was greatest for Child Class (18%), followed by MELD (14%), with DF, Emory Score and Child-Pugh Score not significantly contributing.

Discussion

Cirrhosis is a major public health problem in the United States. It is believed that 20% of patients infected with HCV will progress to cirrhosis, although the mean time to clinical presentation might be 20 years.[20] Similarly, of the more than 15 million alcoholics in the United States, 20% are expected to progress to alcohol-induced liver injury. Liver transplantation is the only curative treatment for cirrhosis with other therapies, such as shunting, providing only palliation. Unfortunately, static numbers of donor livers, relative costs, and lack of access to facilities with liver transplantation programs makes curative surgical treatment often unrealistic. Furthermore, in the majority of patients with cirrhosis, transplantation may not be necessary or may not be a viable option for a host of reasons. Small diameter H-graft portacaval shunts provide a first-line option for long-term palliative therapy for variceal bleeding. This makes predicting survival after operative portal decompression for portal hypertension all the more critical. Herein, we have studied a relatively large, modern population of cirrhotic patients undergoing small-diameter H-graft portacaval shunts and applied prognostic models to their actual survival after shunting to allow, for the first time, a comparison of a broad range of predictors of survival after shunting.

We followed 170 patients who underwent an increasingly rare operation, a small-diameter H-graft prosthetic portacaval shunt. Most patients were middle-aged males with cirrhosis due to alcohol abuse often complicated by HCV. A large minority of patients were infected with HCV. Most patients underwent small-diameter H-graft portacaval

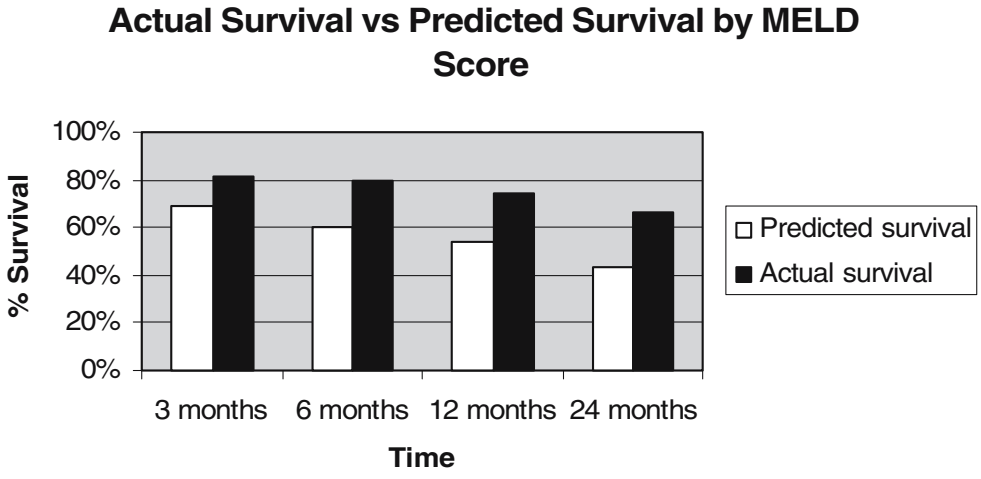

Figure 3 All were superior to predicted survival, Mantel–Haenszel chi-square, $p<0.001$.

shunt as an elective procedure, but almost equal numbers underwent urgent and emergency portal decompression.

More than 40 years ago, Dr. C. Gardner Child, with Dr. Jeremiah Turcotte, proposed a classification that would stratify patients before shunting by probability of survival after shunting. To improve the ability of this classification to predict survival after shunting, Pugh modified this classification (i.e., the Child-Pugh Score). The Child-Pugh score has been criticized for various reasons. One of the criticisms is that it has a limited discriminatory ability.[21] In other words, use of laboratory cutoff points for criteria may be artificial and deceptive. In addition, clinicians are unable to appropriately evaluate patients with markedly deviated laboratory values. For example, the cirrhotic patient with the bilirubin of 3 mg/dL receives the same number of points as the patient with the bilirubin of 30 mg/dL. Certainly, in our patients, large volume transfusion transiently elevated serum bilirubin, thereby, probably transiently skewing the accuracy of the classification systems that utilize the value. Others who criticize the Child-Pugh score note that all the parameters receive the same weight. Finally, the subjective nature of determining the degree of ascites or encephalopathy has also been disputed.[21]

Because of dissatisfaction with the Child-Pugh Score, the Emory classification and the Discriminant Function were developed. The relative abilities of these "systems" to predict outcome after shunting has not previously been studied. Based on this study, those other "systems" add nothing beyond the Child classification's ability to predict survival. The Mayo clinic developed the model for end-stage liver disease (MELD scoring system) to predict survival after TIPS. It is now widely used to predict survival in a diverse population of patients with chronic liver disease not undergoing TIPS.[12,21] Because of problems with TIPS stent patency, MELD is generally not utilized to predict survival beyond 2 years after shunting. In this study, actual survival was better than predicted by MELD. The MELD score, widely utilized as an indicator of severity of liver disease, did not fare so well in this study. At 2 years, actual survival after small-diameter H-graft portacaval shunt was 50% better than predicted by the MELD score. The "conventional" predictor of survival that best predicted survival after shunting was the oldest—the Child classification.

Understanding prognostic models is important for physicians caring for cirrhotic patients. Monitoring the course and outcome of patients after an intervention is essential for clinicians to assess the influence of a given therapy and make adjustments for future practice. With significant segments of the population having cirrhosis with no meaningful opportunity for liver transplant, undergoing a surgical shunt should be an option for extending the cirrhotic patient's survival, improving quality of life, and conserving resources. As we found in this study, after small-diameter H-graft portacaval shunt, actual survival is better than predicted by MELD. Child class explains only a minor variation in survival, although it better predicts survival than MELD, Emory Score, Child Pugh Score, or Discriminant Function. Conventional predictors of survival poorly, and in the case of MELD, significantly, underpredict survival after small-diameter H-graft portacaval shunts and should be used with caution.

Conclusion

Cirrhosis will continue to be a matter of public health urgency because of rising numbers of patients infected with hepatitis C and prevalence of alcoholism. Surgical palliation, specifically shunting, for portal hypertension provides an opportunity to extend survival in these patients. Surgical shunts are unfortunately marginalized because of the popularity of TIPS. We continue to propose that the popularity of TIPS is not supported through controlled trials. Patients with complicated portal hypertension seem well palliated with operative shunting, yet current models of survival underpredict actual survival.

References

1. National Center for Infectious Diseases. Center for Disease Control. Available at http://www.cdc.gov.
2. National Institute on Alcohol Abuse and Alcoholism. Tenth Special Report to the US Congress on Alcohol and Health. Rockville, MD: DHHS Publication, 2000.
3. Grant BF, Harford TC, Dawson DA, Chou P, DuFour M, Pickering R. Prevalence of DSM-IV alcohol abuse and dependence: United States 1992. Epidemiologic Bulletin No 35. Alcohol Health Res World 1994;18(3):243–248.
4. Talwalkar JA, Kamath PS. Influence of recent advances in medical management on clinical outcomes of cirrhosis. Mayo Clin Proc 2005;80:1501–1508.
5. Agency for Healthcare Research and Quality. HCUPnet: heathcare cost and utilization project (HCUP). Available at http://www.ahrq.gov/data/hcup.
6. Coombes JM, Trotter JF. Development of the allocation system for deceased donor liver transplantation. Clin Med Research 2005;3:287–292.
7. Khaitiyar JS, Luthra SK, Prasad N, Ratnakar N, Daruwala DK. TIPS versus distal splenorenal shunt—a comparative study. Hepatogastroenterology 2000;47:492–497.
8. Rosemurgy AS, Bloomston M, Clark WC, Thometz DP, Zervos EE. H-graft portacaval shunts versus TIPS: Ten-year follow up of a randomized trial with comparison to predicted survivals. Ann Surg 2005;241:238–246.
9. Christensen E. Prognostic models in chronic liver disease: validity, usefulness and future roles. J Hepatol 1997;26:1414–1424.
10. Christensen E. Prognostic models including the Child-Pugh, MELD, and Mayo risk scores—where are we and where should we go? J Hepatol 2004;41:344–350.

11. Cholongitas E, Papatheodoridis GV, Vangeli M, Ferreni N, Patch D, Bourroughs AK. Systematic review: The model for end-stage liver disease—should it replace Child-Pugh's classification for assessing prognosis in cirrhosis? Aliment Pharmacol Ther 2005;22:1079–1089.
12. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000;31:864–871.
13. Child CG, Turcotte JG. Surgery and portal hypertension. Major Probl Clin Surg 1964;1:1–85.
14. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of oesophagus for bleeding oesophageal varices. Br J Surg 1973;60:646–648.
15. Rosemurgy AS, Serafini FM, Zweibel BR, Black TJ, Kudryk BT, Nord, HJ, Goode SE. Transjugular intrahepatic portosystemic shunt versus small-diameter prosthetic H-graft portacaval shunt: extended follow-up of an expanded randomized prospective trial. J Gastrointest Surg 2000;4:589–597.
16. Maddrey W, Boitnott J, Bedine M, Weber FJ, Mezey E, White RJ. Corticosteroid therapy of alcoholic hepatitis. Gastroenterology 1978;75:193–199.
17. Chalasani N, Clark WS, Martin LG, Kamean J, Khan MA, Patel NH, Boyer TD. Determinants of mortality in patients with advanced cirrhosis after transjugular intrahepatic portosystemic shunting. Gastroenterology 2000;118:138–144.
18. Rosemurgy AS. Small-diameter interposition shunt. In Baker RJ, Fischer JE, eds. Mastery of Surgery, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001.
19. Rosemurgy AS, Zervos EE, Bloomston M, Durkin AJ, Clark WC, Goff S. Post-shunt resource consumption favors small-diameter prosthetic H-graft portacaval shunt over TIPS for patients with poor hepatic reserve. Ann Surg 2003;237:820–827.
20. Alter MJ. Epidemiology of acute and chronic hepatitis C. Clin Liver Dis 1997;1:559–568.
21. Kamath PS, Niesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464–470.

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Resistin-Like Molecule Alpha Reduces Gallbladder Optimal Tension

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Abstract
Introduction Insulin resistance is associated with increased gallbladder volume and impaired gallbladder emptying. Resistin and resistin-like molecule alpha (RELM-α) are adipose-derived hormones that are believed to mediate insulin resistance. Therefore, we tested the hypothesis that administration of resistin or RELM-α would cause insulin resistance and diminish gallbladder contractility.
Methods In two sequential studies 40 eight-week-old nondiabetic lean mice were fed a chow diet for 4 weeks. In Study A, 10 mice received 20 μg of resistin IP, while in Study B 10 mice received 20 μg of RELM-α IP for seven days. In each study, 10 control mice received an equal volume of saline IP for seven days. At 12 weeks animals were fasted and underwent cholecystectomy, and *in vitro* gallbladder response to neurotransmitters was determined. Serum resistin, RELM-α, glucose, and insulin levels were measured. HOMA index, a measure of insulin resistance, was calculated.
Results RELM-α significantly increased HOMA index. RELM-α decreased gallbladder optimal tension, but did not alter responses to neurotransmitters. Resistin had no effect on HOMA index or on gallbladder optimal tension or response.
Conclusion These data suggest that in nondiabetic lean mice: 1) resistin does not alter insulin resistance or gallbladder optimal tension, but 2) RELM-α increases insulin resistance and reduces gallbladder optimal tension. Therefore, we concluded that RELM-α may play a role in insulin-resistance mediated gallbladder dysmotility.

Keywords Resistin · Resistin-like molecule alpha · Insulin resistance · Optimal tension · Gallbladder motility

Introduction

Diabetes is a major health care problem in the United States, and 18.2 million Americans have this disorder of glucose metabolism.[1] The prevalence of diabetes has increased 61% since 1990, and diabetes has become the sixth leading cause of death of U.S citizens.[1,2] Diabetes is an established risk factor for cholesterol gallstone disease, and 30% of adults with diabetes develop cholelithiasis.[3–5] Recent animal and human data from our laboratory suggest that insulin resistance is associated with increased gallbladder volume and/or impaired gallbladder emptying.[6–10] In addition, gallbladders of diabetic patients have been shown to be enlarged with decreased emptying in response to a meal.[3,11]

Resistin is a member of a family of resistin-like molecules (RELMs), which were earlier discovered as the FIZZ gene family.[12] Resistin, also known as adipocyte-secreted factor and FIZZ3, is a cysteine-rich protein that is specifically expressed in white adipose tissue.[12] Some authorities believe that elevated plasma resistin levels in rodent models of obesity may be causative in the development of insulin resistance and that resistin may be a link between obesity and type II diabetes.[13–17] Initial studies

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have demonstrated that obesity induced by a high-fat diet or mutation of the leptin gene (ob/ob mice) or leptin receptor gene (db/db mice) is associated with elevated circulating resistin concentrations.[13] In keeping with this hypothesis, other studies have demonstrated that rosiglitazone, a PPARγ receptor agonist used clinically to improve insulin sensitivity, decreases insulin resistance and down-regulates resistin expression both *in vitro* and *in vivo*.[13]

RELM-α (or FIZZ1) is also a cysteine-rich secretory protein, which has a 29% homology with resistin and is expressed most abundantly in white adipose tissue.[12] RELM-α is also found in other tissues including heart, lung, and tongue.[18] In addition, we have shown that the administration of leptin to leptin-deficient mice upregulates RELM-α in the gallbladder (unpublished data). Therefore, we hypothesized that daily administration of resistin or RELM-α to lean nondiabetic mice would increase insulin resistance and cause gallbladder dysmotility.

Material and Methods

Animals and Diet

Study A Eight-week old C57BL/6J lean nondiabetic female mice (n=20) (Jackson Laboratory, Bar Harbor, ME) were housed five per cage in a light (6 A.M. to 6 P.M.) and temperature (22°C)-controlled room. These mice were fed a nonlithogenic chow diet (Ralston Purina, St. Louis, MO) for 5 weeks and were used for the resistin study. All animal protocols were approved by the Indiana University Institutional Animal Care and Use Committee (IACUC).

Study B Eight-week old C57BL/6J lean nondiabetic female mice (n=20) (Jackson Laboratory, Bar Harbor, ME) were housed five per cage in a light (6 A.M. to 6 P.M.) and temperature (22°C)-controlled room. These mice also were fed a nonlithogenic chow diet (Ralston Purina, St. Louis, MO) for 4 weeks and were used for the RELM-α study.

Resistin and RELM-α

Study A At 12 weeks, half of the mice (n=10) received daily intraperitoneal injections of 20 μg resistin (US Biological, Swampscott, MA) for 1 week. The remaining mice (n=10) received daily intraperitoneal injections of an equal volume of saline for 1 week.

Study B At 11 weeks, half of the mice (n=10) received daily intraperitoneal injections of 20 μg resistin-like molecule alpha (RELM-α) (US Biological, Swampscott, MA) for 1 week. The remaining mice (n=10) received daily intraperitoneal injections of an equal volume of saline for 1 week.

Tissue Procurement

At 13 and 12 weeks of age, mice from study A and study B, respectively, were fasted overnight with water allowed ad libitum. The mice were anesthetized with an isoflurane-soaked gauze placed in a 2,000-cm^3 glass jar and then received an intraperitoneal injection of xylazine (15 mg/kg) and ketamine (50 mg/kg). The animals then underwent laparotomy and cholecystectomy. Gallbladder bile was immediately aspirated with a 30-gauge needle and syringe. Whole blood was aspirated from the heart and centrifuged to isolate serum. Whole gallbladders were then placed in ice-cold modified Krebs solution consisting of the following in (mmol/L): NaCl, 116.6; $NaHCO_3$, 21.9; KH_2PO_4, 1.2; glucose, 5.4; $MgCl_2$, 1.2; KCl, 3.4; and $CaCl_2$, 2.5, that had been bubbled with 95% O_2/5% CO_2 for 30 min.

Serum Analysis

Whole blood was spun at 15,000 rpm for 5 min to separate serum. Serum glucose was determined by the quantitative colorimetric method using the Glucose Liquicolor Kit (StanBio Laboratory, Boerne, TX). Serum insulin was determined by ELISA, using the Ultra Sensitive Rat Insulin ELISA Kit (Crystal Chem. Inc., Downers Grove, IL). HOMA Index, a measure of insulin resistance, (fasting serum glucose × fasting serum insulin/22.5) was then calculated.[19,20] In study A, serum resistin levels were determined by ELISA using mouse resistin immunoassay kit (R&D, Minneapolis, MN). In study B, serum was pooled, and RELM-α was determined by using a semi-quantitative western blot method.

In Vitro Muscle Bath

Gallbladders were sutured at both ends with 7-0 polypropylene sutures and suspended longitudinally in 3-ml muscle bath chambers filled with modified Krebs' solution, warmed to 38°C, and oxygenated with 95% O_2/5% CO_2 carboxygen mix. Gallbladders were allowed to equilibrate at 0.025 g tension. Optimal length was then determined by stimulation with 10^{-5} mol/L acetylcholine (ACh) (Sigma Chemical, St. Louis, MO) at 0.025 g increases until maximal gallbladder contraction was obtained. The tension that produces the maximum net response is the optimal tension. Optimal length is the length of the gallbladder at the optimal tension. Gallbladders were maintained at their optimal lengths while neuropeptide Y (NPY) (Sigma Chemical) at 10^{-8}, 10^{-7}, and 10^{-6} mol/L doses and cholecystokinin (CCK) (Sigma Chemical) at 10^{-10}, 10^{-9}, 10^{-8},

Table 1 Results of Study A Serum Data

	Resistin (ng/ml)	Glucose (mg/dl)	Insulin (ng/ml)	HOMA Index
Saline group	35±3	140±19	0.08±0.02	0.7±0.2
Resistin group	115±25*	145±22	0.08±0.01	0.6±0.1

Values are the mean±SEM. *P* value was determined by Student's *t* test.
*$P<0.01$ versus saline.

and 10^{-7} mol/L doses were sequentially added to the muscle bath. Responses were measured with WinDaq/Ex (Dataq Instruments, Akron, OH) computer software. Gallbladders were rinsed with modified Krebs' solution every 15 min and after every neurotransmitter dose. Gallbladder lengths and weights were measured and used to calculate the cross-sectional area. Gallbladder contractile responses were then expressed as Newtons per centimeter squared (N/cm^2).

Statistical Analysis

Statistical analyses were performed using Sigma Stat Statistical Software (Jandel Corp., San Rafael, CA). All data are expressed as mean ± SEM. Differences in body weight, serum analyses, HOMA index, and muscle bath data were tested for statistical significance by Student's unpaired *t* test. A *p* value of less than 0.05 was considered statistically significant.

Results

Study A Data

1. Age and Body Weight

The ages of the animals at the time of surgery did not differ between the resistin injected group and the saline group (13.5±0.1 vs. 13.5±0.1 weeks). No significant difference was observed in body weight between the two groups (16.4±0.4 vs. 16.4±0.4 g, $p=0.98$).

2. Serum Resistin, Glucose, Insulin, and HOMA Index

Serum resistin, fasting serum glucose, fasting serum insulin, and HOMA Index are shown in Table 1. Serum resistin level was significantly higher ($p<0.02$) in the resistin-injected group. However, no significant difference in serum glucose, insulin, or HOMA Index was observed between the two groups.

3. Muscle Bath

Gallbladder weight, volume, optimal tension, optimal length, and gallbladder response to ACh, NPY, and CCK are shown in Table 2. No significant difference was observed in any of the gallbladder measurements.

Study B Data

1. Age and Body Weight

The ages of the animals at the time of surgery did not differ between the RELM-α-injected group and the saline group (12.3±0.05 vs. 12.2±0.03 weeks). No significant difference was observed in body weight between the two groups (16.5±0.3 vs. 16.4±0.3 g, $p=0.76$).

2. Serum RELM-α, Glucose, Insulin, and HOMA Index

Serum RELM-α level was only detected in the RELM-α injected group (374 ng/ml). Fasting serum glucose, fasting serum insulin, and HOMA Index are shown in Table 3. Fasting serum glucose and insulin were higher in the RELM-α group, but these differences did not reach statistical significance. However, HOMA Index, a measure of insulin resistance, was significantly higher ($p<0.02$) in the RELM-α group (Fig. 1).

3. Muscle Bath

Gallbladder weight, volume, optimal tension, optimal length, and gallbladder response to ACh, NPY, and CCK are shown in Table 4. No significant differences were observed in gallbladder weight, volume, and optimal length. However, optimal tension was significantly lower ($p<0.02$) in the RELM-α-injected group (Fig. 1). However,

Table 2 Results of Study A Gallbladder Data

	GB weight (mg)	GB bile volume (μl)	Optimal length (mm)	Optimal tension (mg)	Acetylcholine 10^{-5} M (N/cm^2)	NPY 10^{-8} M (N/cm^2)	NPY 10^{-7} M (N/cm^2)	NPY 10^{-6} M (N/cm^2)	CCK 10^{-10} M (N/cm^2)	CCK 10^{-9} M (N/cm^2)	CCK 10^{-8} M (N/cm^2)	CCK 10^{-7} M (N/cm^2)
Saline	1.5±0.1	8.1±2	6.1±0.3	115±10	0.6±0.1	0.2±0.1	0.4±0.0	0.4±0.1	0.6±0.1	1.0±0.1	1.3±0.2	1.3±0.1
Resistin	1.6±0.1	10.5±1	5.8±0.4	135±12	0.6±0.1	0.2±0.1	0.2±0.1	0.4±0.1	0.6±0.1	1.0±0.2	1.2±0.2	1.2±0.2

Values are the mean ± SEM. *P* value was determined by Student's *t* test.
CCK = cholecystokinin, NPY = neuropetide Y.

Table 3 Results of Study B Serum Data

Group	RELM-α (ng/ml)	Glucose (mg/dl)	Insulin (ng/ml)	HOMA Index
Saline group	Undetectable	113±11	0.16±0.03	0.1±0.2
RELM-α group	374	148±19	0.20±0.03	1.8±0.3*

Values are the mean ± SEM. *P* value was determined by Student's *t* test.
*$P<0.02$ versus saline.

no difference was observed in gallbladder response to neurotransmitters between the two groups.

Discussion

In study A, 20 C57BL/6J lean nondiabetic female mice were fed a chow diet for 5 weeks. Half of the mice were injected with 20 μg of resistin IP for 7 days, and the other half were injected with saline. Serum levels of glucose, insulin, and resistin as well as gallbladder bile volume were measured, and HOMA index was calculated. Gallbladder responses to neurotransmitters (ACh, NPY, and CCK) were obtained. Serum resistin level increased significantly in the resistin group, but no significant change was observed in serum glucose, insulin, HOMA Index, gallbladder volume, optimal tension, or response to neurotransmitters.

In study B, 20 C57BL/6J lean nondiabetic female mice were fed a chow diet for 4 weeks. Half of the mice were injected with 20 μg of RELM-α IP for 7 days, and the other half were injected with saline. Serum levels of glucose, insulin, and RELM-α as well as gallbladder bile volume were measured. HOMA index was calculated, and gallbladder responses to neurotransmitters (ACh, NPY, and CCK) were obtained. Serum RELM-α was only detected in the RELM-α-injected group, and HOMA index significantly increased. In addition, gallbladder optimal tension was significantly decreased in the animals receiving RELM-α, but gallbladder responses to neurotransmitters did not differ between the two groups.

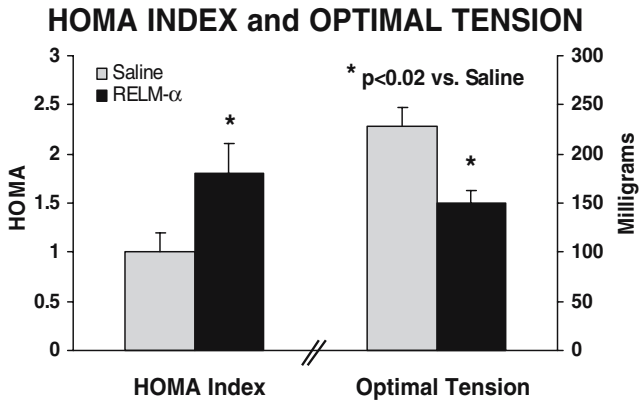

Figure 1 HOMA Index, a measure of insulin resistance, was calculated from fasting serum glucose and insulin (fasting serum glucose × fasting serum insulin/22.5). Optimal tension is the tension of the gallbladder at the optimal length. Daily injections of 20 ug RELM-α IP increased HOMA index, and decreased gallbladder tension at the optimal length (optimal tension). Data are means ± SEM, $n=10$ in each group. * $p<0.02$ vs. Saline group.

Leptin-deficient (Lep^{ob}) and leptin-resistant (Lep^{db}) obese mice serve as murine models for human obesity and insulin-resistant diabetes. Previous studies from our laboratory have demonstrated that Lep^{ob} and Lep^{db} mice have hyperglycemia, insulin-resistance, hyperinsulinemia, hyperlipidemia, enlarged gallbladders, and reduced response of their gallbladder smooth muscle to neurotransmitters such as ACh, NPY, and CCK.[6–9,21,22] The serum glucose, insulin, cholesterol, and triglycerides in these mice correlated inversely with their *in vitro* gallbladder responses.[6] We have also shown that the lipids in the gallbladder wall of lean (C57BL/6J) and obese (Lep^{ob}) mice correlate with the impaired *in vitro* gallbladder response to neurotransmitters.[23] These findings suggest that insulin resistance and/or fat infiltration mediate the gallbladder dysmotility in these diabetic obese mice.

Resistin is a member of the newly discovered family of cysteine-rich secretory proteins called 'resistin-like molecules' (RELMs), 'found in inflammatory zone' (FIZZ) or adipose-derived secretory factors (ADSF). Resistin (also termed FIZZ3 or ADSF) is expressed and secreted by white

Table 4 Results of Study B Gallbladder Data

	GB weight (mg)	GB bile volume (μl)	Optimal length (mm)	Optimal tension (mg)	Acetylcholine 10^{-5} M (N/cm^2)	NPY 10^{-8} M (N/cm^2)	NPY 10^{-7} M (N/cm^2)	NPY 10^{-6} M (N/cm^2)	CCK 10^{-10} M (N/cm^2)	CCK 10^{-9} M (N/cm^2)	CCK 10^{-8} M (N/cm^2)	CCK 10^{-7} M (N/cm^2)
Saline	1.7±0.2	9.4±1	8.0±0.3	228±20	0.8±0.1	0.3±0.1	0.4±0.1	0.7±0.1	1.1±0.1	1.7±0.2	1.9±0.3	1.7±0.2
RELM-α	1.6±0.1	9.8±1	7.7±0.5	150±13*	0.8±0.1	0.2±0.0	0.6±0.1	0.8±0.1	0.8±0.2	1.5±0.3	2.0±0.3	1.7±0.3

Values are the mean ± SEM. *P* value was determined by Student's *t* test.
*$p<0.02$ versus saline.
CCK = cholecystokinin, NPY = neuropetide Y.

adipocyte tissue.[12,13] The protein was originally reported to be an important link between insulin resistance and obesity.[13–17] Steppan et al. have shown that resistin markedly induces the gene expression of suppressor of cytokine signaling 3 (SOCS-3), a known inhibitor of insulin signaling.[24] Resistin also has been shown to be an inhibitor of adipocyte differentiation.[25,26] Initial studies indicated that circulating resistin is increased in diet-induced and genetic obesity in mice.[13] However, one study indicated that high-serum resistin is associated with an increased in adiposity, but not a worsening of insulin resistance in Pima Indians.[27]

In study A, serum resistin levels increased significantly in the resistin-injected group; however, no difference was observed in insulin-resistance (HOMA index) or in gallbladder responses. One possible explanation for these observations is that the mice did not receive enough resistin either due to a low dose or the duration of the study was not long enough to demonstrate an effect on insulin-resistance or gallbladder motility. Another explanation is that resistin receptors are not present in the C57BL/6J murine gallbladder, which is consistent with our observations in Lep^{ob} mice (unpublished data). Finally, resistin may not be associated with insulin resistance and, as a result, is not associated with insulin-resistant-mediated gallbladder dysmotility.

Another member of this cysteine-rich protein family is RELM-α (FIZZ1).[18] RELM-α is expressed most abundantly in white adipose tissue, which is similar to resistin.[12] However, unlike resistin, RELM-α is found in other tissues including heart, lung, and tongue.[18] The function of RELM-α is largely unknown, although expression is markedly increased in allergic pulmonary inflammation.[18] RELM-α also has been shown to inhibit adipocyte as well as muscle differentiation.[28] A recent study has shown that thiazolidinediones inhibit resistin gene expression, but are without effect on RELM-α expression, whereas the β_3-adrenoceptor agonist BRL35135 stimulates RELM-α gene expression but not resistin in db/db mice.[29] These observations suggest that RELM-α and resistin are regulated differently.

In study B, serum RELM-α was only detectable in the RELM-α-injected group and not in the saline group. RELM-α increased the HOMA index, suggesting an alteration in insulin resistance. RELM-α also lowered the gallbladder's optimal tension in response to acetylcholine, but had no effect on responses to neuropeptide Y and cholecystokinin. The influence of RELM-α on gallbladder optimal tension could be due either to the indirect effect of RELM-α on gallbladder motility through an alteration in insulin resistance or to a direct effect of RELM-α on acetylcholine receptors. In comparison, the lack of RELM-α's effect on the gallbladder's response to NPY and CCK suggests no connection with these neurotransmitters. Another possible explanation is that the dose of RELM-α or the duration of the study was not long enough for RELM-α to exert an effect on NPY- or CCK-induced contractility. Further experiments are needed with higher or more frequent doses of RELM-α or administration of RELM-α for a longer period of time to better understand the role of RELM-α on gallbladder motility.

Conclusion

We conclude that the administration of resistin to C57BL/6J lean nondiabetic mice fed a chow diet did not increase insulin resistance and did not alter gallbladder motility compared to controls. However, the administration of RELM-α to C57BL/6J lean nondiabetic mice fed a chow diet increased insulin resistance and decreased gallbladder optimal tension in response to acetylcholine, but did not affect gallbladder response to neuropeptide Y or to cholecystokinin. Thus, RELM-α may play a role in insulin-resistance-mediated gallbladder dysmotility.

References

1. Centers for Disease Control and Prevention. National diabetes fact sheet: General information and national estimates on diabetes in the United States, 2003. Atlanta, GA, 2003, US Dept of Health and Human Services, Centers for Disease Control and Prevention.
2. Mokdad AH, Ford, ES, Bowman, B A, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA 2003;289:76–79.
3. Kayacetin E, Kiasakol G, Kaya A, Akpinar Z. Real-time sonography for screening of gallbladder motility in diabetic patients: Relation to autonomic and peripheral neuropathy. Neuroendocrinol Lett 2003;24:73–76.
4. Paigen B, Carey MC, chapter The Genetic Basis of Common Diseases, 2nd Edition, edited by King, Rotter and Motulsky, 2001.
5. Everhart JE, Khare M, Hill M, Hill M, Maurer KR. Prevalence and ethic differences in gallbladder disease in the United States. Gastroenterology 1999;117:632–639.
6. Tran KQ, Goldblatt MI, Swartz-Basile DA, Svatek C, Nakeeb A, Pitt HA. Diabetes and hyperlipidemia correlate with gallbladder contractility in leptin-related murine obesity. J Gastrointest Surg 2003;7:857–862.
7. Graewin SJ, Lee KH, Kiely JM, Svatek CL, Nakeeb A, Pitt HA. Gallbladder myocytes are short and cholecystokinin-resistant in obese diabetic mice. Surgery 2004;136:431–436.
8. Graewin SJ, Tran KQ, Nuggert JK, Lee KH, Swartz-Basile D, Nakeeb A, Pitt HA. Diminished gallbladder motility in rotund leptin-resistant obese mice. HPB 2005;7:139–143.
9. Graewin SJ, Kiely JM, Svatek CL, Pitt HA. Ciliary neurotrophic factor restores gallbladder contractility in leptin-resistant obese diabetic mice. J Surg Res 2006;130:146–151.
10. Nakeeb A, Comuzzie AG, Al-Azzawi HH, Sonnenberg GE, Kissebah AH, Pitt HA. Insulin resistance causes human gallbladder dysmotility. J Gastro Surg 2006;10:940–949

11. Hahm JS, Park JY, Park KG, Ahn YH, Lee MH, Park KN. Gallbladder motility in diabetes mellitus using real time ultrasonography. Am J Gastroenterol 1996;91:2391–2394.
12. Steppan CM, Brown EJ, Wright CM, Bhat S, Banerjee RR, Dia CY, Enders GH, Silberg DG, Wen X, Wu GD, Lazar MA. A family of tissue-specific resistin-like molecules. Proc Natl Acad Sci U S A 2001;98:502–506.
13. Steppan CM, Baily ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, Patel HR, Ahima RS, Lazar MA. The hormone resistin links obesity to diabetes. Nature 2001;409:307–312.
14. Steppan CM, Lazar MA. Resistin and obesity-associated insulin resistance. Trends Endocrinol Metab 2002;13:18–23.
15. Banerjee RR, Rangwala SM, Shapiro JS. et al. Regulation of fasted blood glucose by resistin. Science 2004;303:1195–1198.
16. Silha JV, Krsek M, Skrha J, Sucharda P, Nyomba BL, Murphy LJ. Plasma resistin, leptin and adiponectin levels in non-diabetic and diabetic obese subjects. Diabet Med 2004;21:497–499.
17. Lehrke M, Reilly MP, Millington SC, Iqbal N, Rader DJ, Lazar MA. An Inflammatory cascade leading to hyperresistinemia in humans. PLoS Med 2004;1:e45.
18. Holcomb IN, Kabakoff RC, Chan B, Baker TW, Gurney A, Henzel W, Nelson C, Lowman HB, Wright BD, Skelton NJ, Frantz GD, Tumas DB, Peale Jr. FV, Shelton DL, Hebert CC. FIZZ1, a novel cysteine-rich secreted protein associated with pulmonary inflammation, defines a new gene family. EMBO J 2000;19:4046–4055.
19. Mathews DR, Hosker JP, Rudenski AS, Taylor BA, Treacher DF, Turner RC. Homeostasis model assessment insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–419.
20. Wallace TM, Levy JC, Mathews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487–1495.
21. Goldblatt MI, Swartz-Basile DA, Svatek CL, Nakeeb A, Pitt HA. Decreased gallbladder response in leptin-deficient obese mice. J Gastrointest Surg 2002;6:438–444.
22. Tran KQ, Swartz-Basile DA, Nakeeb A, Pitt HA. Gallbladder motility in agouti-yellow and leptin-resistant obese mice. J Surg Res 2003;113:56–61.
23. Goldblatt MI, Swartz-Basile DA, Al-Azzawi HH, Tran KQ, Nakeeb A, Pitt HA. Nonalcoholic fatty gallbladder disease: The influence of diet in lean and obese mice. J Gastrointest Surg 2006;10:193–201.
24. Steppan CM, Wang J, Whiteman EL, Birnbaum, MJ, Lazar MA. Activation of SOCS-3 by resistin. Mol Cell Biol 2005;25:1569–1575.
25. Levy JR, Davenport B, Clore JN, Stevens W. Lipid metabolism and resistin gene expression in insulin-resistant Fischer 344 rats. Am J Physiol Endocrinol Metab 2002;282:E626–E633.
26. Kim KII, Lee K, Moon YS, Sul IIS. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. J Biol Chem 2001;276:11252–11256.
27. Volarova de Courten B, Degawa-Yamauchi M, Considine RV, Tataranni PA. High serum resistin is associated with an increase in adiposity but not a worsening of insulin resistance in Pima Indians. Diabetes 2004;53:1279–1284.
28. Blagoev B, Kratchmarova I, Nielsen MM, Fernandez MM, Voldby J, Andersen JS, Kristiansen K, Pandey A, Mann M. Inhibition of adipocyte differentiation by resistin-like molecule alpha. Biochemical characterization of its oligomeric nature. J Biol Chem 2002;277:42011–42016.
29. Moore GB, Chapman H, Holder JC, Lister CA, Piercy V, Smith SA. Differential regulation of adipocytokine mRNAs by rosiglitazone in db/db mice. Biochem Biophys Res Commun 2001;286:735–741.

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The Influence of Transabdominal Gastroplasty: Early Outcomes of Hiatal Hernia Repair

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Abstract
Objective The aim of our study was to review our experience with transabdominal gastroplasty to determine the safety and short-term efficacy of the procedure.
Methods Retrospective review of all patients that underwent transabdominal hiatal hernia repair with concurrent gastroplasty for shortened esophagus between October 1999 and May 2004.
Results There were 63 patients, 27 men and 36 women. Median age was 68 years. The hiatal hernia was classified as type-I in 6 patients, type-II in 10, type-III in 43, and type-IV in 4. The operative approach was laparoscopic in 44 patients and laparotomy in 19. A Nissen fundoplication was performed in 62 patients and a Toupet fundoplication in 1. Wedge gastroplasty was performed in 47 patients and modified Collis gastroplasty in 16. Median hospitalization was 3 days (range, 2–10). Intraoperative complications occurred in 11 patients (17%). One laparoscopic approach (2%) was converted to laparotomy. Postoperative complications occurred in 12 patients (19%), there were no operative deaths. Median follow-up was 12 months (range, 0 to 64). One patient (2%) was found to have a recurrent hiatal hernia diagnosed 14 months, postoperatively. Functional results were excellent in 41 (68%), good in 6 (10%), fair in 12 (20%), and poor in 1 (2%).
Conclusion Transabdominal gastroplasty can be performed safely, with good functional results and a low incidence of recurrent herniation during the short-term follow-up period.

Keywords Short · Esophagus · Fundoplication · Gastroplasty · Lengthening

Introduction

A shortened esophagus is thought to contribute to the high rate of recurrence after transabdominal repair of large hiatal hernias.[1–4] We have previously reported a recurrence rate of 15% after laparoscopic repair of large hiatal hernias and others have noted similar results.[2,5–9] Achieving an adequate length of intra-abdominal esophagus that is tension-free is an important aspect of hiatal hernia repair to prevent recurrence and ensure a proper anti-reflux procedure. However, when a short esophagus is present, transabdominal lengthening is necessary but can be technically challenging.[1] The aim of our study was to review our experience with transabdominal gastroplasty to determine the safety and short-term efficacy of the procedure.

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Materials and Methods

Between October 1999 and May 2004, 526 patients underwent a hiatal hernia repair at the Mayo Clinic in Rochester, MN. Sixty-three (12%) of these underwent transabdominal repair with concurrent gastroplasty for a short esophagus and are the subject of this retrospective review. Medical records were reviewed for information on patient demographics, preoperative symptoms, preoperative

evaluation, operative procedure, postoperative course, morbidity, postoperative evaluation, and outcome. Hiatal hernias were classified by the surgeon at operation according to the method established by Skinner.[10]

In each patient, the surgeon made the diagnosis of a short esophagus intraoperatively. After esophageal mobilization, if less than 2–3 cm of the esophagus could be brought into the abdominal cavity without tension, patients were determined to have a short esophagus.[1] Early in our experience, we performed 16 (25%) transabdominal modified cut Collis gastroplasties.[1,3,11] A single firing of an EEA 25 stapling device (United States Surgical, Norwalk, CT 06858) is applied 2–5 cm distal to the gastroesophageal junction (GEJ) abutting a 50 French bougie, creating a defect through which an Endo GIA Universal Straight 44-4.8 stapling device (United States Surgical, Norwalk, CT 06858) can then be passed. One to two firings of the Endo GIA stapler oriented toward the angle of His along the bougie are then carried out to complete the gastroplasty (Fig. 1). Later in our experience, 47 (75%) wedge gastroplasties were performed (Fig. 2).[12,13] Three to four firings of the Endo GIA stapling device were used to remove a wedge of gastric fundus (15–20-cc volume) from the greater curvature with a 50 French bougie in the esophagus (Fig. 1). Following each type of gastroplasty, a fundoplication was performed as previously described.[2]

Postoperative functional status was evaluated as previously described by our group.[2] Briefly, excellent functional status indicates the patient was asymptomatic without medication; good indicates symptoms were mild without medication or the patient required one postoperative dilation, fair indicates symptoms were controlled with medication or occasional dilation, and poor indicates symptoms were unimproved, hernia recurred or reoperation was required. Major complications were determined to be those that prolonged hospital stay or required additional intervention. Values are reported as the median and range with percentages given in brackets. The Mayo Clinic Institutional Review Board approved this study, and all patients gave consent for research.

Results

During the study period, 63 patients (36 female, 27 male), with a median age of 68 years (range 24–87), underwent hiatal hernia repair and transabdominal gastroplasty at our institution. Median preoperative body mass index (BMI) was 30 kg/m^2 (range 17–41). Signs or symptoms of hiatal hernia were present in all patients, the most common included heartburn in 45 (71%), dysphagia and chest pain in 25 (40% each), regurgitation in 24 (38%), anemia in 15 (24%), abdominal pain and weight loss in 12 (19% each),

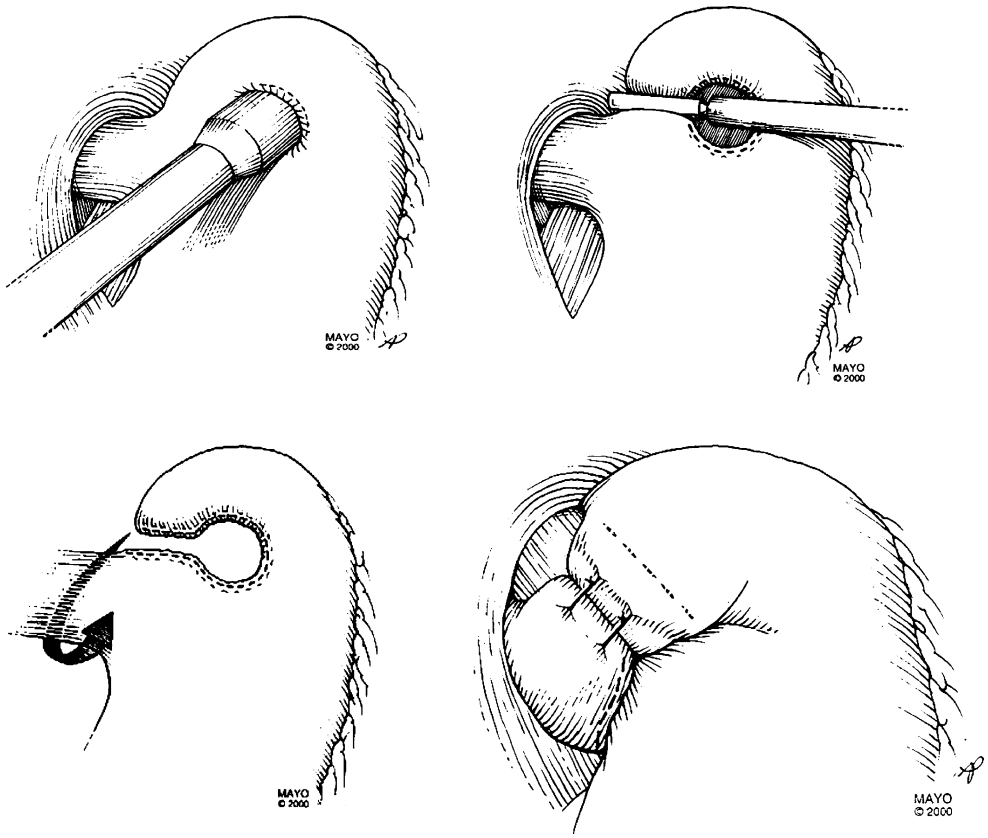

Figure 1 Transabdominal cut Collis gastroplasty utilizing a single firing of an EEA stapler followed by the application of a GIA stapler oriented toward the angle of His as described by Johnson et al.[3]

and aspiration in 6 (10%). Fifty-eight patients (92%) were taking anti-reflux medications at the time of operation. Thirty-nine patients (62%) had undergone prior abdominal operations with 10 of those (16%) having had at least one previously failed fundoplication.

Twenty-four patients (38%) underwent preoperative manometric evaluation. Six patients had normal findings and 18 had abnormal findings including a low lower esophageal sphincter (LES) pressure and abnormal peristalsis. Esophagogastroduodenoscopy (EGD) was performed in 62 patients (98%) and findings included fundic erosions in 11 (18%), esophagitis in 10 (16%), esophageal ulcers in 10 (16%), Barrett's esophagus in 7 (11%), and esophageal stricture 4 (6%). The median hernia size by EGD was 6 cm (range 1–12). Preoperative contrast studies revealed that at least 50% of the stomach (range 20–100%) was intrathoracic in 32 patients (50%). At operation, hiatal hernias were classified as type-I in 6 patients(10%), type-II in 10 (16%), type-III in 43 (68%), and type-IV in 4 (6%).

Operative approach was a laparotomy in 19 patients (30%) and laparoscopy in 44 (70%). One laparoscopic procedure (2%) was converted to laparotomy due to difficulty in safely reducing the stomach. Median esophageal length achieved by gastroplasty was 3.5 cm (range 2.5–5). Median operative time was 190 min (range 89–344). Eight patients (13%) underwent concurrent gastrostomy tube placement. Intraoperative complications occurred in 11 patients (17%) and included pneumothorax in 6, splenic laceration in 2, gastric perforation in 2 and stapled entrapment of a bougie in 1. Postoperative complications occurred in 12 patients (19%) including urinary retention in 5, superficial wound infection in 2, pneumonia in 1, and urosepsis in 1. Two patients were readmitted for dehydration secondary to poor oral intake with one patient ultimately requiring two endoscopic dilatations secondary to stenosis at the gastroplasty site. A third patient was readmitted for a right-sided pleural effusion and subsequently found to have bilateral pulmonary emboli. Overall, 17 patients (27%) experienced at least one complication while 10 (16%) experienced a major complication. There were no leaks or postoperative mortality. Median hospitalization was 3 days (range 2–10).

Follow-up was available in 62 patients (98%) and ranged from 1 to 64 months (median 12 months). Six patients (10%) required postoperative esophageal dilatations including three early (within 4 weeks) and three late (7 to 14 months). One patient who required esophageal dilatation at 7 months postoperatively was subsequently found to have a recurrent hiatal hernia 7 months later. This patient represents the only known recurrence in this series (2%). Fifty-six patients (89%) had a barium swallow performed after an average of 6.5 months (range 1–32) postoperatively. One recurrence was noted as shown above, and the rest showed an intact repair. The patient who developed a recurrence underwent a transthoracic cut Collis–Nissen fundoplication 14 months after the initial laparoscopic Nissen fundoplication and gastroplasty for a 6-cm type-III hiatal hernia. Fourteen months after the second fundoplication, the patient complained of reflux, and a barium swallow again demonstrated a recurrent hernia. He has declined a third repair and is currently being treated with medical therapy.

Sixty-one of 62 patients (98%) reported symptom improvement at last follow-up, and one patient reported that her symptoms were unchanged. Forty-five of 60 patients (75%) with information available on medication use did not require medication for symptom control. Of the 15 patients taking anti-reflux medication, 12 (20%) required daily proton pump inhibitor (PPI) or H_2 blocker therapy while 3 required only occasional antacids. Functional results were available in 60 patients and included excellent results in 42 (70%), good in 6 (10%), fair in 11 (18%), and poor in 1 (2%) Table 1.

Discussion

Achieving a tension-free adequate length of intra-abdominal esophagus is important for successful hiatal hernia repair.[1,14–18] Transabdominal repair of large hiatal hernias has been associated with a higher rate of recurrence which may, in part, be due to a shortened esophagus.[1–7,18] The concept of a short esophagus is not new. In 1957, Collis[16] described his technique for esophageal lengthening. While Collis addressed esophageal shortening, he did not incorporate an anti-reflux procedure. Belsey also realized that achieving an adequate length of intra-abdominal esophagus was an important factor in hiatal hernia repair.[14,17] He advocated a transthoracic approach to hiatal hernia surgery, which allowed for extensive esophageal mobilization resulting in an adequate length of intra-abdominal esophagus without tension on the repair. These two techniques were further expanded upon by Pearson[19,20] with the

Table 1 Functional Results in 60 Patients (Classification Based on the Dominant Symptom/Sign)

Symptoms/Signs	Excellent	Good	Fair	Poor
None	42	–	–	–
Reflux	–	6	5	–
Dysphagia	–		6	–
Bloating	–	–	–	–
Recurrent hernia	–			1
Total	42 (70%)	6 (10%)	11 (18%)	1 (2%)

development and popularization of the Collis–Belsey procedure, for the treatment of patients with large hiatal hernias and a shortened esophagus. It is now widely accepted that the gastroesophageal junction (GEJ) should lie within the abdomen, preferably 2–3 cm below the diaphragm without tension, to achieve the lowest recurrence rate and best results in terms of relief of gastroesophageal reflux.[1,21,22]

Laparoscopic surgery has added yet another challenge to the repair of large hiatal hernias and shortened esophagus.[1] While the laparoscopic technique results in decreased postoperative pain and earlier recovery, this approach has been associated with a higher rate of recurrence after large hiatal hernia repair.[2,5–7,9,23] In the circumstance where the surgeon is unable to achieve 2–3 cm of tension-free intra-abdominal esophagus, most authors would advocate further transhiatal dissection.[1,8,21,24–26] When these maneuvers fail to provide an adequate length of intra-abdominal esophagus, a lengthening gastroplasty is indicated.[1] Laparoscopic Collis gastroplasty was first described by Swanstrom et al.[27] in 1996. This technique involved passing a stapler transthoracically through the diaphragmatic hiatus into the abdominal cavity and performing a gastroplasty. Other techniques have subsequently been described that can be performed totally trans-abdominally.[3,12,13] Johnson et al.[3] described the initial application of an EEA stapler next to a bougie placed along the lesser curvature of the stomach followed by one or two firings of a linear stapler oriented towards the angle of His (Fig. 1). Another technique involves removing a "wedge" of fundus (Fig. 2) which effectively lengthens the esophagus.[12,13] All three techniques are then followed by a fundoplication.

Good results have been reported by various authors after laparoscopic, endoscopic, or open gastroplasty for a short esophagus.[1,3,12,13,28] Jobe et al.[28] reported an overall decrease in reflux symptoms in 15 patients (36% reopera-

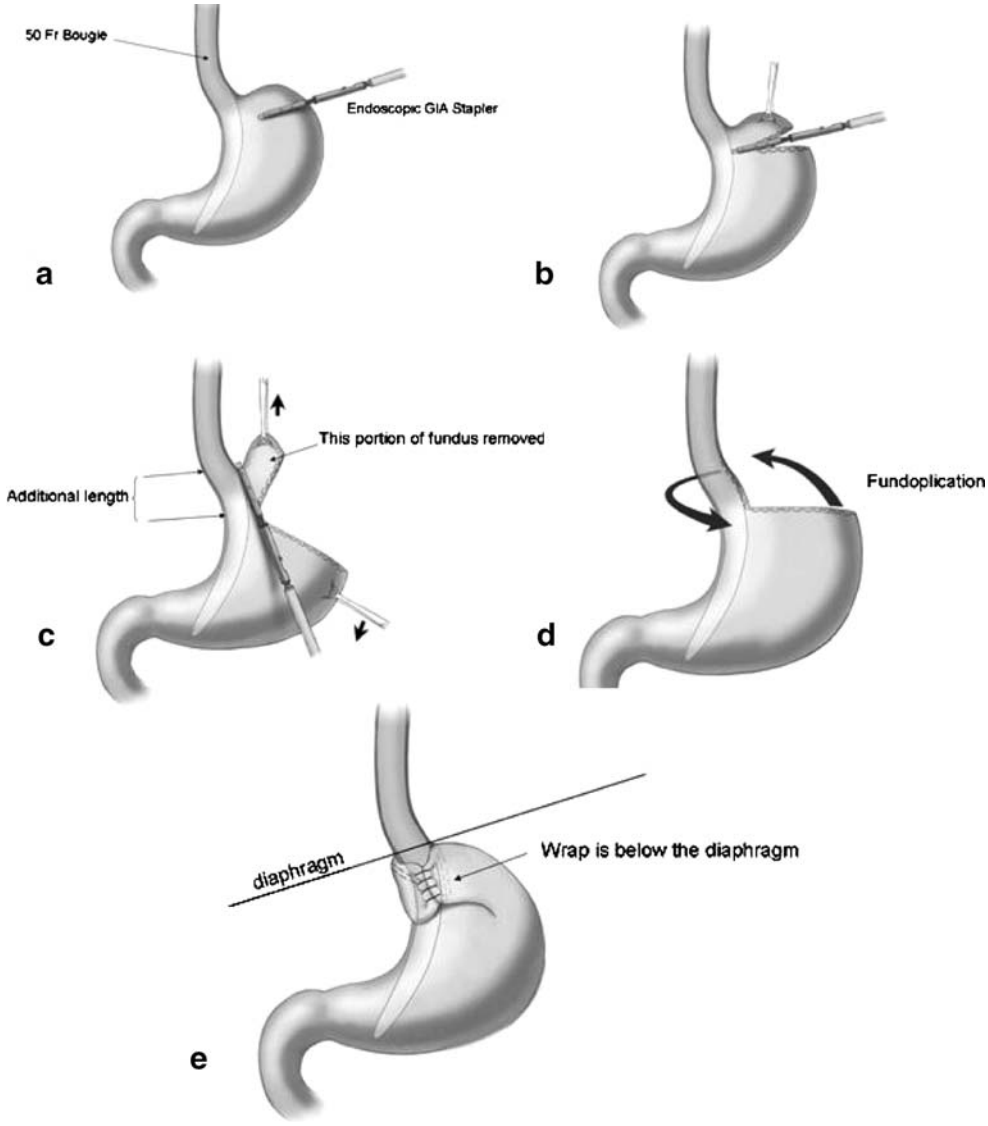

Figure 2 Wedge gastroplasty is performed by removing a wedge of fundus through multiple applications of an endo-GIA stapler.

tions) undergoing a laparoscopic gastroplasty followed by fundoplication. With an average follow-up of 14 months, no recurrences were noted, and the authors concluded that gastroplasty is effective in allowing a tension-free repair in patients with a short esophagus. Lin et al.[12] reported on 68 patients (30% reoperations) undergoing totally transabdominal gastroplasty with a mean follow-up of 30 months. They found the procedure to be safe with a 6% rate of hernia recurrence overall, which is similar to the 2% reported in the current series.

Other authors have advocated alternatives to gastroplasty for obtaining adequate intra-abdominal esophageal length during hiatal hernia repair.[8,21] Madan et al.[21] reported a series of 628 laparoscopic fundoplications without gastroplasties. Their technique involved esophageal mobilization until a 3- to 5-cm length of esophagus was achieved within the abdominal cavity, followed by a fundoplication. In no patient were they unable to achieve adequate intra-abdominal esophageal length, and they concluded that none of the 628 patients had a short esophagus. After 4.3 years of follow-up, the recurrence rate in that series was 2.5%. O'Rourke et al.[8] described applying a mediastinal dissection involving esophageal mobilization of 5 cm or more above the GEJ in 72 patients undergoing hiatal hernia repair. With 10.6 months of follow-up, the recurrence rate in those patients undergoing such a dissection was 10 and 11% in those patients undergoing a less aggressive esophageal mobilization. This led the authors to conclude that extensive mediastinal dissection was an acceptable alternative to gastroplasty resulting in recurrence rates similar to those encountered after a standard dissection. The authors concluded their results made liberal application of a Collis gastroplasty unwarranted.

One concern about increased use of gastroplasties during hiatal hernia repair has been evidence of significant acid production in the neoesophagus.[12,28] Jobe et al.[28] found that 14% of patients had heartburn postoperatively while 36% had persistent esophagitis on EGD. Forty-seven percent of patients had abnormal DeMeester scores during follow-up, and 100% had acid-secreting cells in the neoesophagus. The authors, therefore, recommended that post-gastroplasty patients be maintained on acid-suppression therapy indefinitely. Lin et al.[12] also noted a high rate of patients having abnormal 24-h pH evaluations or esophagitis on EGD postoperatively (80% of those tested). These findings prompted the authors to caution against the liberal use of gastroplasty procedures during hiatal hernia repair, despite the low rate of anatomic recurrence. This contrasts with our findings. Twenty-five percent of our patients require medication for reflux symptoms postoperatively.

In this study, we have shown that transabdominal gastroplasty can be performed safely with good short-term results and a low rate of recurrence. In our study, 12 patients (19%) had either a fair or poor functional outcome. Only one of these patients developed a recurrence. The remaining 11 patients all required daily acid suppression therapy consisting mostly of proton pump inhibitors (PPI). The majority of these patients were otherwise very satisfied with the results of their repair and most importantly, free from their preoperative symptoms.

Conclusion

In summary, transabdominal gastroplasty can be performed safely with a low incidence of significant morbidity. Although only short-term follow-up has as yet been achieved, gastroplasty appears to be associated with a low recurrence rate following transabdominal hiatal hernia repair in patients with a short esophagus. Functional results were satisfactory in the majority of patients. Long-term data on symptoms, recurrence rates, and the effects of acid production in the neoesophagus are needed.

References

1. Horvath KD, Swanstrom LL, Jobe BA. The short esophagus: Pathophysiology, incidence, presentation, and treatment in the era of laparoscopic antireflux surgery. Ann Surg 2000;232:630–640.
2. Dahlberg PS, Deschamps C, Miller DL, Allen MS, Nichols FC, Pairolero PC. Laparoscopic repair of large paraesophageal hiatal hernia. Ann Thorac Surg 2001;72:1125–1129.
3. Johnson AB, Oddsdottir M, Hunter JG. Laparoscopic Collis gastroplasty and Nissen fundoplication: A new technique for the management of esophageal foreshortening. Surg Endosc 1998;12:1055–1060.
4. Yau P, Watson DI, Jamieson GG, Myers J. The influence of esophageal length on outcomes after laparoscopic fundoplication. J Am Coll Surg 2000;191:360–365.
5. Perdikis G, Hinder RA, Filipi CJ, Walenz T, McBride PJ, Smith SL. et al. Laparoscopic paraesophageal hernia repair. Arch Surg 1997;132:586–590.
6. Hashemi M, Peters JH, DeMeester TR, Huprich JE, Quek M, Hagen JA, et al. Laparoscopic repair of large type III hiatal hernia: Objective followup reveals high recurrence rate. J Am Coll Surg 2000;190:553–561.
7. Mattar SG, Bowers SP, Galloway KD, Hunter JG, Smith CD. Long-term outcome of laparoscopic repair of paraesophageal hernia. Surg Endosc 2002;16:745–749.
8. O'Rourke RW, Khafanchee YS, Urbach DR, Lee NN., Lockhart B, Hansen PD, et al. Extended transmediastinal dissection: An alternative to gastroplasty for short esophagus. Arch Surg 2003;138:735–740.
9. Leeder PC, Smith G, Dehn TCB. Laparoscopic management of large paraesophageal hiatal hernia. Surg Endosc 2003;17:1372–1375.
10. Skinner DB. Esophageal hiatal hernia. The condition: Clinical manifestations and diagnosis. In DC Sabiston Jr., FC Spencer (Eds.), Surgery of the chest (6th ed., pp. 1013–1025). Philadelphia: WB Saunders, 1995.
11. Luketich JD, Grondin SC, Pearson FG. Minimally invasive approaches to acquired shortening of the esophagus: Laparoscopic

Collis–Nissen gastroplasty. Semin Thorac Cardiovasc Surg 2000; 12:173–178.
12. Lin E, Swafford V, Chadalavada R, Ramshaw BJ, Smith CD. Disparity between symptomatic and physiologic outcomes following esophageal lengthening procedures for antireflux surgery. J Gastrointest Surg 2004;8:31–39.
13. Terry ML, Vernon A, Hunter JG. Stapled-wedge Collis gastroplasty for the shortened esophagus. Am J Surg 2004;188:195–199.
14. Stylopoulos N, Rattner DW. The history of hiatal hernia surgery: from Bowditch to laparoscopy. Ann Surg 2005;241:185–193.
15. Orringer MB, Sloan H. An improved technique for the combined Collis–Belsey approach to dilatable esophageal strictures. J Thorac Cardiovasc Surg 1974;68:298–302.
16. Collis JL. An operation for hiatus hernia with short esophagus. J Thorac Surg 1957;34:768–788.
17. Skinner DB, Belsey RH. Surgical management of esophageal reflux and hiatus hernia. J Thorac Cardiovasc Surg 1967;53:33–54.
18. Hunter JG, Smith CD, Branum GD, Waring JP, Trus TL, Cornwell M, et al. Laparoscopic fundoplication failures: Patterns of failure and response to fundoplication revision. Ann Surg 1999;230:595–606.
19. Pearson FG, Henderson RD. Long-term follow-up of peptic strictures managed by dilation modified Collis gastroplasty, and Belsey hiatus hernia repair. Surgery 1976;80:396–404.
20. Pearson FG, Langer B, Henderson RD. Gastroplasty and Belsey hiatus hernia repair. J Thorac Cardiovasc Surg 1971;61:50–63.
21. Madan AK, Frantzides CT, Patsavas KL. The myth of the short esophagus. Surg Endosc 2004;18:31–34.
22. Urbach DR, Khajanchee YS, Glasgow RE, Hansen PD, Swanstrom LL. Preoperative determinants of an esophageal lengthening procedure in laparoscopic antireflux surgery. Surg Endosc 2001; 15:1408–1412.
23. Wiechmann RJ, Ferguson MK, Naunheim KS, McKesey P, Hazelrigg SJ, Santucci TS, et al. Laparoscopic management of giant paraesophageal herniation. Ann Thorac Surg 2001;71:1080–1086.
24. Gantert WA, Patti MG, Arcerito M, Feo C, Stewart L, DePinto M, et al. Laparoscopic repair of paraesophageal hiatal hernias. J Am Coll Surg 1998;186:428–433.
25. Awad ZT, Mittal SK, Roth TA, Anderson PI, Wilfley WA, Filipi CJ. Esophageal shortening during the era of laparoscopic surgery. World J Surg 2001;25:558–561.
26. Low DE. The short esophagus—Recognition and management. J Gastrointest Surg 2001;5:458–461
27. Swanstrom LL, Marcus DR, Galloway GQ. Laparoscopic Collis gastroplasty is the treatment of choice for the shortened esophagus. Am J Surg 1996;171:477–481.
28. Jobe BA, Horvath KD, Swanstrom LL. Postoperative function following laparoscopic Collis gastroplasty for shortened esophagus. Arch Surg 1998;133:867–874.

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Palliative Stenting for Late Malignant Gastric Outlet Obstruction

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Abstract Malignant gastric outlet obstruction (MGO) is a late complication of pancreatobiliary and gastric cancers. Although surgical gastrojejunostomy provides good palliation, many of these patients may be nonoperative candidates or underwent previous extensive resection such as a Whipple procedure. Recently, endoscopically placed self-expanding metallic stents (SEMS) have been used to palliate MGO. The aim of this study was to evaluate the efficacy of SEMS for palliation of late MGO. Medical records of patients with endoscopic placement of SEMS for palliation of MGO were reviewed. Results showed that 30 patients with MGO had SEMS placed for late gastroduodenal (n=20) or jejunal (n=10) obstruction. Twenty-one patients (70%) had previous surgery. Return to oral feeding was observed in 90% of patients who presented with recurrent obstruction after prior bypass surgery and in 88% of nonoperative patients in whom SEMS were placed as the primary therapy for obstruction. No major complications were observed, and median survival after SEMS was 4.1 months (0.1 to 10.5 months). SEMS also did not interfere with biliary drainage. In conclusion, endoscopically placed SEMS are safe and provide good palliation for late malignant gastroduodenal and jejunal strictures and are an excellent complement to recurrent obstruction after surgical gastrojejunostomy.

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Introduction

Malignant gastric outlet obstruction (MGO) is a late complication of pancreatic, biliary, and gastric cancers as

well as metastatic tumors. Nonresectable cancers are usually best palliated with surgical gastrojejunostomy which provides adequate relief from nausea and vomiting.[1–4] However, when obstruction occurs in an advanced stage, surgery is often associated with a poor outcome.[5,6] Endoscopically placed self-expanding metallic stents (SEMS) have emerged as viable nonoperative alternatives to the management of MGO.[7–11]

The aim of this retrospective study was to evaluate the restoration of diet, complications, and survival of patients with SEMS when used for palliation of malignant gastroduodenal and jejunal strictures associated with advanced tumors. As many patients with advanced tumors also require biliary stents, the question of whether enteral stenting complicates biliary stenting is not known. The aim of this study was also to determine whether enteral stenting is safe in patients with concurrent biliary stents.

Methods

Patient Population

The Institutional Review Board of the Medical College of Wisconsin and the Zablocki Veterans Affairs Medical Center approved this study.

All patients referred for management of malignant pancreaticobiliary, gastroduodenal, and metastatic disease over a 3-year period from January 2001 through October 2004 at a tertiary center were retrospectively reviewed using the electronic patient database. Patients presenting with MGO requiring palliation were included in the study. Patient demographic data, cancer type and stage, comorbidities, prior treatments including surgery, and the presence of biliary stents were recorded.

Stenting Technique

Standard techniques were used for placing enteral stents. After defining the length and location of the stricture with either a water-soluble contrast study or during endoscopy by dye injection, a guidewire was passed through the stricture. The stent was then passed over the guidewire and deployed from the distal end under fluoroscopic and endoscopic guidance. If needed for a long stricture, a second overlapping stent was deployed. Stenting was performed using a self-expanding metal enteral Wallstent (Microvasive Endoscopy, Boston Scientific Corp., Natick, MA, USA) with a diameter of 22 mm and a length of 60 or 90 mm. An endoscopic expandable metal biliary stent was placed in patients with known or impending biliary obstruction before duodenal or jejunal stent placement (Figs. 1 and 2).

Follow-up and Outcomes

Follow-up and survival information was obtained from clinic notes, hospital records, and the Social Security death index database. The primary end point was the duration (i.e., durability) of successful palliation of MGO defined as time (in days) from SEMS placement to (a) recurrence of outlet obstruction or, (b) patients too ill and requiring hospice care or, (c) death. The secondary end points were: (a) time to beginning of oral feeding after SEMS, (b) reinterventions, (c) complications, and (d) survival.

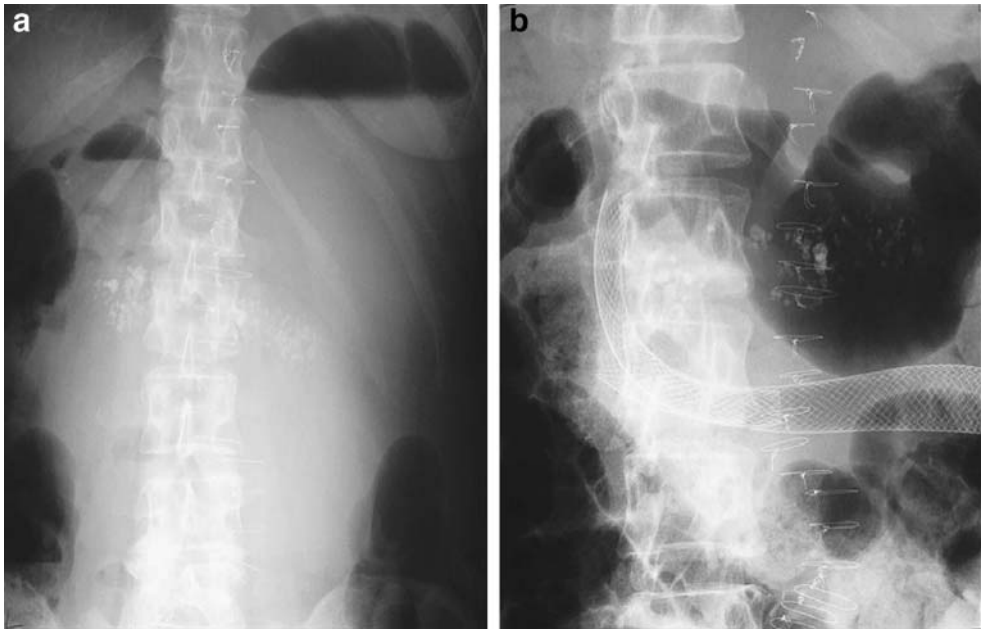

Figure 1 Gastric outlet obstruction from pancreatic adenocarcinoma. A 64-year-old female with unresectable pancreatic cancer, who developed late duodenal obstruction. **a** Enlarged stomach with air fluid levels and paucity of gas in the remainder of the small intestine. She underwent endoscopy and required two stents to relieve the duodenal stricture (**b**).

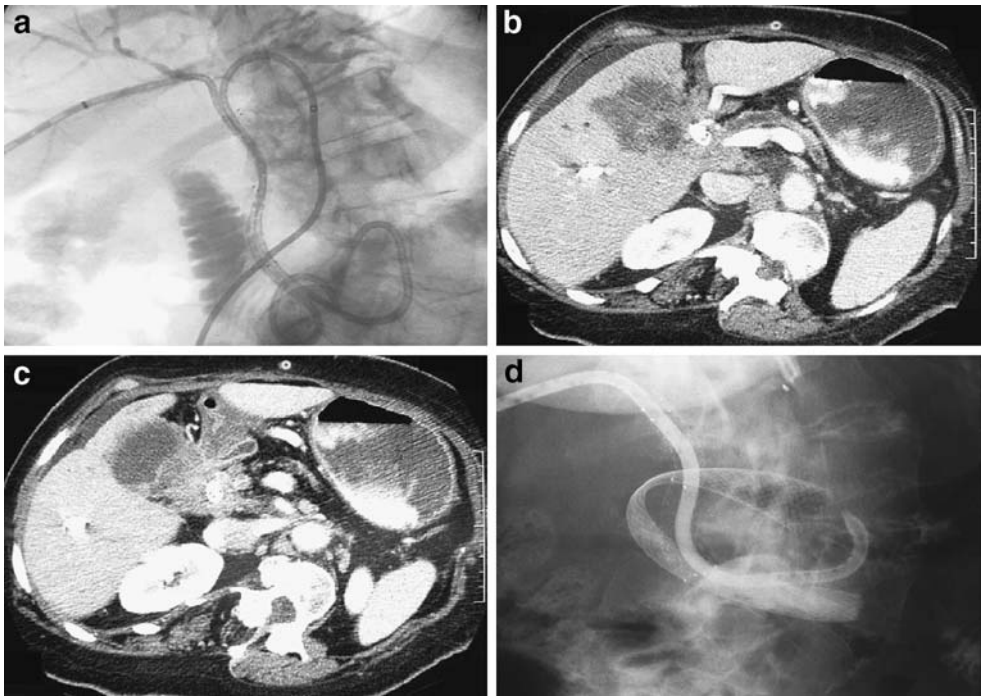

Figure 2 Locally advanced and metastatic gallbladder cancer. 59 year-old patient with locally advanced and metastatic gallbladder cancer. **a** Two percutaneous transhepatic stents, which end in the duodenum. CT scans demonstrate extensive intrahepatic tumor (**b**) and duodenal obstruction (**c**). The patient had a stent placed with return to pureed diet. **d** Both the biliary and the duodenal stents.

Statistical Analysis

Comparisons were performed using the independent sample *t* test, the Mann–Whitney rank sum test, and the chi-square test where appropriate, with statistical significance achieved at the $p<0.05$ level. Survival rates were analyzed by the Kaplan–Meier actuarial method, with statistical significance determined by the log-rank statistic. All data were analyzed using SPSS statistical software (SPSS Inc., Chicago, IL, USA). Data are presented as percentages, mean (± standard deviation), or median with range.

Results

Patient Population

Thirty patients (mean age 60±12.7 years and 53% female) with pancreatic ($n=16$), biliary ($n=6$), gastric ($n=3$), duodenal ($n=1$), carcinoid ($n=1$), and metastatic (breast $n=1$, esophageal $n=1$, and rectal $n=1$) cancers had SEMS placed for late gastroduodenal ($n=20$) or jejunal ($n=10$) obstruction (Table 1). Seventeen of the 30 patients (57%) had undergone prior resective ($n=9$) or palliative surgery ($n=8$). Nineteen patients (63%) had received prior chemoradiation. Twenty-one patients (70%) also had endoscopic, percutaneous, or operatively placed biliary stents (Table 1).

Table 1 Demographics—All Patients

	Pancreatic	Biliary	Other	All
Number	16	6	8	30
Mean age, years	61.3±10.8	51.3±10.1	63.6±16.2	59.9±12.7
Female (%)	56	50	50	53
Duodenal obstruction (%)	63	83	63	67
Prior surgery (%)	50	67	63	57
Chemoradiation (%)	63	83	38	63
Biliary stent (%)	69	100	50	70

Diet

SEMS were successfully placed in all patients using standard endoscopic techniques. Twenty-seven of 30 patients (90%) could tolerate pureed to general diet after SEMS. Of these 27 patients, seven tolerated a general diet, 15 tolerated a pureed diet, and five tolerated a full liquid diet. The mean time to start oral feeding after SEMS was 1.5±0.7 days. The durability of palliation as measured by duration of oral feeding after SEMS until the end point (death or hospice care) averaged 110.8± 88.2 days. The three patients who were unable to resume oral intake were in a sedated, poor functional state probably related to narcotics use for pain management. To rule out stent occlusion as a cause for poor intake, water-soluble contrast, upper GI study done on two of these three patients showed patent stents. We did not gather average daily narcotic usage in our series because of the heterogeneous nature of the pain-relieving effects of narcotics. Narcotic use varied over time, and good data could not be obtained retrospectively.

Complications

Four patients developed reobstruction secondary to tumor ingrowth ranging from 0.5 to 8 months after placement. Of the 27 patients who tolerated an oral diet initially after SEMS, three later reobstructed due to tumor ingrowth. Two of these patients had a second stent placed, and a third underwent surgery for an enterocutaneous fistula 8 months later. Both of the restented patients were discharged to hospice care on a full liquid diet, and the third patient died from sepsis resulting from an intra-abdominal abscess postoperatively. The other patient was terminally ill in hospice care and hence was not restented. None of the 19 patients with biliary stents developed cholangitis or recurrent biliary obstruction. No patients had complications related to the stent placement procedure, and specifically, no perforations or episodes of gastrointestinal bleeding occurred.

Survival

Overall, seven (23%) patients remained alive at the time of survival analysis. Median survival after initial diagnosis was 17.7 months (range 1.9 to 103.3 months). Median survival after stent placement was 4.1 months (range 0.1 to 10.5 months). Figure 3 shows the cumulative poststent survival by Kaplan–Meier analysis. The median survival was 4.8 months in the biliary group, 2.4 months in the pancreatic group, and 10.5 months in the other group. No statistically significant differences in survival were observed among the three groups.

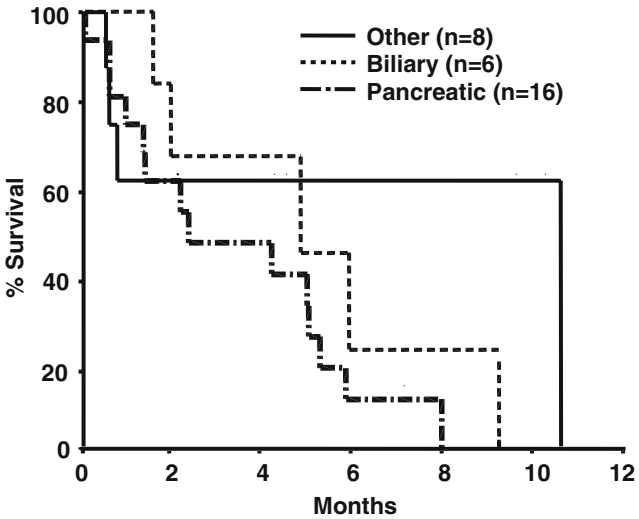

Figure 3 Kaplan–Meier actuarial survival curve comparing patients with pancreatic cancer, biliary cancer, or other types of cancer.

Discussion

This analysis of 30 nonoperative patients over a 3-year period demonstrates that endoscopically placed SEMS are safe and provide good palliation for late malignant gastroduodenal and jejunal strictures. In these patients, endoscopic SEMS allowed return to oral feeding in 90% of patients without further surgery and was not associated with major complications nor did they complicate biliary stenting.

Since the first accounts of SEMS placement for proximal malignant intestinal strictures in 1992,[12,13] several case series report high rates of technical and short-term clinical success. Some authors have recommended stent placement over surgical palliation because stenting has a shorter procedure time, and stented patients have a shorter hospital stay and time to oral intake.[14–16] To date, only three retrospective, comparative studies of SEMS versus surgical bypass exist,[17–19] and only one small, randomized controlled trial has been performed.[20] However, SEMS frequently occlude secondary to tumor granulation tissue or ingrowth at the ends. This may not be an issue in those with a life expectancy of only a few months. In others, several reinterventions may be required to maintain luminal patency. Although SEMS may have an advantage over surgical palliation with regard to the duration of procedure, time to start oral feeding after the procedure, and duration of hospital stay, eventually, it is the total duration of useful relief of MGO with minimal reinterventions that impact more on the patient's quality of remaining life.

In the present series, no patients developed immediate complications related to the procedure, such as perforation or gastrointestinal bleeding. We also report no evidence of stent migration or fistula formation, which can become significant problems in the longer term. Four patients (13%) developed reobstruction secondary to tumor ingrowth for a technical success rate of 87%, which has been defined as proper stent deployment, no major complications, and continued stent patency throughout the duration of follow-up.[21] This technical success rate after SEMS placement compares favorably with other published series which range from 76 to 100%, with the majority of studies concluding that SEMS are safe and effective for MGO.[16,19,22,23] In the larger, more recent series, technical success rates of 95–100% have been achieved.[10,18,24] Adler and Baron[14] demonstrated a technical success rate of 100% in a case series of 36 patients with duodenal strictures using the ultraflex wall stent. Dumas et al.[25] reported a technical success rate of 95% in a series of 42 patients with gastric and duodenal strictures, who underwent enteral wall stenting.

Overall, 90% of patients in the present series tolerated an oral (liquid, pureed, or general) diet after stenting, thus

giving a clinical success rate of 90%, which has been defined as the ability to tolerate oral feeding post-SEMS placement.[21] No differences in percent diet resumption among the three groups were evident; 73% in the pancreatic group, 67% in the biliary group, and 75% in the other group resumed diet poststenting. Our data compare favorably with most published series which report clinical success rates of 75–100%. In a recent large series, Dormann et al.[26] reported a clinical success rate of 89%, with resolution of symptoms occurring on average within 4 days. These rates of resumption of oral intake reflect the improved quality of life and patient comfort after stent intervention. The authors concluded that a standardized enteral feeding protocol should be followed within the first 3–5 days after stent insertion. In the present study, 17% of patients could tolerate a liquid-only diet post-SEMS placement, and three patients (10%) were unable to resume any diet post-SEMS placement. In a multicenter study, Nassif et al.[27] reported a liquid-only diet in 19%, and 8% of patients failed to resume oral intake. The three patients in this series who did not resume oral intake despite enteral stenting were in a sedated, poorly functional state probably related to narcotics use for pain management. Narcotic use has been shown to prolong resumption of diet by slowing intestinal motility by blockade of propulsive peristalsis (mediated by peripheral mu-opioid receptors) and inhibition of intestinal ion and fluid secretion.[28,29] To rule out stent occlusion as a cause for poor intake, water-soluble contrast, upper GI study done on two of these 3 patients showed patent stents. From this study, we could not determine if there was any correlation between narcotic use and resumption of oral feeding. We did not gather average daily narcotic usage in this series because of the heterogeneous nature of the pain-relieving effects of narcotics. Narcotic use varied over time, and good data could not be obtained retrospectively.

The median poststent survival in our series of 4.1 months (16.4 weeks) is comparable to other published series. The mean survival in our series was 4 months, and the wide range (0.1–10.5 months) is a typical feature of this patient population. Patients with pancreatic cancer fared worst in this series (3.2 months), followed by biliary (4.6 months), and then the other group (5.1 months). In comparison, the median patient survival in the multicenter study by Nassif et al.[27] was 7 weeks. Dormann et al.[26] provided data on mean survival time (12.1 weeks, range 1–184 weeks) and concluded that the survival in the pooled population corresponded to the life expectancy range recommended for stent implantation in palliative treatment of malignant gastroduodenal obstruction.

The presence of combined biliary and gastroduodenal stents did not impact negatively on patients in our series. Twenty-one patients (70%) had concurrent biliary stents, and none developed cholangitis or biliary obstruction. A previous study has shown that 61% of patients requiring duodenal stenting also underwent placement of a biliary stent either before (41%), during (18%), or after (2%) enteral stenting.[26] Only 1.3% of these patients experienced biliary complications. Some authors have reported high biliary intervention rates due to secondary biliary obstruction.[14] Therefore, in patients with tumor involvement of the papilla or expected stent application across the papilla, current recommendations are that the biliary tree should undergo primary evaluation and/or stenting to prevent secondary biliary blockage.[30]

With recent advances in abdominal imaging techniques, the nonoperative staging of proximal gastrointestinal tumors has improved. As a result, nonoperative management of these diseases has increased, especially with endoscopically placed SEMS, which has led many authors to question the role of surgical palliation in the form gastrojejunostomy. However, as reported in a large series by Sohn et al., surgical bypass procedures are indicated in a subset of patients with periampullary cancer in whom unresectability cannot be determined without surgical exploration.[4] This study showed that in 70% of patients who underwent gastrojejunostomy (51% with hepaticojejunostomy or 19% alone), only 2% developed recurrent gastric outlet obstruction before death. They also obtained acceptable rates of morbidity (22%) and mortality (3.1%) when compared to other large series of surgical palliative procedures. Therefore, early surgical palliation can be performed safely and remains an excellent method of providing long-term relief of duodenal obstruction, obstructive jaundice, and intractable pain. Early surgical palliation may also be indicated in selected patients with preoperatively determined, localized unresectable disease, who are appropriate surgical candidates with good functional reserve.

The appropriateness of gastrojejunostomy in the latter stages of disease and in the presence of late MGO has been called into question due to some published series reporting high rates of complications and mortality.[5,6] A number of studies have examined the clinical effectiveness of SEMS placement versus surgical palliation in the presence of malignant upper intestinal obstruction. Most series conclude that SEMS placement is more cost effective, requires a shorter hospital stay, and leads to faster resumption of oral intake.[7–11] However, SEMS have not been shown to confer a survival benefit when compared to surgery,[26] but the

Table 2 Protocol for Patient Selection

	Surgery	SEMS
Presentation	Initial	Late
Tumor	Localized	Metastatic/Recurrent
Nutritional status	Good	Poor
Surgical risk	Low	High

ability to resume eating which is a crucial issue in terms of quality of life, especially given the terminal nature of the disease, has been shown to be increased after SEMS.[7–11] Only one randomized prospective clinical trial comparing SEMS versus surgery for palliation of malignant antropyloric strictures currently exists in the literature.[20] Fiori et al.[20] compared nine patients in each group and reported no statistically significant differences with respect to morbidity, mortality, delayed gastric emptying, and clinical outcomes at 3 months. However, SEMS were more effective with respect to procedure times, restoration of oral intake, and median hospitalization.

If a tumor appears localized and is not encasing any vessels when the patient presents, surgical exploration is indicated. If resection is not possible, surgical gastrojejunostomy provides the best long-term palliation. However, in the presence of late MGO with its associated dismal prognosis, a metal gastrointestinal stent offers a better palliative approach than surgery, which is associated with poor outcomes in patients with very advanced disease. A protocol for selection of SEMS versus surgical bypass in patients with MGO is outlined in Table 2. The four criteria are presentation, tumor characteristics, nutritional status, and surgical risk. This algorithm favors surgery if the patient presents early with a localized tumor, has a good nutritional status, and has a low surgical risk. However, if the presentation is late with metastatic or recurrent tumor, the nutritional state is poor, and/or the surgical risk is high, SEMS are preferred.

Endoscopically placed SEMS are safe and provide good palliation for late malignant gastroduodenal and jejunal strictures without compromising biliary stenting. Therefore, we conclude that palliative stenting of late gastric outlet obstruction is an excellent complement to surgical gastrojejunostomy for potentially resectable tumors. This durability of palliation with SEMS as compared to surgery needs further evaluation. In the current study, we showed that surgically inoperable candidates followed by SEMS for late recurrence of outlet obstruction offered a durable palliation and hence, surgical bypass and SEMS should be considered complimentary and not competitive to each other.

References

1. Lillemoe, K. D., Sauter, P. K., Pitt, H. A., Yeo, C. J., & Cameron, J. L. (1993). Current status of surgical palliation of periampullary carcinoma. *Surgery, Gynecology & Obstetrics, 176*, 1–10.
2. Lillemoe, K. D., Cameron, J. L., Hardacre, J. M., Sohn, T. A., Sauter, P. K., Coleman, J., et al. (1999). Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? A prospective randomized trial. *Annals of Surgery, 230*, 322–328.
3. Potts, J. R., Broughan, T. A., & Hermann, R. E. (1990). Palliative operations for pancreatic carcinoma. *American Journal of Surgery, 159*, 72–78.
4. Sohn, T. A., Lillemoe, K. D., Cameron, J. L., Huang, J. J., Pitt, H. A., & Yeo, C. J. (1999). Surgical palliation of unresectable periampullary adenocarcinoma in the 1990s. *Journal of the American College of Surgeons, 188*, 658–666.
5. Doberneck, R. C., & Berndt, G. A. (1987). Delayed gastric emptying after palliative gastrojejunostomy for carcinoma of the pancreas. *Archives of Surgery, 122*, 827–829.
6. Weaver, D. W., Wieneck, M. D., Bowman, D. L., & Walt, A. J. (1987). Gastrojejunostomy: Is it helpful for patients with pancreatic cancer? *Surgery, 102*, 608–613.
7. De Baere, T., Harry, G., Ducreux, M., Elias, D., Briquet, R., Kuoch, V., et al. (1997). Self-expanding metallic stents as palliative treatment of malignant gastroduodenal stenosis. *American Journal of Roentgenology, 169*, 1079–1083.
8. Feretis, C., Benakis, P., Dimopoulos, C., Georgopoulos K., Milas F., Manouras A., et al. (1996). Palliation of malignant gastric outlet obstruction with self-expanding metal stents. *Endoscopy, 28*, 225–228.
9. Feretis, C., Benakis, P., Dimopoulos, C., Manouras, A., Tsimbloulis, B., & Apostolidis, N. (1997). Duodenal obstruction caused by pancreatic head carcinoma: Palliation with self expandable endoprostheses. *Gastrointestinal Endoscopy, 46*, 161–165.
10. Maetani, I., Inoue, H., Sato, M., Ohashi, S., Igarashi, Y., & Sakai, Y. (1996). Peroral insertion techniques of self-expanding metal stents for malignant gastric outlet and duodenal stenosis. *Gastrointestinal Endoscopy, 44*, 468–471.
11. Mauro, M. A., Koehler, R. E., & Baron, T. H. (2000). Advances in gastrointestinal intervention: The treatment of gastroduodenal and colorectal obstructions with metallic stents. *Radiology, 215*, 659–669.
12. Topazian, M., Ring, E., & Grendell, J. (1992). Palliation of obstructing gastric cancer with steel mesh, self-expanding endoprostheses. *Gastrointestinal Endoscopy, 38*, 58–60.
13. Truong, S., Bohndorf, V., Geller, H., Schumpelick, V., & Gunther, R. W. (1992). Self-expanding metal stents for palliation of malignant gastric outlet obstruction. *Endoscopy, 24*, 433–435.
14. Adler, D. G., & Baron, T. H. (2002). Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: Experience in 36 patients. *American Journal of Gastroenterology, 97*, 72–78.
15. Kim, J. H., Yoo, B. M., Lee, K. J., Hahm, K. B., Cho, S. W., Park, J. J., et al. (2001). Self-expanding coil stent with a long delivery system for palliation of unresectable malignant gastric outlet obstruction: A prospective study. *Endoscopy, 33*, 838–842.
16. Pinto Pabon, I. T., Diaz, L. P., Ruiz De Adana, J. C., & Lopez Herrero, J. (2001). Gastric and duodenal stents: Follow-up and complications. *Cardiovascular and Interventional Radiology, 24*, 147–153.
17. Mittal, A., Windsor, J., Woodfield, J., Casey, P., & Lane, M. (2004). Matched study of three methods for palliation of malignant pyloroduodenal obstruction. *British Journal of Surgery, 91*, 205–209.
18. Wong, Y. T., Brams, D. M., Munson, L., Sanders, L., Heiss, F., Chase, M., et al. (2002). Gastric outlet obstruction secondary to pancreatic cancer: Surgical vs endoscopic palliation. *Surgical Endoscopy, 16*, 310–312.
19. Yim, H. B., Jacobson, B. C., Saltzman, J. R., Johannes, R. S., Bounds, B. C., Lee, J. H., et al. (2001). Clinical outcome of the use of enteral stents for palliation of patients with malignant upper GI obstruction. *Gastrointestinal Endoscopy, 53*, 329–332.

20. Fiori, E., Lamazza, A., Volpino, P., Burza, A., Paparelli, C., Cavallaro, G., et al. (2004). Palliative management of malignant antro-pyloric strictures: Gastroenterostomy vs. endoscopic stenting: A randomized prospective trial. *Anticancer Research, 24*, 269–271.
21. Baron, T. H., & Harewood, G. C. (2003). Enteral self-expandable stents. *Gastrointestinal Endoscopy, 58*, 421–433.
22. Jung, G. S., Song, H. Y., Kang, S. G., Huh, J. D., Park, S. J., Koo, J. Y., et al. (2000). Malignant gastroduodenal obstructions: Treatment by means of a covered expandable metallic stent-initial experience. *Radiology, 216*, 758–763.
23. Park, K. B., Do, Y. S., Kang, W. K., Choo, S. W., Han, Y. H., Suh, S. W., et al. (2001). Malignant obstruction of gastric outlet and duodenum: Palliation with flexible covered metallic stents. *Radiology, 219*, 679–683.
24. Jeong, J. Y., Han, J. K., Kim, A. Y., Lee, K. H., Lee, J. Y., Kang, J. W., et al. (2002). Fluoroscopically guided placement of a covered self-expandable metallic stent for malignant antroduodenal obstructions: Preliminary results in 18 patients. *AJR American Journal of Roentgenology, 178*, 847–852.
25. Dumas, R., Demarquay, J. F., Caroli-Bosc, F. X., Paolini, O., Guenenna, D., Peten, E. P., et al. (2000). Palliative endoscopic treatment of malignant duodenal stenosis by metal prosthesis. *GastroenteÂrologie Clinique et Biologique, 24*, 714–718.
26. Dormann, A., Meisner, S., Verin, N., & Wenk Lang, A. (2004). Self-expanding metal stents for gastroduodenal malignancies: Systematic review of their clinical effectiveness. *Endoscopy, 36*, 543–550.
27. Nassif, T., Prat, F., Meduri, B., Fritsch, J., Choury, A. D., Dumont, J. L., et al. (2003). Endoscopic palliation of malignant gastric outlet obstruction using self-expandable metallic stents: Results of a multicenter study. *Endoscopy, 35*, 483–489.
28. De Luca, A., & Coupar, I. M. (1996). Insights into opioid action in the intestinal tract. *Pharmacology & Therapeutics, 69*, 103–115.
29. Kurz, A., & Sessler, D. I. (2003). Opioid-induced bowel dysfunction: Pathophysiology and potential new therapies. *Drugs, 63*, 649–671.
30. Baron, T. H., Schofl, R., Puespoek, A., & Sakai, Y. (2001). Expandable metal stent placement for gastric outlet obstruction. *Endoscopy, 33*, 623–628.

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Surgical Outcomes of Gastrointestinal Sarcoma Including Gastrointestinal Stromal Tumors: A Population-based Examination

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Abstract
Introduction The surgical approaches and outcomes for gastrointestinal sarcoma are determined largely from single institutional series.
Objective We sought to determine patient outcomes after different surgical approaches for gastrointestinal sarcomas, including gastrointestinal stromal tumors (GIST), utilizing a large prospective cancer registry.
Material and Methods The Surveillance, Epidemiology, and End Results (SEER) database was queried from 1991 to 2002.
Results Overall, 1873 gastrointestinal mesenchymal tumors were identified in the SEER data set, with 82% GIST and 18% smooth muscle neoplasms. Surgery was performed in 83% of the cohort. Median survival was 68 months for complete resection (CR), 51 months for partial resection (PR), and 10 months for no resection (NR) ($P<0.001$ each category). Outcomes within the CR group were equivalent for wedge or total organ removal. Median survival rates for localized, regionally advanced, and metastatic disease were 97, 35, and 18 months, respectively, after CR, and in all cases significantly improved relative to patients not undergoing resection. Median survival rates in patients treated after 2000 have substantially improved in this cohort, possibly reflecting the impact of imatinib on overall population-based survival. Multivariate analysis identified organ, histologic grade, surgical resection, and date of surgery (pre-2000 or post-2000) as independent predictors of survival. Conclusions: The outcomes after surgical therapy for gastrointestinal sarcomas, including GIST, support the operative goal of a complete resection. Improved outcomes after 2000 indicate the potential benefit of newer therapies, including imatinib.

Keywords SEER · Sarcoma · Epidemiology · STI-571

Introduction

A minority of soft tissue sarcomas affect the gastrointestinal tract, with an annual incidence of 10 to14.5 cases per million population.[1–4] Gastrointestinal stromal tumors, or GISTs, account for approximately 82% of gastrointestinal mesenchymal tumors, with the remaining 18% being smooth muscle neoplasms.[4,5] Although other sarcomas (most commonly Schwann cell neoplasms) may affect the GI tract, these tumors rarely arise directly from the gastrointestinal tract and represent less than 1% of gastrointestinal sarcomas. GISTs appear to develop not from smooth muscle cells, but from the intestinal pacemaker cells of Cajal (ICC). GISTs may arise from any organ where ICC cells are present, including the stomach, small bowel, colon, rectum, omentum, biliary tree, and liver.[6] ICC and GISTs demonstrate similar ultrastructure, both morphologically and immunophenotypically, including similar high levels of c-kit and CD34 expression.[5–7]

C-kit gain-of-function mutations promote early growth and development of the majority (85%) of sporadic and

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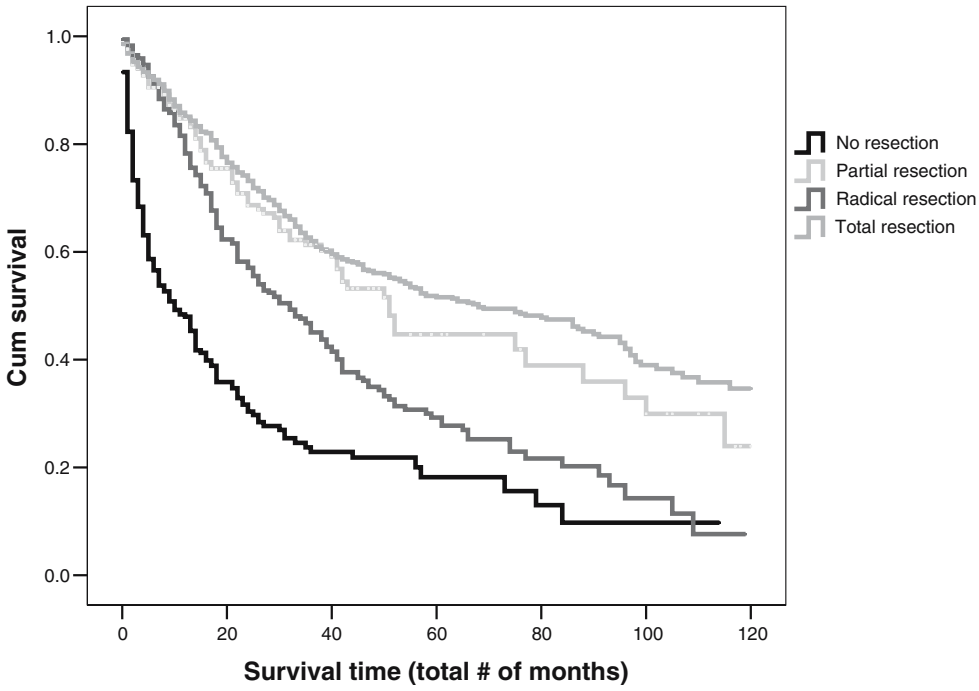


Figure 1 Gastrointestinal mesenchymal tumor overall survival by surgical resection. SEER dataset, 1992–2002.

familial GISTs.[8–11] GISTs also arise from gain-of-function mutations in the closely related type III tyrosine kinase, platelet-derived growth factor-alpha (PDGFRa).[5,12,13] Imatinib mesylate (STI-571, Gleevec or Glevic, Novartis, Basel, Switzerland) is a selective tyrosine kinase inhibitor that has markedly changed both the treatment options and eventual outcomes for patients with GISTs.[1,2,14] Initially developed for the treatment of chronic myelogenous leukemia, imatinib was approved by the FDA for the treatment of KIT-expressing GISTs in early 2002.[15]

We previously examined the epidemiology of GISTs utilizing two large prospective cancer registries—the SEER database organized by the NCI, and the FCDS database sponsored by the University of Miami.[4] These two nonoverlapping cohorts represent approximately 17% and 6% of the US population, respectively. Both registries report dramatic increases in the diagnosis of GISTs, with concomitant decreases in the diagnosis of gastrointestinal leiomyosarcoma after 2000. This finding likely represents a systematic misdiagnosis of GISTs as smooth-muscle neoplasms before a better understanding of their unique immunophenotypic profile in the late 1990s.[4] The SEER data indicate a dramatic improvement in overall survival for patients with GISTs after 2000, most likely associated with the introduction of imatinib.[4]

Several institutional series have defined the important role of surgery for managing gastrointestinal sarcomas. These series have been largely underpowered, with less than 200 cases.[16] Therefore, to determine the outcomes after surgical resection by stage, and to determine if the introduction of new therapies, like imatinib, affects overall survival, we examined the outcomes of patients undergoing resection for gastrointestinal sarcomas in the SEER data registry.

Table 1 Gastrointestinal Mesenchymal Tumor Outcomes by Surgical Resection

	Median survival (mo)	No. of patients	5 year survival %	No resection	Partial resection	Total resection	Radical resection
No resection	10	317	18.2		$P>0.001$	$P>0.001$	$P>0.001$
Partial resection	51	258	44.7	$P>0.001$		$P=0.218$	$P>0.001$
Total resection	68	919	51.6	$P>0.001$	$P=0.218$		$P>0.001$
Radical resection	32	349	29.3	$P>0.001$	$P=0.010$	$P>0.001$	

Five-year and median survival were determined by the Kaplan–Meier method. SEER data set, 1992–2002

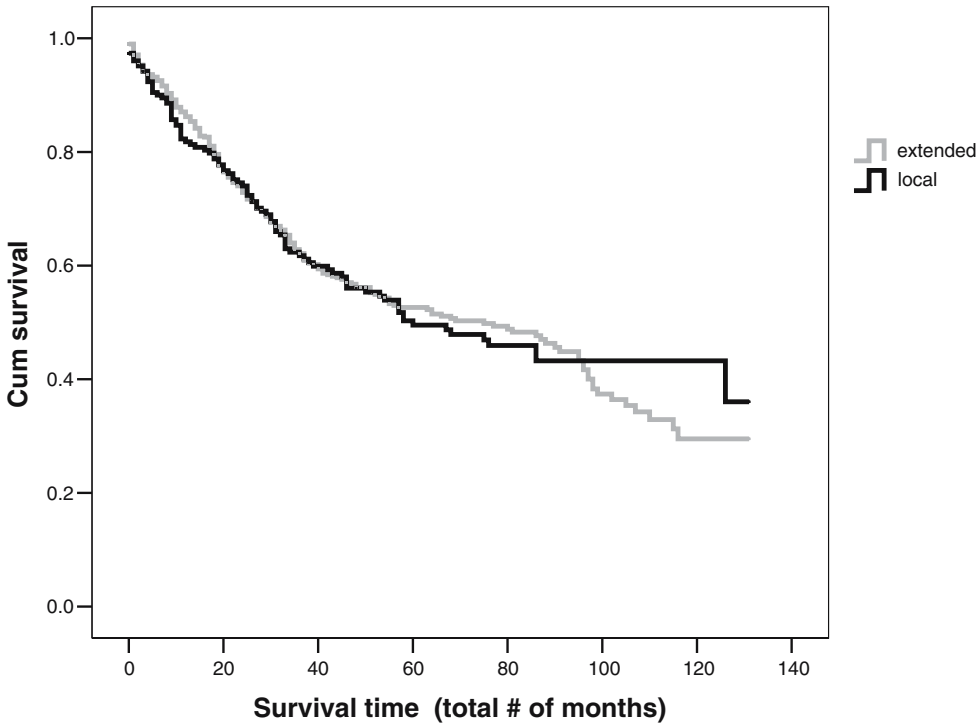


Figure 2 Subset analysis of the total resection cohort into extended resection and local resection. SEER dataset, 1992–2002.

Materials and Methods

The Surveillance, Epidemiology, and End Results (SEER) database is a 13-center cumulative tumor registry supported by the National Cancer Institute. SEER data are representative of approximately 17% of the US population [http://seer.cancer.gov/studies/endresults/study26.html]. This study utilized the SEER-13 public-use data set last updated in November 2004 and released in April 2005.

The SEER registry was examined from 1992 through 2002, with 1,873 cases of GIST, smooth muscle, and nerve-sheath tumors, which were identified using ICD-0 histology codes 8890 (42.7%), 8635 (1.2%), 8636 (56%), and 9560 (0.2%).[17] Of note, the SEER registry only collects data from malignant mesenchymal tumors and does not record cases of indeterminate malignant risk or benign disease.

Table 2 Subset Analysis of the Total Resection Cohort into an Extended Resection and Local Resection

	Median survival (mo)	No. of patients	5-year survival%	*P* value
Local	60	229	49.5	0.933
Extended	75	691	52.6	0.933

Five-year and median survival times were determined by the Kaplan–Meier method. SEER data set, 1992–2002

SEER*Stat version 6.4.1 was used to determine age-adjusted incidence and mortality rates. SPSS software (Statistical Package for the Social Sciences, version 13.0, SSPS Inc, Chicago, IL, USA) was utilized for survival calculations. Overall survival time was calculated as the time from diagnosis to death from any cause and censored at date of last contact. The Kaplan–Meier survival method was used to calculate the median, 2-year, and 5-year survival rates, with Cox regression used for multivariate analysis of survival. The log-rank test was applied to measure differences in survival.

Results

The Changing Diagnosis and Incidence of GIST versus Smooth Muscle Neoplasms

The diagnosis of most smooth muscle neoplasms from the 1990s often represented misdiagnosed GIST tumors.[4,5] Before the introduction of imatinib, this distinction appeared to be irrelevant as similar outcomes were obtained with both true smooth muscle neoplasms and GIST tumors. Similarly, less than 1% of all gastrointestinal stromal tumors are Schwann cell neoplasms. Our previous work was consistent with these findings, showing that the diagnosis of GIST had dramatically increased since the early 1990s so that by 2002, GIST diagnosis accounted for 82% of all gastrointestinal sarcomas.[4]

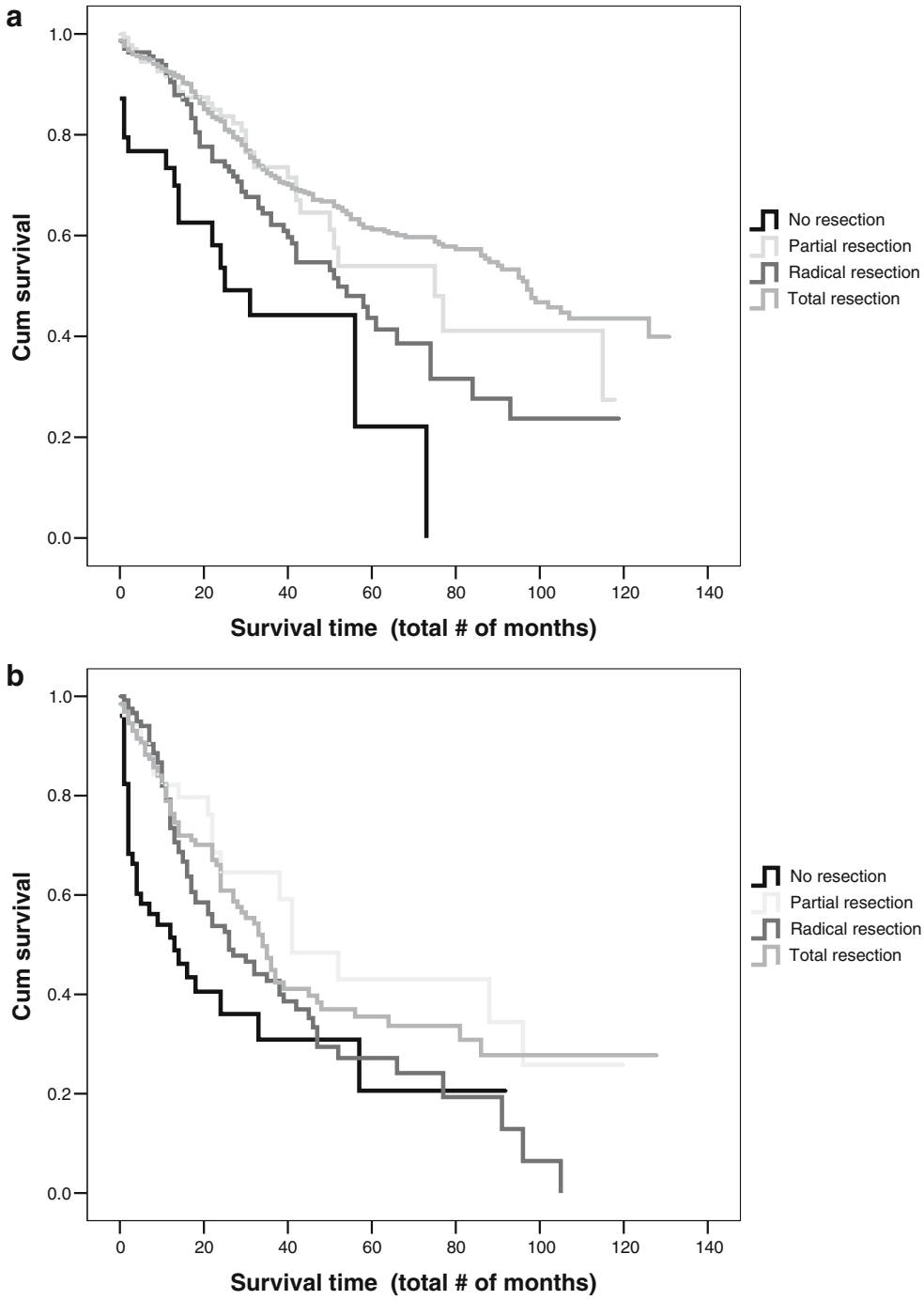
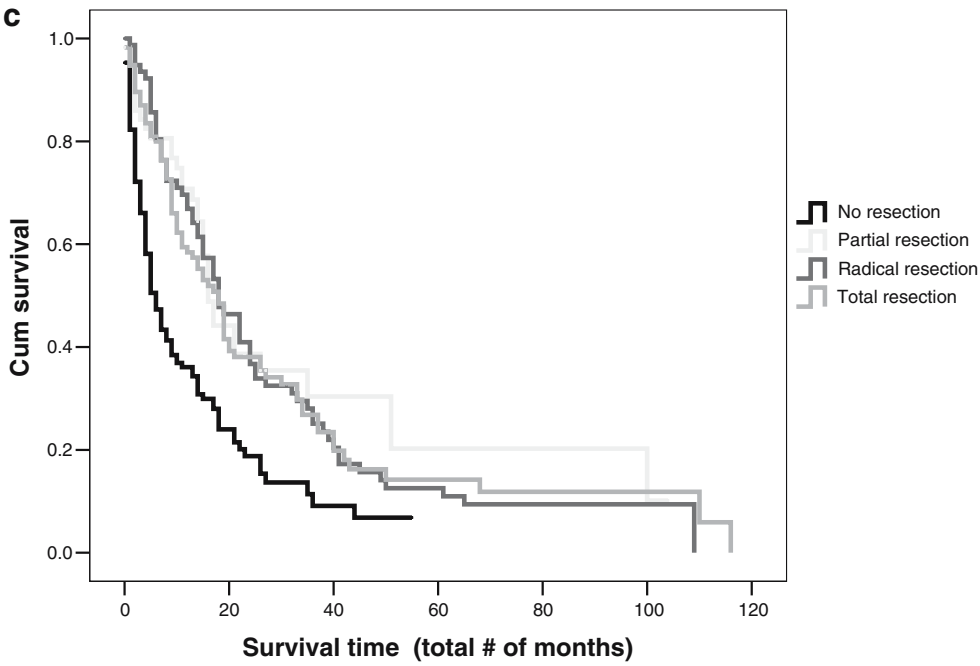


Figure 3 Gastrointestinal mesenchymal tumor survival by surgical resection and stage: a) local, b) regional, c) distant. SEER dataset, 1992–2002.

The Effects of Surgery on Gastrointestinal Sarcoma Outcomes

Of the 1,843 GISTs or gastrointestinal smooth muscle neoplasm cases in the SEER database from 1992 through 2002, 1526 of these cases (83%) underwent surgical resection. Patients were categorized into the following four groups depending on the extent of surgical intervention, without overlaping: no resection, partial resection, radical resection (removal of two or more visceral organs), and complete or total resection. Figure 1 and Table 1 show Kaplan–Meier survival curves for each approach in the cohort. Partial and complete resections had similar outcomes (P=0.218) with considerably improved survival when compared with radical resection, which represents the removal of more than one organ, or no surgical intervention. Margin status is not available in the radical resection subgroup. Splitting the complete resection cohort

Figure 3 (Continued).



into extended resection (such as subtotal gastrectomy) and local resection (local extirpation with negative margins) groups showed equivalent survival rates. Therefore, we did not find an additional benefit for the extended resection of gastrointestinal sarcomas, suggesting that surgical therapy should be limited to achieving negative margins without further radical dissection (Fig. 2 and Table 2).

We next examined outcomes based on the initial stage at presentation by subdividing patients into local, regional (direct invasion into adjacent organs or lymph nodes), and metastatic gastrointestinal sarcoma. Total or partial resection patients showed improved survival for localized disease (Fig. 3a, Table 3). Patients who required a radical resection carried a poor prognosis, suggesting that such tumors represent a more aggressive variant (Tables 4 and 5).

We found improved survival for total or partial resection for tumors larger or smaller than 10 cm (Table 6). In contrast, this is not the case with high-grade tumors (Table 5).

Table 3 Gastrointestinal Mesenchymal Tumor Outcomes by Surgical Resection and Stage

	Median survival (mo)	No. of patients	5-year survival %	No resection	Partial resection	Total resection	Radical resection
Local							
No resection	25	20	22.1		$P<0.001$	$P<0.001$	$P=0.006$
Partial resection	75	107	54.0	$P<0.001$		$P=0.598$	$P=0.101$
Total resection	97	426	61.2	$P<0.001$	$P=0.598$		$P=0.001$
Radical resection	52	80	43.7	$P=0.006$	$P=0.101$	$P=0.001$	
Regional							
No resection	14	13	20.6		$p<0.001$	$P<0.001$	$p=0.011$
Partial resection	41	41	43	$p<0.001$		$P=0.372$	$p=0.027$
Total resection	35	34	35.5	$p<0.001$	$p=0.372$		$p=0.121$
Radical resection	26	26	27.2	$p<0.011$	$p=0.027$	$P=0.121$	
Distal							
No resection	6	6	6.8		$P<0.001$	$P<0.001$	$P<0.001$
Partial resection	17	16	20.3	$P<0.001$		$P=0.507$	$P=0.715$
Total resection	18	18	14.2	$P<0.001$	$P=0.507$		$P<0.946$
Radical resection	18	18	12.5	$P<0.001$	$P=0.715$	$P<0.946$	

Five-year and median survival times were determined by the Kaplan–Meier method. SEER data set, 1992–2002

Table 4 Gastrointestinal Mesenchymal Tumor Outcomes by Site

	No of patients	5-year survival %	Median survival (mo)	Large intestine	Esophagus	Liver	Pancreas	Peritoneum, omentum and mesentery	Small intestine	Stomach
Large intestine	191	45.5	48		$P=0.152$	$P=0.005$	$P<0.001$	$P=0.014$	$P=0.708$	$P=0.476$
Esophagus	20	28.1	19	$P=0.152$		$P=0.389$	$P=0.245$	$P=0.842$	$P=0.131$	$P=0.174$
Liver	14	0	17	$P=0.005$	$P=0.389$		$P=0.960$	$P=0.059$	$P<0.001$	$P=0.007$
Pancreas	18	9.7	14	$P<0.001$	$P=0.245$	$P=0.960$		$P=0.032$	$P<0.001$	$P<0.001$
Peritoneum, omentum and mesentery	87	27.2	26	$P=0.014$	$P=0.842$	$P=0.059$	$P=0.032$		$P=0.005$	$P=0.029$
Small intestine	611	42.3	42	$P=0.708$	$P=0.131$	$P<0.001$	$P<0.001$	$P=0.005$		$P=0.425$
Stomach	832	43.3	42	$P=0.476$	$P=0.174$	$P=0.007$	$P<0.001$	$P=0.029$	$P=0.425$	

Five-year and median survival times were determined by the Kaplan–Meier method. SEER data set, 1992–2002

The Effects of Gastrointestinal Sarcoma Site on Outcome

Similar improved survival rates appear for tumors in the stomach, small bowel, and colon relative to other sites (Fig. 4 and Table 4). The etiology is unclear, but the pancreas, liver, and esophagus had a larger fraction of true smooth muscle neoplasms,[4] with equal distribution of histologic grade and size (data not shown).

Gastrointestinal Sarcoma Survival after 2000

The SEER database does not provide specific information regarding chemotherapy. As outcomes are organized by year, however, they may be used to examine the impact of practice changes, such as the introduction of imatinib, on survival. Imatinib therapy was introduced in 2000 and widely used after 2001 in a large percentage of GIST patients. As a large fraction of patients diagnosed in 2000 and 2001 likely survived to receive imatinib, we compared survival pre-2000 and post-2000 (Table 7). These outcomes were likely conservative and would underestimate differences, as some patients diagnosed pre-2000 received imatinib and some patients after 2000 did not. Nevertheless, a significant increase in overall survival is observed in all groups except radical resections (Fig. 5). To be certain that this phenomenon was not present before 2000, we also compared outcomes from 1992–1996 and 1996–2000. No significant survival difference was observed, suggesting that the improved survival was specific to 2000 and the introduction of imatinib (data not shown).

Multivariate Analysis of GIST Outcomes

Multivariate analyses of the treatment-independent variables showed gender, age, grade, stage, and size to be significant predictors of survival. Tumor site (stomach, small bowel, and colon versus other sites) showed a trend for improved survival ($P=0.074$). The year 2000 cut-off

Table 5 Gastrointestinal Mesenchymal Tumor Outcomes by Grade and Resection Type

Histological grade	Type of surgery	Median survival (mo)	5-year survival %	No. of patients	No resection	Partial resection	Total resection	Radical resection
Low grade I, II	No resection	14	41.3	36		$P<0.0001$	$P<0.0001$	$P=0.0153$
	Partial resection	77	61.1	91	$P<0.0000$		$P=0.8964$	$P=0.0124$
	Total resection	97	63.5	286	$P<0.0001$	$P=0.8964$		$P=0.0002$
	Radical resection	50	40.5	84	$P=0.0153$	$P=0.0124$	$P=0.0002$	
High Grade III, IV	No resection	9	0	45		$P=0.0018$	$P<0.0001$	$P=0.0047$
	Partial resection	22	27.1	45	$P=0.0018$		$P=0.5413$	$P=0.3323$
	Total resection	25	29.0	180	$P<0.0001$	$P=0.5413$		$P=0.0258$
	Radical resection	16	18.1	84	$P=0.0047$	$P=0.3323$	$P=0.0258$	

Two-year and median survival times were determined by the Kaplan–Meier method. SEER data set, 1992–2002

Table 6 Gastrointestinal Mesenchymal Tumor Outcomes by Size and Resection Type

Tumor size	Type of surgery	Median survival (mo)	5 year survival %	No. of patients	No resection	Partial resection	Total resection	Radical resection
Less than 9.9 cm	No resection	14	27.2	85		$P<0.0001$	$P<0.0001$	$P=0.0003$
	Partial resection	52	48.7	144	$P<0.0001$		$P=0.4944$	$P=0.0966$
	Total resection	91	58.6	531	$P<0.0001$	$P=0.4944$		$P=0.0010$
	Radical resection	49	37.4	128	$P=0.0003$	$P=0.0966$	$P=0.0010$	
Greater than 10 cm	No resection	7	14.6	232		$P<0.0001$	$P<0.0001$	$P<0.0001$
	Partial resection	42	40.8	114	$P<0.0001$		$P=0.3780$	$P=0.0338$
	Total resection	40	41.8	388	$P<0.0001$	$P=0.3780$		$P<0.0001$
	Radical resection	24	24.7	221	$P<0.0001$	$P=0.0338$	$P<0.0001$	

Two-year and median survival times were determined by the Kaplan-Meier method. SEER data set, 1992–2002.

and a resection (surgery) were significant predictors of survival (Table 8). Forward and backward stepwise analysis, with variables of surgery and year, did not alter results (data not shown).

Discussion

Treatment of gastrointestinal sarcomas, including GIST, historically has relied on surgical extirpation in cases of localized disease. Most series represent either a subset of true GISTs or also include smooth muscle tumors. These series report an overall 5-year survival rate of approximately 50%.[16,18,19] More advanced disease reduced median survival to less than 21 months.[20] The surgical approach for GISTs should be similar to other sarcomas,[16,18–20] and neither chemotherapy using traditional antineoplastic agents nor radiotherapy has any survival benefit for either GISTs or smooth muscle tumors.[21] As recently as 2000, there was little difference in therapy for a diagnosis of smooth muscle tumor or GIST—surgical resection would be offered to appropriate patients, and others would be offered a phase-1 or a phase-2 trial with chemotherapy and/or radiation, without evidence of significant survival benefit.[2,21] More recently, however, imatinib has markedly changed the outcome and treatment options after surgery as well as in nonresectable disease. Markedly improved survival was reported in a phase-1 trial published in *The Lancet*,[22] with findings confirmed in subsequent phase-2 studies.[14,23,24]

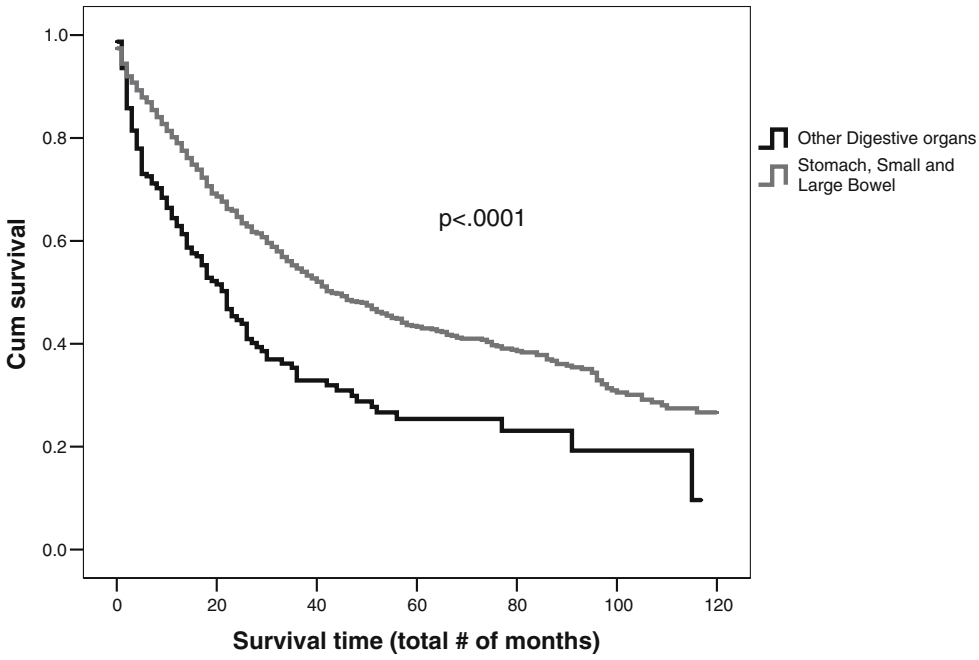


Figure 4 Gastrointestinal mesenchymal tumor overall survival by site. SEER dataset, 1992–2002.

Table 7 Gastric Mesenchymal Tumor Outcomes After Resection by Stage, Tumor Size, Grade, and Site Before and After 2000 Based on the SEER Data Set

	Before 2000			After 2000			
Overall	2-year survival %	No. of patients	Median Survival	2-year survival %	No. of patients	Median survival	*P* value
No resection	22	166	5	42.6	151	24	0.001
Partial resection	62.5	118	>35	79.0	140	>35	0.027
Total resection	70.04	620	>35	84.7	299	>35	0.003
Radical resection	55.5	245	30	68.9	104	>35	0.419
All	59	1,149	35	72.9	694	>35	0.001
Stage							
Local							
No resection	56.3	16	25	46.2	23	24	0.957
Partial resection	79.7	64	>35	92.0	77	>35	0.229
Total resection	81.6	421	>35	88.5	212	>35	0.159
Radical resection	72.3	94	>35	88.1	45	>35	0.132
All	79.1	598	>35	86.5	359	>35	0.057
Distant							
No resection	7.4	97	4	48.9	73	17	0.001
Partial resection	26.2	32	16	68.2	26	>35	0.049
Total resection	30.4	79	14	69.1	37	27	0.021
Radical resection	41.1	61	22	18.7	19	8	0.008
All	23.6		27	53.3		>35	0.001
Regional							
No resection	33	21	4	23.8	30	14	0.464
Partial resection	60	20	>35	70.1	33	>35	0.553
Total resection	73.6	91	32	84.0	40	>35	0.031
Radical resection	48.2	83	22	76.4	38	>35	0.101
All	51.7		11	68.1		26	0.031
Histological Grade							
Grade 1							
No resection	45.5	11	>35	100.0	2	>35	0.225
Partial resection	84.6	13	>35	66.7	10	>35	0.924
Total resection	86.2	66	>35	90.9	21	>35	0.605
Radical resection	81.3	16	>35	100.0	7	>35	0.467
All	81.10			87.3			
Grade 2							
No resection	50	10	7	23.1	13	5	0.416
Partial resection	71.9	32	>35	96.9	36	>35	0.041
Total resection	81.3	163	>35	86.8	36	>35	0.625
Radical resection	66	53	>35	100.0	8	27	0.658
All	75.8			81.6			
Grade 3							
No resection	33.3	12	16	0	7	24	0.545
Partial resection	41.7	12	15	80.0	5	>35	0.567
Total resection	52.9	51	25	59.2	17	14	0.929
Radical resection	23.5	17	11	46.7	11	12	0.364
All	44.1			36.9			
Grade 4							
No resection	6.7	15	4	17.0	11	14	0.347
Partial resection	42.9	14	22	53.8	14	30	0.956
Total resection	50	74	24	55.7	55.5	27	0.994
Radical resection	38.1	42	17	65.6	14	25	0.509
All	40.5			51.6			
Site							
Colon							
No resection	18.8	16	2	60.0	14	>35	0.018
Partial resection		1					
Total resection	75.8	99	>35	80.3	41	>35	0.881

Table 7 (Continued)

	Before 2000			After 2000			
Overall	2-year survival %	No. of patients	Median Survival	2-year survival %	No. of patients	Median survival	*P* value
Radical resection	61.5	13	>35	40.0	5	6	0.277
All	66.2			50.0			0.474
Small bowel							
No resection	36.8	19	8	34.2	27	24	0.208
Partial resection	67	94	>35	79.7	128	>35	0.089
Total resection	66.7	184	>35	83.0	45	>35	0.623
Radical resection	62.9	73	>35	94.4	33	>35	0.235
All	64			77.1			0.035
Stomach							
No resection	20.7	82	6	27.9	58	13	0.339
Partial resection							
Total resection	73.6	303	>35	87.6	197	>35	0.004
Radical resection	50.3	130	25	63.6	50	>35	0.408
All	58.9			73.1			0.003
Size							
Less than 9.9 cm							
No resection	41.5	41	10	75.5	44	>35	0.014
Partial resection	74.2	66	>35	81.1	78	>35	0.291
Total resection	76.9	359	>35	85.9	172	>35	0.167
Radical resection	65.5	82	>35	94.6	46	>35	0.025
All	71.1		>35	82.8		>35	0.006
Greater than 10 cm							
No resection	18.7	125	5	37.3	107	17	0.005
Partial resection	47.3	52	22	75.9	62	>35	0.026
Total resection	61.7	261	>35	83.0	127	>35	0.004
Radical resection	50.5	163	25	39.2	58	16	0.170
All	48.3	163	23	63.8	58	>35	0.006

Two-year and median survival times were determined by the Kaplan–Meier method.

We first set out to determine patient outcomes from the SEER registry based on stage and surgical intervention. Operative therapy was associated with a broad range of outcomes based on both stage and surgical approaches. Understanding these differences appears to be critical in planning operative approaches for patients with GISTs. For localized disease, simple tumor extirpation with negative margins was as effective as more extensive resections of regional tissue. For the treatment of a gastric GIST, for example, resection with simple negative margins appears to be equally effective as a more extensive resection such as a subtotal or total gastrectomy, with a decreased morbidity rate.[25] Patients with a partial GIST resection, which includes those with positive microscopic margins (R1) and residual disease (R2), show significantly better outcomes than the no-surgery group, and actually approach that of total (R0) resection, similar to what has been observed for other sarcomas.[26]

We next examined the role of radical surgery for patients with gastrointestinal sarcomas for regionally advanced disease. Patients with aggressive radical resections involving removal of more than one organ showed improved outcomes to nonsurgical treatment. There is still evidence to support a less-aggressive resective approach to reduce morbidity, but the decision should be left to the discretion of the surgeon. Similarly, the tumor biology of a larger multiorgan gastrointestinal sarcoma may represent metastatic or aggressive disease versus tumors confined to a single organ. Nonetheless, patients with gastrointestinal sarcoma should undergo surgical evaluation as substantial palliation or an instant cure may result from an operative approach.

We next examined the role of surgery in the palliative care of patients with metastatic gastrointestinal sarcoma. Patients that underwent partial or total resection of the primary tumor showed significantly improved survival. Although these survival differences may be due to a selection bias among this group, with patients with advanced disease not having surgery, these data support a palliative therapeutic role for resection of the primary malignancy in all patients with metastatic GIST. Further studies are warranted to confirm these findings.

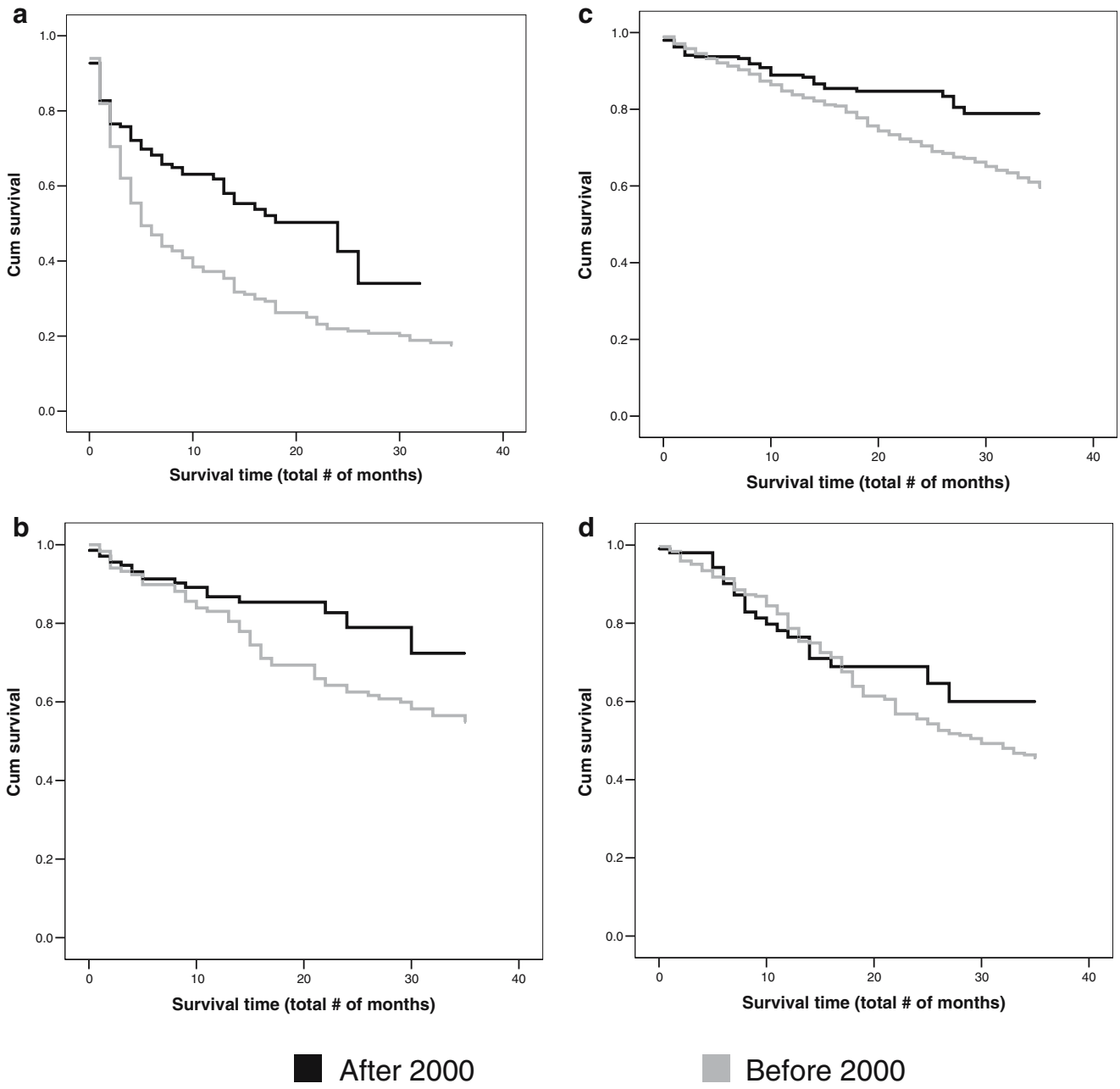


Figure 5 Gastric mesenchymal tumor survival before (gray) and after (black) 2000 by: a) no resection, b) partial resection, c) total resection, and d) radical resection.

We next attempted to determine the effect of newer therapies, particularly imatinib, on survival for patients with GIST. Since the SEER database does not include information on pharmacologic therapy, and current data on GIST may underestimate the true frequency of GIST, this question could not be directly examined. We therefore took an indirect approach by comparing survival of patients with all mesenchymal tumors both before and after 2000 (the year imatinib received FDA approval), truncating follow-up at 35 months. Widespread application of imatinib therapy did not occur until 2001, but an assumption was made that a large fraction of patients diagnosed in 2000 went on to receive imatinib. Both GISTs and smooth muscle tumors were included to correct for the systematic underdiagnosis of GISTs in earlier years of the study period.[5] Including tumors from 2000 in the imatinib group also probably underestimated the treatment benefit and provided a conservative measure that should be reexamined in the

Table 8 Multivariate Analysis of Independent and Dependent Variables Using the Cox Regression Model

	df	Sig.	HR	95 % CI for HR	
				Lower	Upper
Independent variables					
Gender	1	0.001	1.469385	1.20417	1.793014
Age at diagnosis	1	0.001	1.029456	1.021667	1.037304
Grade	1	0.001	2.241424	1.820429	2.759778
Stage (local)	2	0.001			
Stage (regional)	1	0.001	1.925605	1.493718	2.482366
Stage (distant)	1	0.001	3.553286	2.768624	4.560332
Size	1	0.006	1.335922	1.087979	1.640369
Site	1	0.074	1.302168	0.974698	1.739658
Treatment variables					
Year 2000 cutoff	1	0.001	1.610656	1.335367	1.942697
Surgery	1	0.001	3.428272	2.918703	4.026805

SEER data set, 1992–2002

postimatinib era as additional years of the SEER dataset become available. Nonetheless, given these intrinsic biases toward a null result, a dramatic improvement in survival in local, regional, and advanced disease was noted.

There are several limitations in the SEER database. One major limitation is the historic inability to separate smooth muscle neoplasms from GISTs, which plagues all studies before 2000 without retrospective pathologic reassignment. The second is inaccuracies in tumor origin may be present in the dataset. Furthermore, we have been unable to determine the role of repeat surgical intervention on survival, as the SEER registry does not provide this information. Since chemotherapy information is not provided in SEER, approaches to integrate imatinib therapy as an adjunct to surgical resection also remain unclear. In addition, the failure to observe differences in patient subsets before and after 2000 may be due to insufficient power or a large fraction of imatinib-resistant malignancies. Prospective trials will examine these questions.

Using the SEER data set, we conclude that margin-negative resection of gastrointestinal sarcoma is associated with an increased cure rate, and that patient outcomes are improving in recent years, possibly due to imatinib mesylate chemotherapy. Furthermore, based on these data there appears to be a palliative role for surgery, even in patients with advanced disease. Subset analysis demonstrates improved survival in most subsets of patients. Among patients with low-grade GIST, smaller than 5–10 cm, localized to stomach, small or large bowel, a small improvement in survival has been observed since 2000, suggesting that these patients may not require adjuvant imatinib, but should undergo close observation for potential recurrence. Prospective trials and further maturation of the SEER cohort will allow better delineation of those patients who may benefit from combined imatinib and surgery in the future.

References

1. Joensuu H, Fletcher C, Dimitrijevic S, et al. Management of malignant gastrointestinal stromal tumours. Lancet Oncol 2002;3 (11):655–664.
2. Connolly EM, Gaffney E, Reynolds JV. Gastrointestinal stromal tumours. Br J Surg 2003;90(10):1178–1186.
3. Nilsson B, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era—a population-based study in western Sweden. Cancer 2005;103(4):821–829.
4. Perez EA, Livingstone AS, Franceschi D, et al. Current incidence and outcomes of gastrointestinal mesenchymal tumors including GIST. J Am Coll Surg 2006;202(4):623–629, Apr.
5. Miettinen M, Sobin LH, Lasota J. Gastrointestinal stromal tumors of the stomach: a clinicopathologic, immunohistochemical, and molecular genetic study of 1765 cases with long-term follow-up. Am J Surg Pathol 2005;29(1):52–68.
6. Kindblom LG, Remotti HE, Aldenborg F, Meis-Kindblom JM. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol 1998;152(5):1259–1269.
7. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Human Pathol 2002;33(5):459–465.
8. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279(5350):577–580.
9. Hirota S, Isozaki K, Nishida T, Kitamura Y. Effects of loss-of-function and gain-of-function mutations of c-kit on the gastrointestinal tract. J Gastroenterol 2000;35(Suppl 12):75–79.
10. Hirota S, Nishida T, Isozaki K, et al. Familial gastrointestinal stromal tumors associated with dysphagia and novel type germline mutation of KIT gene. Gastroenterology 2002;122(5):1493–1499.
11. Li FP, Fletcher JA, Heinrich MC, et al. Familial gastrointestinal stromal tumor syndrome: phenotypic and molecular features in a kindred. J Clin Oncol 2005;23(12):2735–2743.

12. Fletcher JA, Fletcher CD, Rubin BP, et al. KIT gene mutations in gastrointestinal stromal tumors: more complex than previously recognized? Am J Pathol 2002;161(2):737–738, author reply 738–739.
13. Medeiros F, Corless CL, Duensing A, et al. KIT-negative gastrointestinal stromal tumors: proof of concept and therapeutic implications. Am J Surg Pathol 2004;28(7):889–894.
14. Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347(7):472–480.
15. Dagher R, Cohen M, Williams G, et al. Approval summary: imatinib mesylate in the treatment of metastatic and/or unresectable malignant gastrointestinal stromal tumors. Clin Cancer Res 2002;8(10):3034–3038.
16. Clary BM, DeMatteo RP, Lewis JJ, et al. Gastrointestinal stromal tumors and leiomyosarcoma of the abdomen and retroperitoneum: a clinical comparison. Ann Surg Oncol 2002;8(4):290–299.
17. Fritz A, Percy C, Jack A, Shanmugaratnam K, Sobin L, Parkin DM, Whelan S. International Classification of Diseases for Oncology. Third Edition. Geneva: World Heath Organization, 2000.
18. DeMatteo RP, Lewis JJ, Leung D, et al. Two hundred gastrointestinal stromal tumors: recurrence patterns and prognostic factors for survival. Ann Surg 2000;231(1):51–58.
19. Ng EH, Pollock RE, Romsdahl MM. Prognostic implications of patterns of failure for gastrointestinal leiomyosarcomas. Cancer 1992;69(6):1334–1341.
20. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005;100(1):162–168.
21. Plaat BE, Hollema H, Molenaar WM, et al. Soft tissue leiomyosarcomas and malignant gastrointestinal stromal tumors: differences in clinical outcome and expression of multidrug resistance proteins. J Clin Oncol 2000;18(18):3211–3220.
22. van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (STI571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet 2001;358(9291):1421–1423.
23. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364(9440):1127–1134.
24. Wu PC, Langerman A, Ryan CW, et al. Surgical treatment of gastrointestinal stromal tumors in the imatinib (STI-571) era. Surgery 2003;134(4):656–665, discussion 665–666.
25. Cunningham SC, Kamangar F, Kim MP, et al. Survival after gastric adenocarcinoma resection: eighteen-year experience at a single institution. J Gastrointest Surg 2005;9(5):718–725.
26. Singer S, Antonescu CR, Riedel E, Brennan MF. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. Ann Surg 2003;238 (3):358–370, discussion 370–371.