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2011 SSAT POSTER PRESENTATION

Total Abdominal Colectomy for Refractory Ulcerative Colitis. Surgical Treatment in Evolution

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Abstract
Introduction Total abdominal colectomy is the procedure of choice for debilitated patients with acute, medical refractory ulcerative colitis in our practice. A laparoscopic approach has been previously shown to be safe and effective, and has become our preferred strategy. This study illustrates the laparoscopic evolution towards a truly minimally invasive approach comparing three phases of a single colorectal surgeon experience.
Material and methods In May 2010 single incision laparoscopy was introduced in our practice and has become our preferred approach. Ten consecutive ulcerative colitis patients were case matched and compared with 10 previous laparoscopic-assisted (Feb 2003–Jan 2007) and 10 hand-assisted (Feb 2006–Apr 2010) total abdominal colectomies. Patient, disease and surgery-related factors were analyzed and short-term outcomes were compared.
Results Given the study design, there were no differences in demographics, smoking history, disease duration and severity, nutritional and inflammatory parameters, and indication for surgery between groups. Single incision patients were more likely to have received immunosuppressive therapy within 30 days of the surgery ($p=0.016$). In the single incision group we noticed significantly shorter duration of surgery ($p<0.001$) and faster resumption of solid diet ($p=0.019$) compared to the other groups. Other short-term outcomes did not differ between groups.
Conclusion Single incision laparoscopy offers a safe alternative to other laparoscopic approaches. Despite the higher technical complexity, the duration of surgery is shorter with faster resumption of oral intake. Studies with larger sample size and longer follow-up will be required to confirm the benefits of this approach.

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Introduction

The standard of care for patients with ulcerative colitis (UC) referred for surgery is a restorative proctocolectomy with an ileal pouch anal anastomosis. When they present acutely with active disease non-responsive to aggressive medical treatment a staged approach is advisable. Often these patients present in poor general medical conditions and nutritional status, with severe immunosuppression secondary to corticosteroids, immunomodulators, and biological agents, and, hence, at high risk of postoperative complications.[1,2] After reviewing our own experience we have adopted a staged strategy for these patients that offers a significant reduction in morbidity

and complications and improvement in short-term outcomes.[3] The first stage is a total abdominal colectomy (TAC) that allows for fast recovery and improvement of patients' general and nutritional status and since laparoscopy has been shown to be safe and effective it has become the preferred strategy in our practice.[4–10] Considering the magnitude of the procedure and the poor quality of severely inflamed tissues, a hand-assisted technique has been popularized as a valuable alternative to laparoscopic-assisted surgery, for a faster and safer procedure, still maintaining the benefit of laparoscopy.[11,12] In this severely debilitated patients population the reduction of surgical trauma does not just have cosmetic implications—still of high importance in this young patient population—but is mostly advocated for reduction of morbidity and faster resumption of normal activity.[13–15]

Single incision laparoscopic surgery (SILS) represents the latest move towards a true minimally invasive approach, and several reports have already been published in general, gynecologic and urologic surgery.[16–37] Particularly for TAC, SILS in our hands represents a true "scarless" procedure, with the only access to the abdominal cavity at the site of the future stoma, and in our experience it has been shown to be safe and effective.[38]

This study illustrates the evolution towards a truly minimally invasive approach to acute and medically refractory UC with the goal of assessing safety and feasibility of this new approach by comparing three subsequent phases of the experience of a single colorectal surgeon.

Material and methods

Since May 2010 single incision laparoscopy (SIL) has become the preferred approach for active UC refractory to aggressive medical therapy in our practice. Ten consecutive patients underwent SIL TAC and were case matched with 10 laparoscopic-assisted (LA) (Feb 2003–Jan 2007) and 10 hand-assisted (HA) (Feb 2006–Apr 2010) TAC. Prospectively collected data were retrospectively reviewed. Patient, disease and surgery-related factors were analyzed and short-term outcomes were compared. Statistical analysis was performed with SPSS 16.0 for Mac OSX using the Student's t-test, Mann–Whitney U test, chi-square test, Kruskal-Wallis test, and one-way ANOVA. A p value of 0.05 was considered statistically significant.

Preoperative care

Independently from the surgical approach, the ileostomy site was marked preoperatively by an ostomy care nurse. When not contraindicated, epidural analgesia was routinely recommended for reduction of intraoperative bowel distension and postoperative pain management. Mechanical bowel preparation was administered the day prior to surgery and antibiotic, antithrombotic prophylaxis, and corticosteroids—when appropriate—were administered before the start of the procedure. Pneumatic compression stockings for deep venous thrombosis prophylaxis and gastric and urinary catheters were routinely utilized. We placed the patient in lithotomy position, with the legs bent and abducted in stirrups and both arms tucked along the body.

Surgical technique

Our surgical technique for both LA TAC and HA TAC has been previously described.[3]

SIL TAC The access to the abdominal cavity was obtained by inserting a GelPoint® Advanced Access Platform (Applied Medical, Rancho Santa Margarita, CA) through a circular incision at the future ileostomy site (Fig. 1a). One 12-mm and three 5-mm trocars were introduced into the gel platform, and the procedure was performed with conventional, non-articulated laparoscopic instruments (Fig. 1b). We used a 12-mm 30-degree laparoscope and a 5-mm bipolar vessel sealing device. The Trendelenburg and tilt position varied during the procedure for optimal exposure.

In our experience, the most challenging portion and therefore at greater risk of conversion is the initial dissection and division of the ileocolic pedicle, located right below the access site, and we have typically addressed this part first. We started the dissection from the right colon, proceeding clockwise to the rectosigmoid junction. The ileocolic pedicle was dissected and divided, under visualization of right ureter and duodenum, and medial-to-lateral mobilization of the right colon was accomplished (Fig. 2). After dividing sharply the hepatocolic ligament, the transverse colon was fully mobilized by sequentially dividing the greater omentum, just distal to the gastroepiploic arcade and the transverse mesocolon (Fig. 3). Subsequently the lateral attachments of the descending colon were taken sharply and the avascular line of Told was bluntly dissected, with exposure of the left ureter (Fig. 4). Eventually, the inferior mesenteric vein and the branches of the sigmoid arteries were dissected and divided. A laparoscopic stapler was used at this point to transect the rectosigmoid junction after dissection of the mesentery. The specimen was extracted through the access device, the terminal ileum was divided extracorporeally and the ileostomy was matured in the standard Brooke fashion (Fig. 5). A rectal tube was routinely placed to decompress the rectal stump.

Subsequent to the abdominal colectomy eight of these patients underwent the second operation, six by SILS and two by conventional laparoscopy, all of them with a diverting loop ileostomy. Of this initial cohort six had the

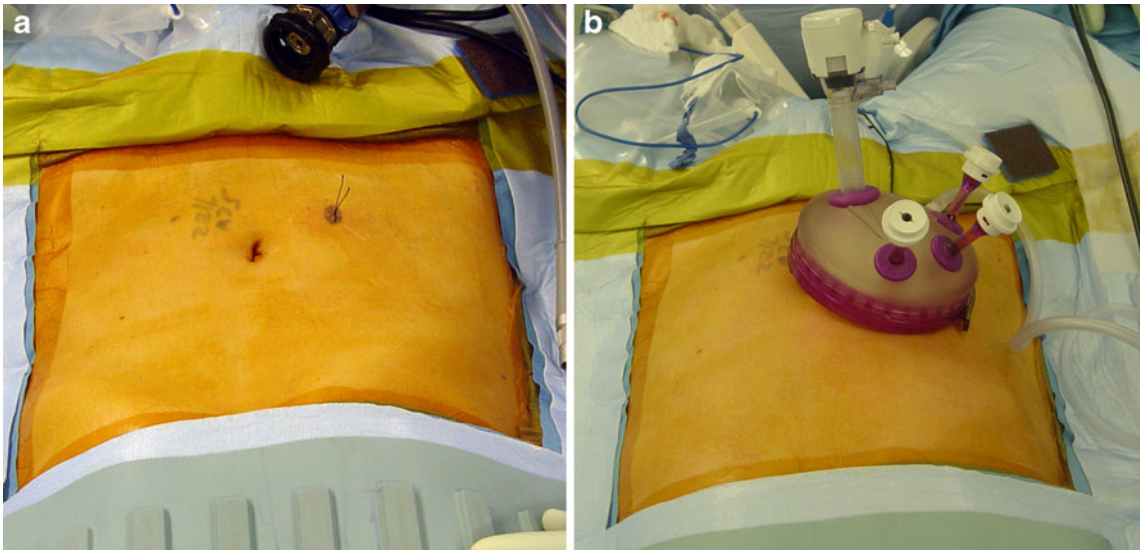

Fig. 1 **a**) Right lower quadrant ileostomy site marked preoperative by the enterostomal nurse. **b**) Single access device with the trocars in place

ileostomy taken down. Briefly, at the beginning of the second procedure the ileostomy was mobilized and the pouch was constructed extracorporeally, as previously described[39] and the center rod and anvil of the circular stapler was secured at the apex of the pouch. The pouch was then placed back into the abdominal cavity. Through the same ileostomy site the GelPoint® Advanced Access Platform (Applied Medical, Rancho Santa Margarita, CA) was inserted. One 12-mm and three 5-mm trocars were introduced into the gel platform, and the procedure was performed with conventional, non-articulated laparoscopic instruments. As for the TAC we used a 12-mm 30-degree laparoscope and a 5-mm bipolar vessel sealing device with the patient in the Trendelenburg position for optimal exposure. The terminal ileal mesentery was mobilized back to the root at the level of the duodenum to allow for adequate length and limit the tension on the anastomosis. The proctectomy was then performed in the avascular mesorectal plane after identification of the left ureter. The rectum was mobilized all the way to the pelvic floor circumferentially and transected intracorporeally with multiple fires of a laparoscopic stapling device. The specimen was removed through the access device. The ileoanal anastomosis was then constructed intracorporeally under direct laparoscopic vision. The anastomosis was always protected with a diverting loop ileostomy.

Results

All the 30 patients had a confirmed preoperative diagnosis of UC. Demographics, patient and disease specific characteristics were analyzed. Statistical analysis was performed comparing the three groups individually and also comparing the SIL group with the other two groups pooled together.

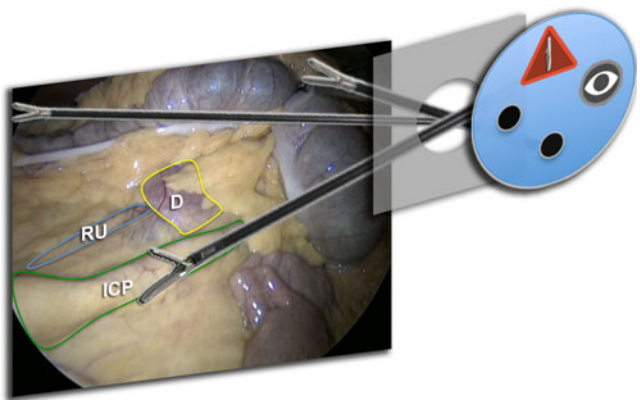

Fig. 2 Photographic schema of the initial portion of the procedure: The ileocolic dissection and transection. On the right of the picture is a diagram of the access device. D: duodenum, RU: right ureter, ICP: ileocolic pedicle

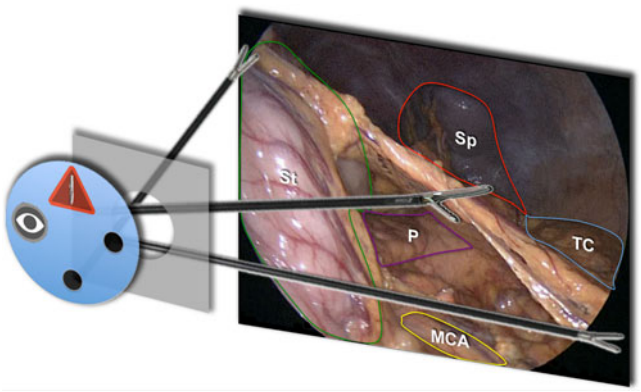

Fig. 3 Photographic schema of the transverse colon mobilization. On the left of the picture is a diagram of the access device. Sp: spleen, St: stomach, TC: transverse colon, P: pancreas; MCA: middle colic artery

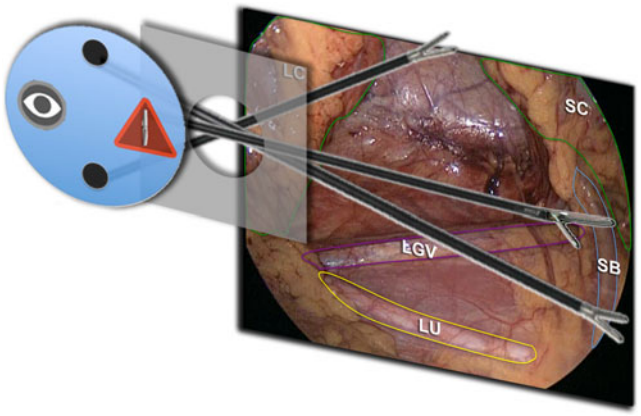

Fig. 4 Photographic schema of the descending colon mobilization. On the left of the picture is a diagram of the access device. LC: left colon, SC: sigmoid colon, LGV: left gonadal vessels, SB: sigmoidal branches

There were no statistical differences in age, gender, BMI and smoking history between the groups as expected per the study design (Table 1). Even if not statistical significant, given the small sample size, a higher rate of comorbidities was observed in SIL patients (40% versus 20% in HA and 10% in LA), likely reflecting a change in medical therapy with the introduction of biologic therapy for UC and an increase in the acuity of these patients. Similarly, disease duration, disease activity, defined as pathologic degree of inflammation in the resected specimen, Mayo score for UC, and nutritional and inflammatory parameters, assessed by preoperative c-Reactive Protein (CRP), albumin and white cells blood count (WBC) did not differ between groups (Table 1). No patients had undergone prior abdominal surgery in the SIL group, while one and two patients had had previous surgery in the LA and HA groups respectively (p=NS) (Table 1). All the patients were on corticosteroid

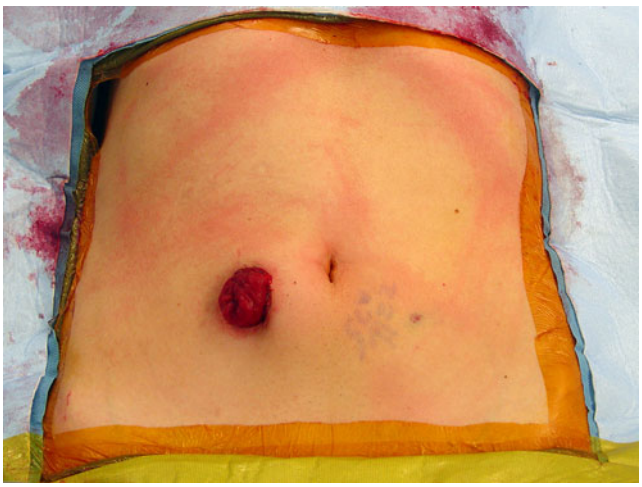

Fig. 5 After the specimen was extracted through the access device and the terminal ileum divided extracorporeally, the ileostomy was matured in the standard Brooke fashion

Table 1 Summary of results

	SILS	HA	LA	*p*
Age	28±6	32±14	36±9	ns
		34±11		ns
Sex *(m/f)*	8/2	4/6	6/4	ns
		10/10		ns
BMI	21.9±2.3	24.4±4.6	26.0±4.7	ns
		25.2±4.6		ns
Duration of disease *(months)*	58±63	27±27	83±88	ns
		55±70		ns
CRP *(mg/L)*	63.0±60.1	53.1±39.8	13.0±0.0	ns
		48.1±39.5		ns
WBC *(K/uL)*	11.3±7.0	10.8±5.0	10.0±1.6	ns
		10.4±3.7		ns
Albumin *(g/dl)*	3.5±0.7	3.4±0.9	3.5±0.6	ns
		3.4±0.8		ns
MAYO score	10.1±1.4	10.2±1.0	9.5±1.0	ns
		9.8±1.0		ns
Prior abd. surgery *(%)*	0	20	10	ns
		18		ns
Steroids 30-days prior *(%)*	80	100	100	ns
		100		ns
Immunosuppressors 30-days prior *(%)*	70	10	60	0.016
		35		ns
Anti-TNF 30-days prior *(%)*	40	40	10	ns
		25		ns
Length of surgery *(minutes)*	139±24	183±32	271±45	<0.001
		227±50		<0.001
EBL *(ml)*	100±121	85±123	144±174	ns
		115±150		ns
Intraop. complications *(%)*	0	0	20	ns
		10		ns
Return of bowel funct. *(p.o. day)*	1.6±0.7	1.0±0.0	2,5±0.7	ns
		2.0±1.0		ns
Diet resumption *(p.o. day)*	3.0±4.7	4.0±0.0	3.5±0.6	0.036
		3.7±5.1		0.019
Length of stay *(days)*	5.1±1.3	7.2±3.7	5.5±1.5	ns
		6.3±2.9		ns
Short-term complications *(%)*	0	30	20	ns
		25		ns

therapy at the time of the operation, including high dose intravenous steroids (Table 1). Furthermore, SIL TAC patients were more likely to have received immunosuppressive therapy within 30 days of the surgery than the other groups individually (p=0.016) once again likely reflecting a change in medical treatment protocol (Table 1). Intraoperative outcomes were recorded. The length of surgery was significantly shorter for SIL TAC (139.0+23.7 minutes)

when compared with LA (270.9+45.4) and HA (182.8+31.6) ($p<0.001$) (Table 1). Estimate blood loss (EBL) was minimal in all case (100±121 ml for SIL, 85±123 ml for HA and 144±174 ml for LA; p=NS) with no need for intraoperative transfusions (Table 1). There were no conversions. Only two intraoperative complications occurred in the laparoscopic group, represented in both cases by accidental enterotomies, which were noted intraoperatively and immediately repaired uneventfully (Table 1).

Postoperative outcomes were assessed. Return of bowel function was arbitrarily considered to have occurred when the recorded ileostomy output exceeded 100 ml per 8 hours. This was noted on postoperative day 1.6 for SIL patients, 1.0 for HA patients, and 2.5 for LA patients (p=NS) (Table 1). Resumption of diet, assessed by the time to tolerance of a low residue diet, was significantly faster in the SIL group (day 3.0 vs. 4.0 and 3.5 for HA and LA groups respectively; $p=0.036$ for individual groups analysis and $p=0.019$ for pooled analysis) (Table 1). No postoperative complication occurred in the SIL group, while 3 patients in the HA group and 2 in the LA group had grade II (Clavien-Dindo classification[40]) complications (one deep venous thrombosis and two postoperative small bowel obstructions in the HA group and two case of readmission for dehydration in the LA group) (Table 1). Length of stay was 5.1±1.3 days for SIL, 7.2±3.7 days for HA and 5.5±1.5 days for LA, with no significant difference between groups (Table 1).

Discussion

Our study summarized the laparoscopic evolution in the treatment of UC. SIL TAC offers a truly minimally invasive and virtually "scarless" approach in selected UC patients in experienced hands. While the experience is still very preliminary and the follow-up very short, SIL TAC should be considered a promising alternative to "conventional" laparoscopy in selected UC patients.

A laparoscopic assisted approach to restorative surgery for UC was introduced in our practice in 2002, and progressively it has become our approach of choice, on the basis of the observed advantages in short-term, potential long-term outcomes, excellent functional results, with the more obvious improvements in cosmesis and patients' perception of body image.[10] More recently, HA laparoscopy started gaining popularity, especially for the most complex and extensive colorectal procedures.[41,42] Compared to standard laparoscopic surgery, HA was shown to be effective in reducing the operative time as well as the need for conversion, while preserving the benefits offered by a minimally invasive approach.[43,44] The initial technical issues related to the access device, and specifically the challenge to maintain a stable pneumoperitoneum during long procedures with high mechanical stress on the access device for repeated hand insertion/withdrawal, were rapidly overcome leading us to adopt this technique in 2006.[45] SIL is the last advance in the field of minimally invasive surgery, made possible by the development of single multilumen ports, which can accommodate multiple laparoscopic instruments.[46–50] Several general abdominal, urologic and gynecologic procedures have been shown to be feasible with a SIL approach.[16–37] This technique has been adopted also by the colorectal surgical community and most of the standard resections both for benign and malignant disease have been performed, with only few SIL procedures reported for UC.[17–22,51,52] The TAC step of the procedure results in a temporary stoma, it is therefore our opinion that SILS has an unique value, allowing to perform the whole procedure through the site of the future ileostomy, thus avoiding the morbidity of additional incisions and trocar sites.[38] Since May 2010 we adopted SIL as the technique of choice UC patients requiring a TAC as the first stage of their surgical treatment. Offering this approach to consecutive patients referred to the senior author (AF) for treatment has generated a study group of UC patients comparable to our previous experience with typical BMI (21.9), long standing (58 months) and severely active disease (as demonstrated by the high average MAYO score [10.1], CRP [63.0], WBC [11.3]) and a 40% rate of comorbidities. We used these parameters, together with the demographics, to select an equal number of LA and HA patients and perform a case-match analyses on homogeneous groups, despite the lack of randomization. All the patients were treated with high dose steroids in the immediate preoperative period and SIL patients significantly more likely to be on immunosuppressive therapy in the month prior to surgery, this difference likely being a reflection of changes in medical treatment protocols.

Surprisingly, even if the technical complexity of SILS is intuitively higher, the duration of surgery was significantly shorter in the SIL group, likely due to the limited time needed to access the abdomen and for closure of the incisions. The safety profile, defined as EBL and intraoperative complication rate, was similar to the other two groups. In part these findings can be attributed to the increased proficiency of the surgical team. However, with the introduction of new surgical techniques, a learning cure was expected also for SILS. In order to minimize the impact of the learning curve, we purposely elected to perform the procedure following the same steps of our conventional laparoscopic approach. We start with an incision exactly the same size as the future ileostomy, but by using a gel cap single access device that provides a working platform larger than the actual abdominal incision, we are able to achieve appropriate tissue triangulation with

our standard laparoscopic instruments, thus avoiding the added costs of articulated ones. We are able to perform the exact same procedure, including the removal of the omentum, the use of a single sealing device for the whole operation, and the dynamic adjustment of the surgical table for optimal exposure of the working area. We are able to achieve adequate retraction and exposure, and no external sling suture are need, in contrast with other published reports.[18] Furthermore the majority of UC SIL TAC patients have already undergone a SIL ileoanal anastomosis (six out of eight patients, with the other two treated with conventional laparoscopy), thus, at least theoretically, maintaining the expected benefits of a truly minimally invasive approach.

Even if not statistically significant, a faster resumption on solid diet (postoperative day 3) and a shorter length of postoperative stay (5.1 days) was observed in the SIL group, particularly when compared to the HA group (4 and 7.2 days respectively). As previously observed by other authors, the avoidance of additional incisions may result in faster recovery and earlier discharge, as a consequence of less postoperative pain, less use of narcotic pain medication and earlier resumption of physical activity, further improvement over the known benefits of conventional minimally invasive techniques.[20,24,25,53,54] While no postoperative complications were recorded in the SIL group, postoperative complications were observed in three HA patients and two LA patients, which resolved after conservative management. The data available in the literature show that laparoscopy has lowered the incidence of postoperative complication after TAC for UC, but the reported rates of short term complication after laparoscopy surgery are still as high as 40%.[55] Particularly, post-operative small bowel obstruction and significant persisting abdominal pain can be consequences of the entity of surgical trauma and tissue manipulation, both minimized with SILS.

The patients presented in this study continue to progress along the stages of their surgical treatment and to date eight of these patients underwent a completion restorative proctectomy with a stapled ileoanal anastomosis, six through a single incision approach and two through conventional laparoscopy, all of them with a diverting loop ileostomy. Of this initial cohort six had the ileostomy taken down, with a resulting single scar of an average 5 cm length at the ileostomy site.

Our study has several limitations including the lack of randomization, the very small number of patients and short follow-up and therefore our results should be considered preliminary with the need for further studies to validate these findings. While randomizing these patients that usually present acutely ill and the most unusual times of the day and night may be an impossible task, the other two limitations will correct themselves as the experience accumulates and the follow-up lengthens, since the results obtained with SIL TAC are encouraging we will continue to consider SILS for the surgical treatment of UC. In absence of obvious contraindications to laparoscopy in general, SILS represents a valuable tool in the hands of experienced laparoscopic surgeons, in an effort to optimize surgical outcomes in this group of particularly complex patients.

Conclusion

SIL TAC offers a safe alternative to other more invasive, conventional" laparoscopic approaches in highly selected UC patients. Our preliminary results suggest that despite the higher technical complexity, the duration of surgery is shorter with faster resumption of oral intake. Studies with larger sample size and longer follow-up will be required to confirm the benefits of this approach.

Authors disclosures Drs. Zoccali, Felice, Fichera, and Rubin have no conflicts of interest or financial ties to disclose.

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2011 SSAT QUICK SHOT PRESENTATION

Palliative Surgical Management of Patients with Unresectable Pancreatic Adenocarcinoma: Trends and Lessons Learned from a Large, Single Institution Experience

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Abstract
Introduction Routine palliative bypass has been advocated for palliation of patients with pancreatic adenocarcinoma who have inoperable disease discovered at the time of surgery. We examined trends in the relative use of palliative bypass over time with an emphasis on identifying changes in surgical indications, type of bypass performed, as well as perioperative outcomes associated with surgical palliation.
Methods Between 1996 and 2010, 1,913 patients with pancreatic adenocarcinoma in the head of the pancreas were surgically explored. Data regarding preoperative symptoms, intraoperative findings, type of surgical procedure performed, as well as perioperative and long-term outcomes were collected and analyzed.
Results Of the 1,913 patients, 583 (30.5%) underwent a palliative procedure. Most patients presented with jaundice (72.2%). The majority of patients were evaluated by CT scan (97.4%), which revealed a median tumor size of 3.2 cm. Most patients who underwent surgical palliation (64.5%) had a double bypass, while a minority had either gastrojejunostomy (28.2%) or hepaticojejunostomy (7.2%) alone. While the number of pancreaticoduodenectomies remained relatively stable over time, there was a temporal decrease in the utilization of palliative bypass ($P<0.001$). Unanticipated locally advanced disease vs. liver/peritoneal metastasis as the indication for palliative surgery also changed over time (1996–2001: 47.8% vs. 52.2%; 2002–2007: 49.2% vs. 50.8%; 2008–2010: 17.2% vs. 82.7%) ($P=0.005$). Palliative failure rates were 2.3% after hepaticojejunostomy and 3.1% after grastrojejunostomy. Patients with unsuspected metastatic disease had a worse survival compared with patients who had locally unresectable disease (median survival: 5 vs. 8 months, respectively; HR=1.43, $P=0.001$).
Conclusion Palliative bypass procedures were less frequently performed over time, probably due to a significant decrease in the rate of unanticipated advanced locoregional disease at the time of exploration. While palliative bypass was effective, survival in the setting of metastatic disease was extremely short.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in Western society, with an estimated 43,000 new cases diagnosed in the United States in 2010.[1] Resection, in conjunction with adjuvant chemoradiation therapy, is associated with a 5-year survival of 20%.[2,3] The majority of patients, however, present with advanced disease, making curative intent surgery not a therapeutic option. In fact, up to 80% of patients with pancreatic cancer are inoperable at the time of presentation either due to locally advanced or metastatic disease. The care of patients with advanced pancreatic cancer is challenging. While systemic chemotherapy aims to prolong survival, one of the main goals in caring for these patients is palliation, to ensure adequate and effective management of symptoms. Patients with pancreatic cancer located in the head of the gland can present with debilitating symptoms including gastric outlet obstruction, biliary tract obstruction, pruritis and pain.[4–6] Palliation is, therefore, a key component of the therapeutic management of patients with pancreatic cancer.

While chemoradiation may be a reasonable palliative approach to some patients with advanced pancreatic cancer,[7] surgery has traditionally been an important modality to palliate many of these patients. Specifically, routine palliative bypass has been advocated for palliation of patients with adenocarcinoma in the head of the pancreas who were explored with curative intent but have inoperable disease discovered at the time of surgery. Surgical palliative procedures may include bypasses such as hepaticojejonostomy or gastroejunostomy, as well as chemical celiac splanchiectomy. Over the last several decades, with the development and refinement of endoscopically placed biliary and enteric stents, there have been significant advances in nonoperative palliation.[8] In addition, better preoperative cross-sectional imaging has decreased the likelihood of finding locally unresectable disease at the time of surgery. As such, the role, indication, and relative utilization of palliative surgical procedures for advanced pancreatic cancer are ill-defined. While some surgeons favor the traditional "double bypass" procedure that combines hepatico- and gastrojejusnostomy at the time of laparotomy, other surgeons are more selective and perform bypass procedures based on individual patient's preoperative laboratory values (e.g. bilirubin) or symptoms. In addition, some surgeons question the benefit of surgical palliation itself, given the limited life expectancy of patients with advanced pancreatic cancer. The objective of the current study was to examine the trends over time in the relative use of palliative bypass among patients with adenocarcinoma of the head of the pancreas in a large single institution series. In particular, we sought to identify any changes in surgical indications, type of bypass performed, as well as perioperative outcomes associated with surgical palliation.

Methods

Patients and Data Collection

Between January 1, 1996 and July 1, 2010, 1,913 patients who underwent surgery for pancreatic adenocarcinoma were identified from the Johns Hopkins Hospital pancreas database. Patients undergoing palliative surgical procedures, including biliary and enteric bypass, as well as celiac plexus block were identified through a retrospective chart review, as well as a query of hospital billing records using the appropriate Current Procedural Terminology (CPT) codes [43820, 47760, 47765, 47780, 47785, 64530, 64680]. The study was approved by the Johns Hopkins Institutional Review Board.

Data were collected regarding patient demographics, preoperative symptoms, intraoperative findings, type of surgical procedure performed, as well as perioperative and long-term outcomes. Specifically, standard demographic and clinicopathologic data were collected including sex, age, and American Society of Anesthesia (ASA) classification. Data on preoperative symptoms, laboratory values (i.e. total bilirubin, carbohydrate antigen 19–91 [CA-19-9], etc.), findings on preoperative imaging, as well as history of endoscopic/percutaneous procedures were recorded. Data were also collected on the primary tumor and the presence of any metastatic disease. Operative reports were reviewed to determine initial operative intent, type of procedure performed, as well as the indication for palliation. Postoperative complications were assessed and graded according to the Clavien-Dindo classification system.[9] Length of hospital stay and readmissions were recorded. Postoperative mortality was defined as death in the hospital or within 30 days of operation. Long-term complications including late biliary and enteric obstruction were recorded. Survival status was determined using both hospital records as well as the Social Security Death Index.

Statistical Analysis

Mean and median values were used to describe continuous data, with discrete variables displayed as totals and frequencies. Univariate comparisons were assessed using the chi-square test for dichotomous and categorical variables and ANOVA for continuous variables. When assessing

temporal trends, the data were separated into terciles (1996–2001, 2002–2007, and 2008–2010) based upon the year of operation. Trends in ordinal data were evaluated using the linear-by-linear association test and variables among the three terciles were compared using ANOVA for continuous variables and Pearson's chi-square tests were used to compare categorical variables as appropriate.

Cumulative event rates were calculated using the method of Kaplan and Meier and survival curves were compared using the log-rank test. Overall survival time was calculated from the date of the operation to the date of last follow-up or death. Univariate and multivariate modeling of survival were performed using Cox proportional hazards models. Covariates were included in the multivariate Cox model based on statistical significance in the univariate models ($P \leq 0.05$). Relative risks were expressed as hazard ratios (HR) with a 95% confidence interval (CI). All reported P-values are two-tailed, and for all tests, $P<0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS version 19.0 for Microsoft Windows (LEAD Technologies, Inc., Chicago, IL) statistical software package.

Results

Patient and Surgical Details

Of the 1,913 patients who underwent surgery for pancreatic adenocarcinoma in the head of the pancreas, 1,330 patients (69.5%) underwent a pancreaticoduodenectomy; 583 patients (30.5%) underwent surgical palliation and are the focus of the current study. Table 1 outlines the demographic and clinical characteristics of the 583 patients managed with surgical palliation; in general, these data were not substantially different than the summary data previously published on patients undergoing curative intent pancreaticodudenectomy from our institution.[10] Median patient age was 66 years (range, 36–98 years) and there was a slight male predominance (n=320, 54.9%) in the cohort. While most patients did not have many medical comorbidities as reflected in their low 1–2 ASA classification (n=393; 67.4%), one-third of patients had an ASA classification of 3–4 (n=190; 32.6%). At the time of presentation, most patients had jaundice (n=421, 72.2%) with a median peak bilirubin level of 3.0 mg/dl (range, 0.2–42.4 mg/dl). Gastric outlet obstruction (n=66, 11.3%) and emesis (n=105, 18.0%) were less common on presentation. The diagnostic imaging modality of choice was a computed tomographic (CT) scan in the overwhelming majority of patients (n=568, 97.4%); fewer patients underwent magnetic resonance imaging (MRI) (n=31, 5.3%). Median tumor size on cross-sectional imaging was 3.2 cm (range 1.0–15.0 cm). On

Table 1 Demographics, preoperative presentation and operative details of patients undergoing surgical palliation (n=583)

Variable	N (%)/median (range)
Demographics	
Median age (years)	66 (36–98)
Gender	
Female	263 (45.1%)
Male	320 (54.9%)
ASA	
1–2	393 (67.4%)
3–4	190 (32.6%)
Preoperative presentation	
Symptoms	
Vomiting	105 (18.0%)
Jaundice	421 (72.2%)
Gastric outlet obstruction	66 (11.3%)
Enteric stent	7 (1.2%)
Biliary stent	370 (63.5%)
Endoscopic	274 (47.0%)
Percutaneous	96 (16.5%)
Laboratory values	
Peak bilirubin (mg/dl)	3.0 (0.2–42.4)
Last preoperative bilirubin (mg/dl)	1.4 (0.2–35.4)
CA 19–9 (U/ml)	351.3 (1.0–50119.0)
CEA (ng/ml)	5.4 (0.6–176.8)
Imaging	
CT	568 (97.4%)
MRI	31 (5.3%)
PET	5 (0.9%)
Radiographic tumor size (cm)	3.2 (1.0–15.0)
Preoperative chemotherapy	38 (6.5%)
Preoperative radiation	25 (4.3%)
Operative details	
Reason for palliation	
Locally advanced disease	237 (40.6%)
Presence of liver metastases	218 (37.4%)
Presence of peritoneal/other metastases	67 (11.5%)
Known inoperable with obstructive symptoms	61 (10.5%)
Extent of palliative surgery	
Bypass	553 (94.9%)
Exploration and biopsy	30 (5.1%)
Celiac block	523 (89.7%)
Type of bypass (n=553)	
Hepaticojejunostomy only	40 (7.2%)
Gastrojejunostomy only	156 (28.2%)
Double bypass	357 (64.6%)
Type of gastrojejunostomy (n=513)	
Antecolic	29 (5.7%)
Retrocolic	484 (94.3%)

imaging, 61 patients (10.5%) had disease that was preoperatively deemed to be either locoregionally unresectable (n=33, 5.7%) or metastatic in nature (n=28, 4.8%). Prior to surgery, two-thirds of patients (n=370; 63.5%) had undergone biliary drainage either via an endoscopic (n=274, 47.0%) or percutaneous (n=96, 16.5%) approach. Seven patients (1.2%) had an endoscopic enteric stent placed prior to surgery. Among the 583 patients who underwent surgical palliation, few received neoadjuvant therapy (n=38, 6.5%; chemoradiation therapy, n=25 vs. chemotherapy only, n=13).

At the time of surgery, 522 patients (89.5%) who were explored with curative intent were discovered to have unanticipated locally advanced disease (n=237, 40.6%) or distant metastases (n=285, 48.9%) that precluded pancreaticoduodenectomy. Of those patients with distant metastases, most patients had incidental liver metastases (n=218, 37.4%) discovered at surgery while fewer patients had peritoneal carcinomatosis or other distant metastases (n=67, 11.5%). In addition to the 522 patients with unanticipated advanced disease, 61 patients (10.5%) had known advanced disease and underwent planned surgical palliation for failed nonsurgical management of obstructive symptoms.

Surgical palliation consisted of a bypass procedure in the majority of patients (n=553, 94.9%) while 30 patients (5.1%) underwent exploratory laparotomy, biopsy, and chemical celiac block only. The type of palliative surgical bypass consisted of a classic double bypass (i.e., hepaticojejunostomy combined with gastrojejunostomy) in the majority of patients (n=357, 64.6%); 40 patients (7.2%) underwent hepaticojejunostomy only and 156 patients (28.2%) underwent gastrojejunostomy only.

Palliative Surgery for Pancreatic Cancer: Trends Over Time

Certain patient characteristics varied over time (Table 2). Patients undergoing palliative bypass for pancreatic cancer had fewer preoperative comorbidities as reflected by improving ASA scores (ASA score 1–2: 1996–2001, 60.2% vs. 2002–2007, 77.5% vs. 2008–2010, 83.9%; P=0.001). There was an increase in the number of patients who presented with jaundice (1996–2001, 69.6% vs. 2002–2007, 82.6% vs. 2008–2010, 80.6%; P=0.002) with a corresponding increase in the use of preoperative biliary stents (1996–2001, 59.5% vs. 2002–2007, 71.8% vs. 2008–2010, 70.9%; P=0.01). Among those patients undergoing palliative bypass, the median tumor size based on cross-sectional imaging deceased over time (1996–2001, 3.9 cm vs. 2002–2007, 3.3 vs. 2008–2010, 3.2 cm; P=0.006). In addition, the proportion of patients who ultimately underwent palliative bypass, but who were initially treated with neoadjuvant therapy increased over the time periods examined (1996–2001, 3.2% vs. 2002–2007, 5.2% vs. 2008–2010, 29.0%; P=0.001).

The overall utilization of surgical palliation dramatically decreased over the time periods examined (P<0.001) (Fig. 1). Of note, the temporal change in the relative utilization of surgical palliation was most pronounced over the last 5 years examined. Specifically, while the total number of annual pancreaticoduodenectomies remained relatively stable over time, the case volumes of palliative bypass procedures for pancreatic adenocarcinoma substantially decreased (average annual volume: 1996–2001, 39.2% vs. 2002–2007, 26.5% vs. 2008–2010, 10.7%; P=0.001). The specific palliative operative intervention utilized at the time of surgery also changed over time. Intraoperative celiac plexus block was employed with decreasing frequency (1996–2001, 94.5% vs. 2002–2007, 87.3% vs. 2008–2010, 77.4%; P=0.003). While the use of hepaticojejunostomy alone (1996–2001, 10.0% vs. 2002–2007, 3.8% vs. 2008–2010, 3.2%; P=0.02) gradually decreased over time, the use of the classic double bypass (1996–2001, 57.9% vs. 2002–2007, 75.1% vs. 2008–2010, 58.1%; P=0.001) and gastrojejunostomy alone (1996–2001, 32.0% vs. 2002–2007, 21.1% vs. 2008–2010, 38.7%; P=0.01) varied over time (Table 2). There was also a trend toward fewer patients undergoing planned palliative surgery over time (1996–2001, 12.6% vs. 2002–2007, 8.5% vs. 2008–2010, 6.5%; P=0.22). In addition to the general decline in palliative surgical operations for pancreatic cancer, the indications for palliative surgery also changed. Specially, over time fewer patients were found to be unresectable due to unanticipated locally advanced disease at the time of surgery (1996–2001: 47.8% vs. 2002–2007: 49.2% 2008–2010: 17.3%; P=0.005). In contrast, among patients who were explored with curative intent but ultimately underwent palliative surgery, distant metastases as the indication for palliation became more prevalent (1996–2001: 52.2% vs. 2002–2007: 50.8% vs. 2008–2010: 82.7%; P=0.005) (Fig. 2).

Short- and Long-term Outcome

Following palliative bypass, the mean length of stay was 10 days (median, 8 days; range, 1–85 days) (Table 3). The mean length of stay following palliative bypass decreased over time (1996–2001: 11 days vs. 2002–2007: 9 days vs. 2008–2010: 10 days; P=0.007). Morbidity occurred in 203 patients (36.7%) (major complication: n=78, 14.1%) with most complications being infectious in nature (n=74, 13.4%), including wound infections (n=24, 4.3%), cholangitis (n=11, 2.0%) and intraabdominal abscess (n=5, 0.9%). Overall morbidity rates decreased over time (1996–2001: 41.4% vs. 2002–2007: 41.3% vs. 2008–2010: 29.0%; P=0.03) (Table 2). There were only nine perioperative

Table 2 Trends in indication and outcomes after palliative bypass between 1996 and 2010 (N, %)

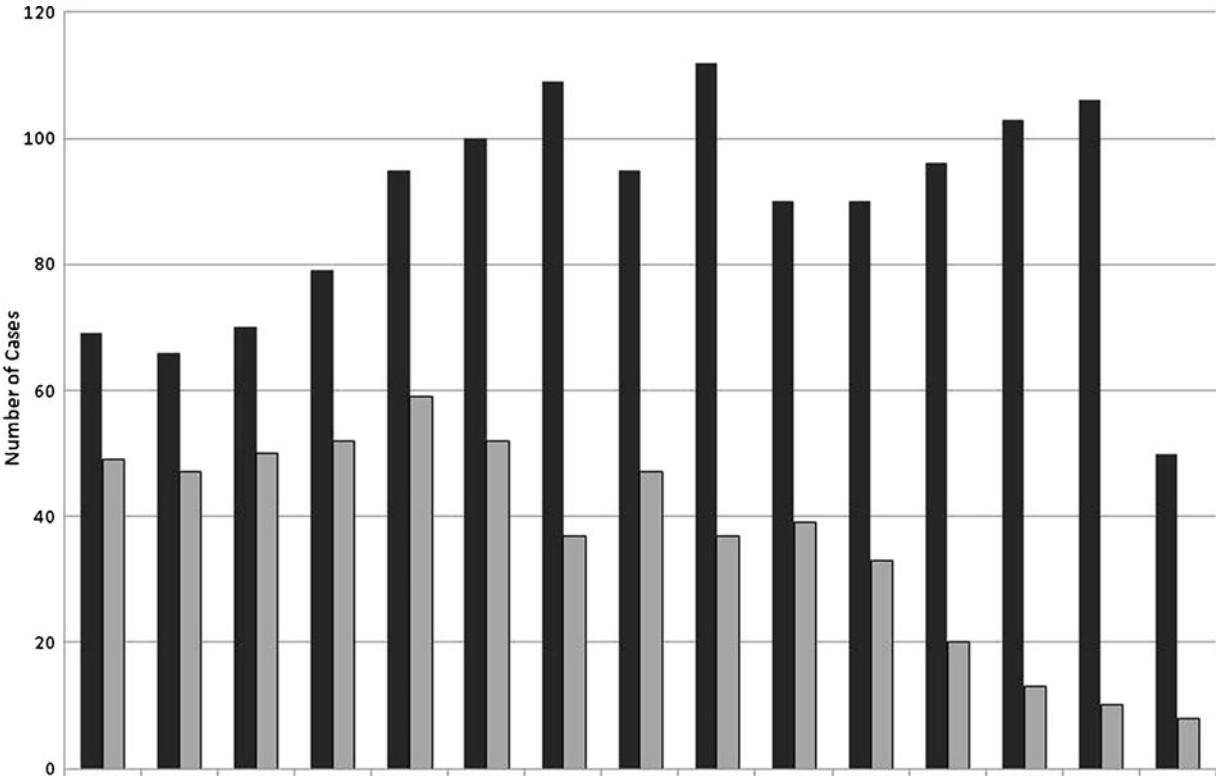
Variable	1996–2001 (n=309)	2002–2007 (n=213)	2008–2010 (n=31)	p-value
Age (years), mean ± SD	65±10.9	66±11.1	67±11.3	0.37
Male gender	169 (54.7%)	110 (51.6%)	21 (67.7%)	0.24
ASA score				**0.001**
1–2	186 (60.2%)	165 (77.5%)	26 (83.9%)	
3–4	123 (39.8%)	48 (22.5%)	5 (16.1%)	
Jaundice	215 (69.6%)	176 (82.6%)	25 (80.6%)	**0.002**
Preoperative gastric outlet obstruction	42 (13.6%)	19 (8.9%)	4 (12.9%)	0.26
Preoperative biliary stent	184 (60%)	153 (71.8%)	22 (70.9%)	**0.01**
Preoperative enteric stent	3 (1.0%)	3 (1.4%)	0 (0%)	0.75
Radiographic tumor size (cm), mean ± SD	3.9±1.9	3.3±1.3	3.2±0.9	**0.006**
Neoadjuvant therapy	10 (3.2%)	11 (5.2%)	9 (29.0%)	**0.001**
Planed operative intent				
Curative	270 (87.4%)	195 (91.5%)	29 (93.5%)	0.22
Palliative	39 (12.6%)	18 (8.5%)	2 (6.5%)	
Reason for unresectability[a]				**0.005**
Locally advanced disease	129 (47.8%)	96 (49.2%)	5 (17.2%)	
Unanticipated metastases	141 (52.2%)	99 (50.8%)	24 (82.7%)	
Diagnostic laparoscopy	7 (2.2%)	4 (1.9%)	3 (9.6%)	**0.03**
Type of bypass				**0.001**
Hepaticojejunostomy only	31 (10.0%)	8 (3.8%)	1 (3.2%)	
Gastrojejunostomy only	99 (32.0%)	45 (21.1%)	12 (38.7%)	
Double bypass	179 (57.9%)	160 (75.1%)	18 (58.1%)	
Type of gastrojejunostomy				0.28
Antecolic	12 (4.3%)	14 (6.8%)	3 (10.0%)	
Retrocolic	266 (95.7%)	191 (93.2%)	27 (90.0%)	
Celiac block	292 (94.5%)	186 (87.3%)	24 (77.4%)	**0.003**
Length of hospitalization (days), mean ± SD	11±8.0	9±7.1	10±12.0	**0.007**
Any complication	128 (41.4%)	88 (41.3%)	9 (29.0%)	**0.03**
Major complication	51 (16.5%)	26 (12.2%)	1 (3.2%)	0.08
Mortality	5 (1.6%)	4 (1.9%)	0 (0%)	0.74
Readmissions	59 (19.1%)	35 (16.4%)	5 (16.1%)	0.71
Late enteric obstruction	13 (4.2%)	9 (4.2%)	0 (0%)	0.51
Late biliary obstruction	16 (5.2%)	13 (6.1%)	0 (0%)	0.36

P-values of <0.05 are highlighted in bold

[a] Patients explored with curative intent

deaths during the entire study period for an overall mortality of 1.6%. Postoperatively, 99 patients (17.9%) were readmitted after a median of 30 days (range, 4–353 days). Post-palliative surgery readmissions were related to recurrent late biliary (n=29, 5%) and gastric outlet obstruction (n=22, 4%), with a subset of these patients representing palliative surgical "failures." Specifically, among patients who underwent hepaticojejunostomy (n=397), 9 patients (2.3%) had a recurrent biliary obstruction; among patients who underwent gastrojejunostomy (n=513), 16 patients (3.1%) had recurrent gastric outlet obstruction.

Median survival following palliative bypass for pancreatic adenocarcinoma was 6 months (Fig. 3). On univariate analysis, several factors were associated with a worse outcome including ASA score 3–4, elevated preoperative CA 19–9 level ≥350 U/ml, tumor size ≥3.5 cm, and presence of unanticipated metastatic disease (Table 4). Patients who were explored with curative intent and were found unresectable due to locally advanced disease had a median survival of 8 months compared with only 5 months for patients who had unanticipated liver metastasis and 4 months for patients with metastatic peritoneal disease (P=0.001) (Fig. 4).



	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Pancreatico-duodenectomy	69	66	70	79	95	100	109	95	112	90	90	96	103	106	50
Palliative Bypass	49	47	50	52	59	52	37	47	37	39	33	20	13	10	8

Fig. 1 Annual case volumes of pancreaticoduodenectomy vs. palliative bypass for pancreatic adenocarcinoma between January 1996 and July 2010 at the Johns Hopkins Hospital

The median survival of the 30 patients who underwent exploratory laparotomy, biopsy, and chemical celiac block only was 3 months. On multivariate analysis, after controlling for competing risk factors,

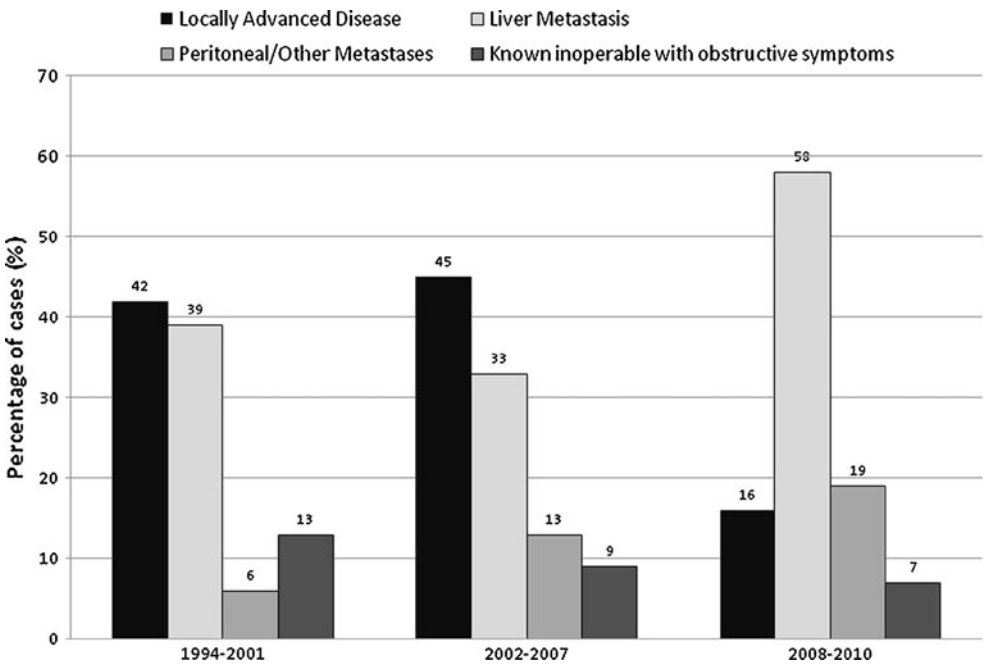


Fig. 2 Trends in the relative indications for palliative bypass surgery over the time periods examined

Table 3 Perioperative and long-term outcomes after palliative bypass for pancreatic ductal adenocarcinoma in the head of the pancreas (n=553)

Variable	N (%)
In hospital morbidity and mortality	
Complications	203 (36.7%)
Minor complications (I–II)	125 (22.6%)
Major complications (III–V)	78 (14.1%)
Mortality (V)	9 (1.6%)
Specific complications	
Liver abscess	5 (0.9%)
Cholangitis	11 (2.0%)
Pleural effusion	14 (2.5%)
Biliary fistula	8 (1.4%)
Sepsis	11 (2.0%)
Hemorrhage	6 (1.1%)
Wound infection	24 (4.3%)
Intraabdominal abscess	11 (2.0%)
Other	107 (19.3%)
Median length of stay (days)	8 (1–85)
Late morbidity and mortality	
Readmission	99 (17.9%)
Median time to readmission (days)	30 (4–853)
Reason for readmission	
Liver abscess	3 (0.5%)
Cholangitis	11 (2.0%)
Pleural effusion	2 (0.4%)
Biliary fistula	2 (0.4%)
Sepsis	2 (0.4%)
Hemorrhage	2 (0.4%)
Wound infection	7 (17.5%)
Intraabdominal abscess	6 (1.1%)
PV thrombosis	2 (0.4%)
Biliary obstruction	29 (5.2%)
Enteric obstruction	9 (1.6%)
Gastric outlet obstruction	13 (2.3%)
Other	28 (5.1%)
Postoperative stenting	
Biliary stent	29 (5.2%)
Enteric stent	11 (1.9%)
Overall late obstruction	
Biliary	25 (4.5%)
Enteric	18 (3.2%)
Both	4 (0.7%)
Median time to obstruction (months)	1 (0–28)

CA 19–9 (HR 1.64, 95% CI 1.19–1.28; P=0.003), tumor size (HR 1.47, 95% CI 1.07–2.04; P=0.02), and the presence of unanticipated metastatic disease (HR 1.52, 95%CI 1.08–2.14; P=0.02) remained independently associated with a worse survival.

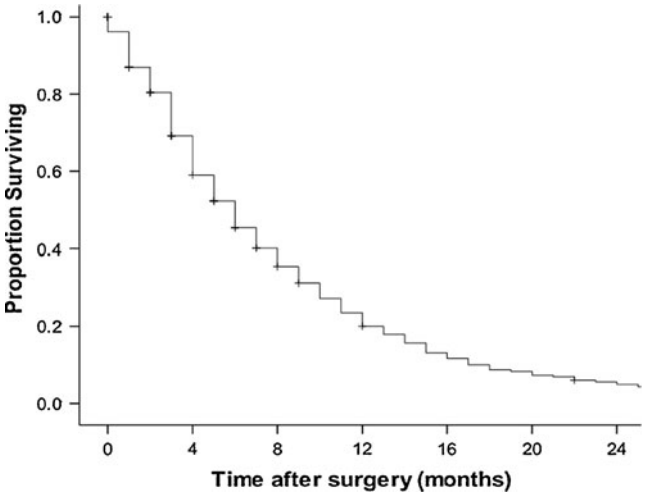


Fig. 3 Overall survival of all patients undergoing palliative bypass for pancreatic adenocarcinoma (n=553)

Discussion

In caring for patients with pancreatic cancer, while the ultimate aim of surgery is cure, palliation is also an important goal. The palliation of pain, obstruction, and other symptoms from advanced malignancies has always been an intrinsic element of the surgical management of cancer. This is particularly important among patients with pancreatic adenocarcinoma, as only 10% to 20% of patients present with resectable disease while the majority of patients are simply candidates for medical palliation.[11,12] The role of surgical palliation has evolved over the past several decades concurrent with advances in nonoperative percutaneous and endoscopic palliative approaches.[6] The relative role of operative vs. nonoperative palliative approaches remains somewhat ill-defined with randomized data showing advantages to surgical palliative bypass vs. endoscopic stenting with less reobstruction following surgery.[13–16] However, patients with distant metastasis are generally considered worse candidates for surgical palliation compared with patients who have locally advanced disease.[12,17] As such, the role of surgical palliation in the current era of nonoperative palliative techniques is controversial, with little data to suggest which patients may benefit the most from surgical palliation. The current study is important because it reports, to our knowledge, the largest single institution experience with palliative surgical management of pancreatic cancer. We were able to examine trends in indication, utilization, and outcomes after palliative bypass over a 15-year period. We noted that the relative use of palliative pancreatic operations dramatically de-

Table 4 Univariate and multivariate analyses of survival after palliative bypass for pancreatic ductal adenocarcinoma in the head of the pancreas

Variable	Univariate analysis		Multivariate analysis	
	Crude hazard ratio [95%CI]	*p*-Value	Adjusted hazard ratio [95%CI]	*p*-Value
Age ≥65 years	1.22 [1.02–1.46]	0.03	1.17 [0.85–1.62]	0.34
Male gender	0.96 [0.80–1.14]	0.64		
Ethnicity				
White	Reference group			
Black	1.22 [0.89–1.66]	0.22		
Other	0.63 [0.35–1.15]	0.13		
ASA score 3–4	1.22 [1.02–1.47]	0.04	1.08 [0.76–1.52]	0.69
Peak bilirubin ≥3 mg/dl	1.03 [0.85–1.25]	0.74		
Last preop bilirubin ≥2 mg/dl	1.18 [0.98–1.18]	0.08		
Preop CA19-9 ≥350 U/ml	1.58 [1.25–1.99]	**0.001**	1.64 [1.19–2.28]	**0.003**
Preop CEA ≥5 ng/ml	1.00 [0.99–1.01]	0.47		
Tumor size ≥3.5 cm	1.30 [1.01–1.66]	**0.04**	1.47 [1.07–2.04]	**0.02**
Preoperative biliary stent	1.38 [0.57–3.33]	0.46		
Preoperative enteric stent	0.97 [0.85–1.11]	0.65		
Preoperative chemo/XRT	0.96 [0.64–1.44]	0.85		
Diagnostic laparoscopy	0.94 [0.53–1.68]	0.84		
Type of bypass				
Hepaticojejunostomy only	Reference group			
Gastrojejunostomy only	1.28 [0.89–1.83]	0.19		
Double bypass	0.94 [0.67–1.33]	0.73		
Laparoscopically completed bypass	2.07 [0.66–6.45]	0.21		
Reason for bypass				
Locally advanced disease	Reference group		Reference group	
Unanticipated metastatic disease	1.43 [1.18–1.72]	**0.001**	1.52 [1.08–2.14]	**0.02**
Palliation for obstructive symptoms (known unresectable)	1.62 [1.20–2.20]	0.002	0.93 [0.54–1.61]	0.54
Celiac block	0.95 [0.69–1.31]	0.76		

P-values of <0.05 are highlighted in bold

creased over time, with a decrease in the proportion of palliative bypass procedures in relation to potentially curative pancreaticoduodenectomy from over 40% in the 1990s to less than 10% by 2009. The relative decrease in the use of palliative bypass was probably related to our finding that over time fewer patients were found to be unresectable due to unanticipated locally advanced disease at the time of surgery (1996–2001: 47.8% vs. 2002–2007: 49.2% 2008–2010: 17.3%; $P=0.005$).

Data from the current study show that surgical palliation can be accomplished with low morbidity and near zero mortality. Previous studies have reported morbidity and mortality of 30% and 2%, respectively.[4,18] We report an overall morbidity of 36.7%, but importantly also found that morbidity had decreased over the time periods examined (Table 2). In addition, most complications were minor in nature with only nine patient deaths in the perioperative period for an overall mortality of 1.6%. These data compare favorably with short-term outcome data from series of patients treated with endoscopic palliative treatments. For example, in a series of 221 patients with pancreatic carcinoma who were palliated with an endoscopic approach, Huibregtse et al. reported a procedure-related morality of 2%.[19] Not only is surgical palliation of pancreatic cancer safe, it also was found to be efficacious. Specifically, the readmission rate following surgical palliation was only 17.9% with readmissions being related to recurrent late biliary ($n=29$, 5%) or gastric outlet obstruction ($n=22$, 4%). In fact, when we examined those patients who underwent hepaticojejunostomy ($n=397$) or gastrojejunostomy ($n=513$), only nine patients (2.3%) and 16 patients (3.1%), respectively, re-presented with biliary or gastric obstruction. Taken together, our data strongly suggest that palliative bypass for pancreatic

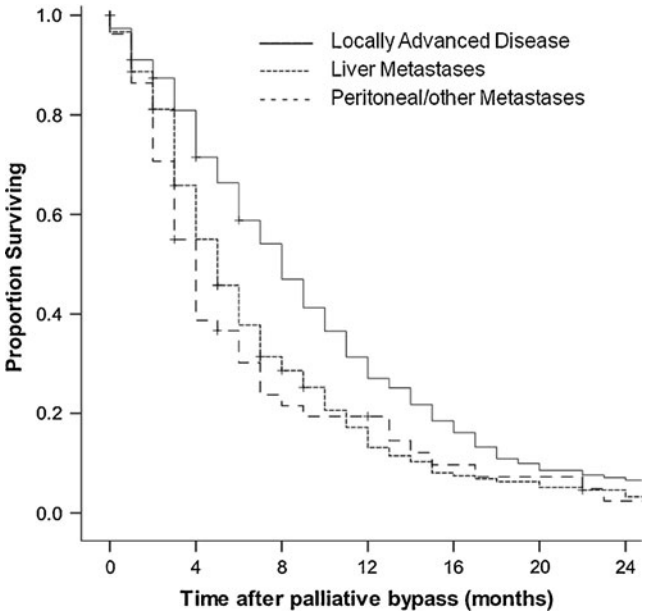


Fig. 4 Survival after palliative bypass for patients explored with curative intent (n=494), stratified by indication for palliative bypass. Median survival: locally advanced disease, 8 months vs. liver metastases, 5 months vs. peritoneal/other metastases, 4 months (P=0.001)

adenocarcinoma is both safe and efficacious in relieving symptoms.

Data on the trends in the use of palliative surgical bypass are lacking, providing little insight into how often surgical palliation is currently still being used at major pancreatic surgical centers. In the current study, we report an overall utilization of palliative surgery of 30.5% among patients explored for pancreatic cancer in the head of the gland. In what is probably the second largest reported series (n=136), Muller et al. reported an overall 22% utilization of palliative bypass procedures among 627 patients diagnosed with pancreatic adenocarcinoma between 2001 and 2005 at the University of Heidelberg.[20] Unlike the previous study by Muller et al., we were able to characterize the relative annual volume of palliative pancreatic surgery over time and noted a dramatic incremental decrease. In fact, only 10% of surgical procedures for pancreatic head cancers were palliative in nature by 2009 (Fig. 1). The reason for the decrease in the use of palliative surgery for inoperable pancreatic cancer is undoubtedly multifactorial. Among the reasons for the decrease may be the greater use of nonoperative palliative approaches among those patients identified preoperatively to have inoperable disease. In addition to the general decline in palliative surgical operations for pancreatic cancer, another interesting finding of the current study was that the indications for palliative surgery also changed. Specially, among patients who were explored with curative intent but ultimately underwent palliative surgery, the main indication changed over time from unanticipated locally advanced disease to distant metastasis (Fig. 2). As such, the decrease in palliative surgery performed at our institution was probably related, in part, to the dramatic decrease in the number of patients found to be unresectable due to unanticipated locally advanced disease at the time of surgery. Part of this change may reflect an increase utilization of concomitant portal vein resection by our group and others to extirpate locally advanced disease at the time of surgery.[21] Another reason for this change probably reflects an evolution in cross-sectional imaging. Specifically, with the introduction of multidetector CT imaging that can be reconstructed in a 3-D format, the relation of the pancreatic tumor to adjacent critical vascular structures such as the superior mesenteric artery and superior mesenteric vein can be very accurately characterized.[22] In contrast, small hepatic metastases (<1 cm) often still cannot be reliably identified on preoperative CT imaging.[23] In fact, the sensitivity of CT to detect metastasis ranges from only 38% to 73%.[22,24,25] For this reason, some surgeons advocate routine diagnostic laparoscopy to avoid unnecessary laparotomy.[26] Diagnostic laparoscopy appears to have the highest yield in the setting of elevated CA-19-9 levels (>130 U/ml).[27] Using a more selective approach based on preoperative suspicion of metastatic disease, we noted a temporal increase in the utilization of diagnostic laparoscopy at our institution (Table 2). As metastatic disease has become the main reason for inoperability, it is increasingly important to determine the benefit of palliative surgical bypass in this cohort of patients.

When trying to assess the benefit of any surgical procedure, the life expectancy of the patient obviously factors heavily into the decision making process. This is particularly true among patients with noncurative pancreatic cancer. In the current study, similar to previous reports,[12,17,28] we noted that patients who were explored with curative intent and were found unresectable due to locally advanced disease had a longer median survival compared with patients who had unsuspected liver metastasis (8 months vs. 5 months, respectively; P= 0.001). In addition, even after controlling for metastatic disease site on multivariate analysis, we noted that several other factors were independently associated with a significantly worse survival. These factors included ASA score 3–4, elevated preoperative CA 19–9 level, and tumor size. Interestingly, Muller et al.[20] had also identified both ASA score and CA 19–9 as being independent indicators of poor survival. In the current study, the median survival of the 30 patients who underwent exploratory laparotomy, biopsy, and chemical celiac block only was 3 months. While this survival was less than the survival of patients with local advanced disease (8 months), it was comparable to the survival of patients with liver metastases (5 months) or peritoneal/other

metastases (4 months). In aggregate, these data suggest that survival among patients with metastatic disease is particularly poor (<6 months) and the use of surgical bypass should be considered carefully in this subset of patients—especially if the patient also has a high ASA score and CA 19–9 level. Since these patients have a life expectancy of less than 6 months, if the patient is asymptomatic from a gastrointestinal standpoint and is already palliated with a biliary stent, surgical palliation may not be warranted.

The current study had several limitations. Although the data reflect a single institutional experience, there have been changes in the surgical staff over time that may have introduced a "provider" effect on the relative use of palliative surgery over time. While our data established a clear decrease over time in the relative utilization and indication for palliative surgical procedures for pancreatic cancer, we were not able to fully define the reasons for these trends. Attempts at correlating the temporal shifts with changes in cross-sectional imaging at our institution proved not to be feasible due to the staggered nature of how new equipment was introduced and the variability related to which equipment was used on any given day. In addition, we did not correlate the relative use of surgical procedures with nonoperative palliative approaches for patients with pancreatic cancer at our institution over the same time period. Because data were derived from a surgical database, accurate acquisition of nonoperative palliative procedures was not feasible. The use of nonoperative palliative procedures for pancreatic cancer was, however, not the focus of the current study. Rather, we sought to examine the role of surgical palliation for pancreatic cancer with regards to its safety, efficacy, and relative use over time.

In conclusion, we demonstrate that surgery remains an effective palliative method of pancreatic cancer. While a "general" clinical decision making algorithm would not be appropriate—as each clinical situation needs to be individualized—data from our study should help to inform the practice of surgeons operating on this complex group of patients. Specifically, we have shown that overall morbidity after palliative bypass has decreased over time and perioperative mortality is minimal. Palliative bypass procedures were less frequently performed over time, probably due to a significant decrease in the rate of unanticipated advanced locoregional disease at time of exploration. In contrast, intraoperative discovery of distant metastasis at the time of surgery was found to be the most common indication for surgical bypass in the current era. Survival in the setting of metastatic disease following palliative bypass was, however, extremely short. Although we identified several factors (ASA score 3–4, elevated preoperative CA 19–9 level, tumor size ≥3.5 cm) that may aid in selection, future molecular markers such as DPC4[29] will hopefully better identify that subset of patients with a nonmetastatic phenotype who may benefit the most from surgical palliation.

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2011 SSAT QUICK SHOT PRESENTATION

Laparoscopic and Open Abdominoperineal Resection for Cancer: How Patient Selection and Complications Differ by Approach

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Abstract
Background Outcomes between laparoscopic (LAPR) and open abdominoperineal resections (OAPR) are poorly described.
Methods After IRB approval, 2005–2008 NSQIP data were used to identify patients undergoing LAPR and OAPR for rectal cancer. Logistic regression identified variables influencing the selection of LAPR vs. OAPR as well as the likelihood of postoperative events. Chi-square analysis was used to compare the incidence of 30-day postoperative events.
Results One thousand one hundred ninety-seven OAPRs and 143 LAPRs were identified. LAPRs were less likely to have a body mass index (BMI) of ≥30 (p=0.04) and were associated with equivalent mean operative times (p=0.36). LAPRs and OAPRs were found to have similar rates of surgical site infections (p=0.13), transfusion requirements (p=0.17), myocardial infarction (p=0.48), and need for reoperation within 30 days (p=0.20). Neoadjuvant radiotherapy did not directly increase complication rates in either group. Few factors predicted choice of LAPR but included BMI <25 (OR, 1.54; p=0.02).
Conclusion Complication rates between LAPR and OAPR were similar despite the greater technical challenge of LAPR. Wound infection rates were equivalent, which may reflect similar rates of perineal wound infections. Few patients are offered LAPR, possibly due to surgeon preferance as opposed to patient factors.

Keywords Rectal cancer · Abdominoperineal resection · Risk factors · Postoperative complications · NSQIP

Introduction

Laparoscopic surgery for rectal adenocarcinoma has, up to the present time, remained a form of oncologic surgery with less cancer survival and safety data to commend it, compared to the larger volume of surgical research[1–4] establishing laparoscopic colon cancer surgery as being equivalent to open forms of surgery with respect to the same measures. By its very nature, rectal cancer surgery, regardless of the surgical approach employed, represents a more complex surgical disease than colon cancer. A multidisciplinary approach is often required in the form of neoadjuvant chemoradiation therapy for stage II and III disease, while the technical challenges of a pelvic dissection and total mesorectal excision with their attendant higher rate of complications[5–8] qualify rectal cancer surgery as distinct both in concept and in practice from colon cancer. Given the limited confines of the pelvis and the sheer number of vital structures compacted within its volume, the unique challenges encountered in rectal cancer surgery are evinced in laparoscopic rectal cancer surgery, representing an even greater technical challenge compared to minimally invasive surgery for the colon.

For those rectal cancers requiring an abdominoperineal resection (APR), only limited data regarding the feasibility, safety, and oncologic outcome of a laparoscopic approach is available, as is the case with minimally invasive rectal cancer outcomes in general. While avoiding the risk of complications related to an anastomosis, patients undergoing an APR incur other postoperative morbidities such as

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the risk of pelvic infections related to postoperative fluid collections,[9] urologic[10] dysfunction which can occur in up to 50% of patients, sexual dysfunction[11,12] present in 10–75% of postoperative patients, and issues related to perineal wound infections and delayed wound healing[13,14] in as many as 50% of patients in some series. With a greater number of rectal cancers today being treated with sphincter-sparing surgeries, patients requiring APR currently comprise a group of cancers which tend to be, by selection, bulkier and more advanced and which are thus associated with a higher incidence of requiring neoadjuvant therapy as well as demanding a greater technical challenge to proper oncologic resection. The interplay of all of these factors, including their combined effect on outcomes with a minimally invasive surgical approach, has yet to be fully worked out.

While the pattern and rates of complications following laparoscopic colon cancer resections have been well described, complications following laparoscopic rectal cancer surgery have been studied very little. In particular, it is unclear whether a laparoscopic APR (LAPR) offers any material, substantial advantages to an open APR (OAPR) with respect to complication rates in the early postoperative period. The objective of this study was to identify factors predicting short-term complication rates for patients undergoing LAPR and OAPR for rectal cancer and to identify factors associated with the choice of either approach.

Methods

Data

A retrospective analysis of the National Surgical Quality Improvement Program's (NSQIP) Participant User File was performed by studying patients undergoing either LAPR or OAPR between 2005 and 2008. This data set is maintained by the American College of Surgeons (ACS) and contains information from 211 participating hospitals regarding surgical patients. Variables in the database include demographics, comorbidities, laboratory values, intraoperative patient characteristics, and postoperative outcomes.

NSQIP methodology has been described in great detail in the literature.[15–17] Briefly, selected cases included in the data set were the first 40 eligible vascular and general surgery operations during an 8-day cycle, where each cycle started on a different day of the week, thus capturing approximately 20% of an individual hospital's surgical volume. A trained clinical nurse reviewer collected data on 60 preoperative patient characteristics, 18 intraoperative factors, and 22 postoperative occurrences up to 30 days following the procedure. To maintain data reliability, the clinical nurse reviewer completed in-depth training on study definitions and participated in conference calls, annual meetings, and site visits. Chart reviews, information from morbidity and mortality conferences, and communication with patients by telephone or letter completed the 30-day postoperative data collection.[15–19]

Postoperative occurrences in the NSQIP program are divided into five categories: wound occurrences (superficial, deep, organ–space surgical site infections, and fascial dehiscence); respiratory occurrences (pneumonia, unplanned intubation, pulmonary embolism, and intubated >48 h duration); urinary occurrences (progressive renal insufficiency, acute renal failure requiring dialysis, and urinary tract infection); CNS occurrences (cerebral vascular accident, coma >24 h, and peripheral nerve injury); cardiac occurrences (cardiac arrest requiring CPR and myocardial infarction); and other occurrences (postoperative blood transfusions, deep venous thrombosis, sepsis/septic shock, and graft/flap failure). In order to assign a postoperative occurrence, the clinical nurse reviewer identifies medical documentation that specifically meets the ACS NSQIP definitions criteria for the selected postoperative occurrence. The criteria in the definitions are adapted from those used by national regulatory agencies and contained in the ACS NSQIP Operations Manual, which is available on the secure ACS NSQIP website.[20]

Of the adult general and vascular surgery patients included in the NSQIP database during 2005 to 2008, 1,340 patients were identified as undergoing LAPR or OAPR by Current Procedural Terminology codes 45395 and 45110, respectively.

Statistical Analysis

The statistical analysis was designed to determine which patient variables influenced the selection of LAPR vs. OAPR and the likelihood of developing a postoperative event for each procedure.

Patient characteristics were compared using Student's t test for continuous variables and chi-square test for binary and categorical variables. Logistic regression was used to determine which patient demographics and preoperative characteristics had a significant effect on the choice of OAPR vs. LAPR. Open and laparoscopic procedures were fit to logistic regression models to estimate the effect of developing a specific postoperative event. Confounders including age, sex, ethnicity, and preoperative patient comorbidities were controlled for as these variables are associated with increased risk of developing postoperative complications. All statistical analyses were performed using STATA software (version 11, StataCorp, College Station, TX, USA). Statistical significance was defined as a p value <0.05.

Table 1 Characteristics of 1,340 patients undergoing OAPR and LAPR for rectal cancer in 2005–2008

Variable	OAPR (*N*=1,197)	LAPR (*N*=143)	*p* value
Age group			
Age (mean in years)	63.91	64.71	0.4922
18–39 years	2.84%	2.10%	0.6090
40–49 years	11.19%	13.99%	0.3230
50–59 years	24.98%	20.28%	0.2170
60–69 years	24.73%	24.48%	0.9470
70+years	36.17%	39.16%	0.4830
Gender			
Female	36.42%	47.55%	0.0090
Male	63.58%	52.45%	0.0090
Race/ethnicity			
White	48.71%	38.46%	0.0200
Non-White	51.29%	61.54%	0.0200
Past medical history			
BMI (mean in kg/m^2)	27.82	26.25	0.0102
BMI <18.5 kg/m^2	4.51%	6.29%	0.3410
BMI 18.5–24.9 kg/m^2	32.16%	41.26%	0.0290
BMI 25–29.9 kg/m^2	32.75%	30.77%	0.6330
BMI 30+kg/m^2	29.74%	21.68%	0.0440
Dyspnea: none	88.89%	91.61%	0.3220
Dyspnea: moderate	10.36%	8.39%	0.4610
Dyspnea: at rest	0.75%	0.00%	0.2980
Smoker	21.39%	23.08%	0.6420
Alcohol use	5.18%	6.29%	0.5740
Nondiabetic	84.88%	86.71%	0.5610
Diabetic: insulin-dependent	3.68%	2.80%	0.5930
Diabetic: non-insulin-dependent	11.45%	10.49%	0.7330
History of COPD	4.68%	2.80%	0.3040
Ascites	0.08%	0.70%	0.0710
Congestive heart failure	0.42%	0.00%	0.4390
Myocardial infarction, <6 months prior to surgery	0.25%	0.00%	0.5490
Percutaneous coronary intervention	5.01%	4.90%	0.9510
Previous cardiac surgery	5.26%	2.80%	0.2010
Hypertension	49.37%	50.35%	0.8250
Peripheral vascular disease	0.92%	0.00%	0.2500
Acute renal failure	0.17%	0.00%	0.6250
Currently requiring hemodialysis	0.17%	0.70%	0.2030
History of transient ischemic attack	2.76%	1.40%	0.3360
Cerebrovascular accident	2.09%	2.80%	0.5820
Disseminated cancer	9.36%	5.59%	0.1360
Open wound	1.84%	0.00%	0.1020
Chronic steroid use	2.17%	1.40%	0.5410
Weight loss, >10% body weight in last 6 months	9.86%	6.99%	0.2710
Bleeding disorders	2.76%	2.10%	0.6450
Preoperative transfusion	0.25%	0.00%	0.5490
Chemotherapy	9.02%	10.49%	0.5660
Radiotherapy	39.93%	46.15%	0.1520
Intraoperative			
ASA class 1	1.17%	0.00%	0.1940
ASA class 2	40.69%	48.25%	0.0830
ASA class 3	53.80%	48.95%	0.2720
ASA class 4 or 5	4.18%	2.80%	0.4280
Wound class			
Clean	0.08%	2.10%	0.0000
Clean-contaminated	88.64%	89.51%	0.7550
Contaminated	8.94%	8.39%	0.8280
Dirty	2.34%	0.00%	0.0650
Operative time (mean in hours)	4.21	4.36	0.3676
<4 h	54.97%	42.66%	0.0050
4–7:59 h	40.18%	56.64%	0.0000
8–11:59 h	4.51%	0.70%	0.0300
12+h	0.33%	0.00%	0.4890
Emergent case	0.84%	0.00%	0.2730

BMI body mass index, *ASA* American Society of Anesthesiologists

Results

Demographics and Patient Characteristics

A total of 1,197 OAPRs and 143 LAPRs were identified. Patient characteristics stratified by OAPR vs. LAPR are reported in Table 1. No significant difference was noted between the groups with respect to such characteristics as mean age (p=0.49), tobacco use (p=0.64), insulin-dependent diabetes (p=0.59), steroid use (p=0.54), preoperative chemotherapy (p=0.57), and preoperative radiation therapy (p=0.15). Forty-eight percent of the LAPR group were female compared to only 36% of the OAPR group (p=0.009). The OAPR group had a higher proportion of Caucasian patients than the LAPR group (49% vs. 38%; p=0.02).

Though the mean body mass indices (BMI) were similar between both groups, a slight but statistically significant difference was observed, with OAPR patients having a slightly higher mean BMI of 27.8 kg/m^2 vs. 26.3 kg/m^2 in the LAPR group (p=0.01). Based upon NIH categorization of BMI, there was no significant difference between either cohort with regard to underweight (p=0.34) or overweight (p=0.63) patients. Patients undergoing LAPR had a greater tendency toward normal body weight (41.3% vs.32.2%; p=0.03) and a lesser incidence of obesity (21.6% vs. 29.7%; p=0.04) compared to OAPR patients.

In terms of wound classification, there was no statistically significant difference between either cohort with respect to the incidence of clean-contaminated (p=0.76), contaminated (p=0.83), and dirty wounds (p=0.07). However, the LAPR group had a higher incidence of clean wounds (2.1%) compared to the OAPR group (0.08%), which represented a statistically significant difference (p<0.0001).

Operative times were also stratified and compared between both groups. There was no difference in mean operative times between the two groups (OAPR, 260±68 min vs. LAPR, 270±90 min; p=0.36). The OAPR group had a statistically significantly higher percentage of operative times of <4 h (54.9% vs. 42.6%; p=0.005) and of 8:00–11:59 h (4.5% vs. 0.7%; p=0.03), while having a lower incidence of operative times in the 4–7:59 h range (40.2% vs. 56.6%; p<0.0001) compared to the laparoscopic group. Results of univariate analysis comparing preoperative laboratory values between the OAPR and LAPR cohorts are presented in Table 2, showing no statistically significant differences between them.

Mean length of hospital stay was 10.3±7.7 days for the OAPR group vs. 8.1±10.9 days for the LAPR group (p=0.002).

Selection Factors for Laparoscopic vs. Open Abdominoperineal Resection

The logistic regression results presented in Tables 3 and 4 indicate several patient characteristics that were important in predicting whether a patient underwent either an OAPR or LAPR, and therefore, are a reflection of choice of surgical approach based upon these characteristics. OAPR (Table 3) patients were more likely to be male (odds ratio [OR], 1.64; p=0.008) and Caucasian (OR, 1.54; p=0.02) and were more likely to have a BMI >25 kg/m^2 (OR, 1.48; p=0.04). Other factors such as insulin-dependent diabetes (OR, 1.22; p=0.72), previous cardiac surgery (OR, 1.74; p=0.31), disseminated cancer (OR, 1.77; p=0.14), steroid use (OR, 1.3, p=0.73), and American Society of Anesthesiologists class 3, 4, or 5 designation (OR, 1.27; p=0.23) affected the odds of undergoing an OAPR, but were not statistically significant.

Factors affecting the likelihood of undergoing an LAPR are listed in Table 4. Most patient factors, including serious comorbidities, did not significantly affect the likelihood of a patient undergoing an LAPR. Patients undergoing a laparoscopic resection were more likely to be female (OR, 1.63; p=0.009) and non-Caucasian (OR, 1.53; p=0.02) and

Table 2 Comparison of preoperative laboratory values for patients undergoing OAPR vs. LAPR

Variable	OAPR (N=1,197)	LAPR (N=143)	p value
Albumin (mean in g/dL)	3.87, n=857	3.88, n=97	0.9386
Albumin >3 g/dL	93.00%	94.85%	0.4940
Albumin <3 g/dL	7.00%	5.15%	0.4400
White blood cell (WBC) count (mean in k/μL)	6.44, n=1,163	6.27, n=135	0.4477
WBC <4.5 k/μL	2.84%	2.22%	0.6800
WBC >11+ k/μL	18.66%	16.30%	0.5030
Hematocrit (HCT, mean in %)	38.10, n=1,170	38.29, n=137	0.6652
HCT >45%	6.75%	3.65%	0.1610
HCT <28%	1.62%	1.46%	0.8850
Blood urea nitrogen (BUN, mean in mg/dL)	14.70, n=1,090	13.95, n=117	0.2202
BUN >30 mg/dL	2.66%	2.56%	0.9510
Creatinine (mean in mg/dL)	0.97, n=1,147	0.92, n=130	0.3880
Creatinine >1.2 mg/dL	17.70%	13.08%	0.1860
Total bilirubin (mean in mg/dL)	0.56, n=885	0.58, n=97	0.7385
Total bilirubin >1 mg/dL	6.55%	7.22%	0.8030
Aspartate transaminase (SGOT, mean in U/L)	23.41, n=881	23.53, n=99	0.9343
SGOT >40 U/L	5.79%	7.07%	0.6080
Alkaline phosphatase (mean in U/L)	85.18, n=902	79.60, n=97	0.1171
Alkaline phosphatase >125 U/L	9.09%	7.22%	0.5380
Platelets (mean in k/μL)	264.89, n=1,158	260.65, n=134	0.5768
Platelets <150,000 k/μL	6.74%	2.24%	0.0420
Platelets >400,000 k/μL	2.25%	0.75%	0.2510
Partial thromboplastin time (PTT, mean in seconds)	29.50, n=613	29.03, n=60	0.5690
PTT <35 s	92.17%	95.00%	0.4290

Table 3 Logistic regression of factors affecting likelihood of undergoing an OAPR

Variable	OR	95% confidence		*p* value
		Lower	Upper	
Age group				
18–39 years	Reference			
40–49 years	0.56	0.15	2.03	0.3760
50–59 years	0.85	0.24	3.01	0.8030
60–69 years	0.63	0.18	2.24	0.4770
70+years	0.56	0.16	1.98	0.3670
Female	Reference			
Male	1.64	1.14	2.36	0.0080
Non-White	Reference			
White	1.54	1.07	2.20	0.0200
BMI <25 kg/m^2	Reference			
BMI 25+ kg/m^2	1.48	1.02	2.15	0.0380
Dyspnea: at rest	Reference			
Dyspnea: none	0.76	0.40	1.44	0.3960
Nonsmoker	Reference			
Smoker	0.94	0.60	1.47	0.7980
No alcohol use	Reference			
Alcohol use	0.71	0.33	1.53	0.3830
Nondiabetic	Reference			
Diabetic: insulin-dependent	1.22	0.41	3.59	0.7220
Diabetic: non-insulin-dependent	0.99	0.54	1.81	0.9750
No previous percutaneous coronary intervention	Reference			
Percutaneous coronary intervention	0.81	0.35	1.88	0.6240
No previous cardiac surgery	Reference			
Previous cardiac surgery	1.74	0.60	5.07	0.3100
No history of hypertension	Reference			
Hypertension	0.87	0.58	1.30	0.4840
No history of transient ischemic attack	Reference			
History of transient ischemic attack	2.53	0.58	11.03	0.2180
No history of cerebrovascular accident	Reference			
Cerebrovascular accident	0.54	0.18	1.67	0.2870
No disseminated cancer	Reference			
Disseminated cancer	1.77	0.83	3.76	0.1380
No previous history of steroid use	Reference			
Steroid use	1.30	0.29	5.72	0.7300
No weight loss	Reference			
Weight loss, >10% body weight in last 6 months	1.57	0.79	3.15	0.2010
No history of bleeding disorders	Reference			
Bleeding disorders	1.14	0.33	3.91	0.8350
No history of prior chemotherapy	Reference			
Chemotherapy	0.87	0.48	1.59	0.6540
No history of prior radiotherapy	Reference			
Radiotherapy	0.71	0.49	1.04	0.0780
ASA class 1 and 2	Reference			
ASA class 3, 4, and 5	1.27	0.86	1.86	0.2290

BMI body mass index, *ASA* American Society of Anesthesiologists

were more likely to have a BMI <25 kg/m^2 (OR, 1.54; p=0.02). Interestingly, patients with a prior history of chemotherapy (OR, 1.15; p=0.65) or radiation therapy (OR, 1.4; p=0.08) preferentially underwent an LAPR, though these findings failed to reach statistical significance.

Risk Factors for Postoperative Complications

Tables 5 and 6 present the results of a multivariable analysis used to describe the likelihood of developing a postoperative event associated with various patient factors and comorbidities and stratified by open and laparoscopic approaches. Within the OAPR group, tobacco use (OR, 1.82; p=<0.0001), a history of a previous cerebrovascular accident (OR, 2.41; p=0.04), and a >10% weight loss prior to surgery (OR, 1.64; p=0.02) were associated with a higher likelihood of developing postoperative complications. None of the other factors studied, including radiotherapy (OR, 0.81; p=0.12), affected the odds of complications within the OAPR cohort. The only factor predictive of postoperative complications within the LAPR group was systemic hypertension (OR, 2.53; p=0.05). Patients undergoing radiotherapy prior to LAPR were actually 63% less likely to develop a postoperative event (OR, 0.37; p=0.04)

Postoperative Complications

Table 7 describes the 30-day incidence of postoperative outcomes for both groups. There was no statistically significant difference between the overall rate of postoperative complications between OAPRs and LAPRs (OAPR, 64% vs. LAPR, 53%; p=NS). The only statistically significant differences found between the groups was a slightly higher incidence of cardiac arrest requiring CPR within the LAPR group (1.4% vs. 0.08%; p=0.002) and a higher incidence of postoperative sepsis (6.3% vs. 2.1%; p=0.04) within the OAPR group. Of note was the absence of a statistically significant difference between both

Table 4 Logistic regression of factors affecting likelihood of undergoing an LAPR

Variable	OR	95% confidence		*p* value
		Lower	Upper	
Age group				
18–39 years	Reference			
40–49 years	1.79	0.49	6.50	0.3760
50–59 years	1.17	0.33	4.15	0.8030
60–69 years	1.58	0.45	5.60	0.4770
70+years	1.79	0.51	6.30	0.3670
Female	Reference			
Male	0.61	0.42	0.88	0.0080
Non-White	Reference			
White	0.65	0.45	0.94	0.0200
BMI <25 kg/m^2	Reference			
BMI 25+kg/m^2	0.67	0.47	0.98	0.0380
Dyspnea: at rest	Reference			
Dyspnea: none	1.32	0.69	2.51	0.3960
Nonsmoker	Reference			
Smoker	1.06	0.68	1.65	0.7980
No alcohol use	Reference			
Alcohol use	1.40	0.66	3.01	0.3830
Nondiabetic	Reference			
Diabetic: insulin-dependent	0.82	0.28	2.43	0.7220
Diabetic: non-insulin-dependent	1.01	0.55	1.84	0.9750
No previous percutaneous coronary intervention	Reference			
Percutaneous coronary intervention	1.23	0.53	2.85	0.6240
No previous cardiac surgery	Reference			
Previous cardiac surgery	0.57	0.20	1.67	0.3100
No history of hypertension	Reference			
Hypertension	1.16	0.77	1.74	0.4840
No history of transient ischemic attack	Reference			
History of transient ischemic attack	0.40	0.09	1.73	0.2180
No history of cerebrovascular accident	Reference			
Cerebrovascular accident	1.85	0.60	5.70	0.2870
No disseminated cancer	Reference			
Disseminated cancer	0.57	0.27	1.20	0.1380
No previous history of steroid use	Reference			
Steroid use	0.77	0.17	3.39	0.7300
No weight loss	Reference			
Weight loss, >10% body weight in last 6 months	0.64	0.32	1.27	0.2010
No history of bleeding disorders	Reference			
Bleeding disorders	0.88	0.26	3.01	0.8350
No history of prior chemotherapy	Reference			
Chemotherapy	1.15	0.63	2.10	0.6540
No history of prior radiotherapy	Reference			
Radiotherapy	1.40	0.96	2.05	0.0780
ASA class 1 and 2	Reference			
ASA class 3, 4, and 5	0.79	0.54	1.16	0.2290

BMI body mass index, *ASA* American Society of Anesthesiologists

groups regarding surgical site infections (OAPR, 22.3% vs. LAPR, 16.7%; $p=0.13$), wound disruption (OAPR, 3% vs. LAPR, 3.5%; $p=0.74$), transfusion requirements (OAPR, 1.2% vs. LAPR, 0%; $p=0.17$), myocardial infarction (OAPR, 0.33% vs. LAPR, 0%; $p=0.49$), pneumonia (OAPR, 3.3% vs. LAPR, 1.4%; $p=0.20$), and urinary tract infections (OAPR, 7.1% vs. LAPR, 6.9%; $p=0.96$). There was also no difference between OAPR and LAPR regarding the need to reoperate within 30 days of the index surgery (OAPR, 7.8% vs. LAPR, 4.9%; $p=0.20$). Information regarding the incidence of incisional hernias was not available in the data set. Table 8 compares the number of postoperative complications between OAPR and LAPR patients. No significant difference in complication rates existed between the cohorts, regardless of how the number of outcomes was stratified.

Tables 9 and 10 present the likelihood for developing postoperative complications associated with OAPRs and LAPRs, respectively. Neither group was found to have statistically significant greater odds of accruing any of the listed adverse outcomes based upon the type of surgical approach. This lack of statistically significant higher or lower odds of occurrence included surgical site infections, wound disruption, and sepsis for both OAPR and LAPR patients.

Discussion

While in general minimally invasive approaches to surgery are thought to offer advantages compared to open surgery regarding such outcomes as length of stay, return to normal activity, and incisional pain,[21] what benefit is consistently granted by minimally invasive rectal cancer surgery has yet to be defined or consistently demonstrated in the surgical literature. Much of the initial data for laparoscopic rectal cancer surgery has been provided by large, multicenter studies which were heavily weighted toward and primarily focused on studying colon cancer rather than rectal cancer. Data from the CLASSIC[2,3] trial demonstrated that there

Table 5 Logistic regression of factors affecting likelihood of developing a postoperative event with OAPR

Variable	OR	95% confidence		*p* value
		Lower	Upper	
Age	1.01	1.00	1.02	0.1650
Female	Reference			
Male	1.10	0.84	1.42	0.4890
Non-White	Reference			
White	1.08	0.84	1.38	0.5410
BMI <25 kg/m^2	Reference			
BMI 25+kg/m^2	1.29	0.99	1.69	0.0600
Dyspnea: at rest	Reference			
Dyspnea: none	1.03	0.69	1.52	0.8880
Nonsmoker	Reference			
Smoker	1.82	1.34	2.47	0.0000
No alcohol use	Reference			
Alcohol use	1.16	0.67	2.01	0.5970
Nondiabetic	Reference			
Diabetic: insulin-dependent	1.77	0.94	3.32	0.0770
Diabetic: non-insulin-dependent	0.92	0.61	1.37	0.6730
No previous percutaneous coronary intervention	Reference			
Percutaneous coronary intervention	1.44	0.83	2.48	0.1920
No history of hypertension	Reference			
Hypertension	1.23	0.93	1.63	0.1500
No history of cerebrovascular accident	Reference			
Cerebrovascular accident	2.41	1.05	5.56	0.0390
No disseminated cancer	Reference			
Disseminated cancer	1.26	0.83	1.91	0.2730
No weight loss	Reference			
Weight loss, >10% body weight in last 6 months	1.64	1.10	2.46	0.0160
No history of bleeding disorders	Reference			
Bleeding disorders	0.84	0.39	1.80	0.6590
No history of prior chemotherapy	Reference			
Chemotherapy	1.21	0.78	1.88	0.3910
No history of prior radiotherapy	Reference			
Radiotherapy	0.81	0.62	1.06	0.1280
ASA class 1 and 2	Reference			
ASA class 3, 4, and 5	1.09	0.83	1.42	0.5550

BMI body mass index, *ASA* American Society of Anesthesiologists

Table 6 Logistic regression of factors affecting likelihood of developing a postoperative event with LAPR

Variable	OR	95% confidence		*p* value
		Lower	Upper	
Age	0.97	0.93	1.00	0.0800
Female	Reference			
Male	1.08	0.45	2.56	0.8700
Non-White	Reference			
White	1.37	0.59	3.21	0.4640
BMI <25 kg/m^2	Reference			
BMI 25+kg/m^2	1.27	0.55	2.96	0.5740
Dyspnea: at rest	Reference			
Dyspnea: none	1.10	0.21	5.77	0.9060
Nonsmoker	Reference			
Smoker	0.84	0.28	2.53	0.7530
No alcohol use	Reference			
Alcohol use	0.35	0.03	4.73	0.4260
Nondiabetic	Reference			
Diabetic: insulin-dependent	2.30	0.17	30.54	0.5270
Diabetic: non-insulin-dependent	1.04	0.23	4.67	0.9570
No previous percutaneous coronary intervention	Reference			
Percutaneous coronary intervention	1.44	0.20	10.21	0.7150
No history of hypertension	Reference			
Hypertension	2.53	0.98	6.53	0.0550
No history of cerebrovascular accident	Reference			
Cerebrovascular accident	2.92	0.22	38.67	0.4160
No disseminated cancer	Reference			
Disseminated cancer	3.90	0.66	23.03	0.1330
No weight loss	Reference			
Weight loss, >10% body weight in last 6 months	4.83	0.94	24.85	0.0600
No history of bleeding disorders	Reference			
Bleeding disorders	2.94	0.14	60.07	0.4830
No history of prior chemotherapy	Reference			
Chemotherapy	2.75	0.67	11.20	0.1590
No history of prior radiotherapy	Reference			
Radiotherapy	0.37	0.14	0.97	0.0430
ASA class 1 and 2	Reference			
ASA class 3, 4, and 5	0.76	0.31	1.90	0.5610

BMI body mass index, *ASA* American Society of Anesthesiologists

was no advantage for laparoscopic resections with respect to urinary or sexual dysfunction, while there was a higher rate of positive circumferential margins of resection with a conversion rate >30%. The high conversion rate is an especially daunting figure considering the degree of specialization of the surgeons involved in this trial.[22] More recent, smaller, and often single-institution studies[23–25] have suggested that short-term outcomes following laparoscopic rectal cancer resections are similar to open surgery and that conversion rates are lower than those seen in earlier trials, reflecting a greater current experience with

Table 7 Thirty-day postoperative complications for OAPR compared to LAPR

Postoperative complication	OAPR (N=1,197), n (%)	LAPR (N=143), n (%)	p value
Surgical site infection	267 (22.31)	24 (16.78)	0.1300
Wound disruption	26 (3.01)	5 (3.50)	0.7480
Pneumonia	40 (3.34)	2 (1.4)	0.2080
Unplanned intubation	35 (2.92)	4 (2.80)	0.9320
Pulmonary embolus	8 (0.67)	1 (0.70)	0.9660
Ventilator dependence >48 h	31 (2.59)	3 (2.10)	0.7240
Progressive renal insufficiency	10 (0.84)	0 (0.00)	0.2730
Acute renal failure	9 (0.75)	1 (0.70)	0.9450
Urinary tract infection	85 (7.10)	10 (6.99)	0.9620
Cerebrovascular accident	4 (0.33)	0 (0.00)	0.4890
Cardiac arrest requiring CPR	1 (0.08)	2 (1.40)	0.0020
Myocardial infarction	4 (0.33)	0 (0.00)	0.4890
Transfusion requirement	15 (1.25)	0 (0.00)	0.1780
DVT	23 (1.92)	1 (0.70)	0.2980
Sepsis	75 (6.27)	3 (2.10)	0.0440
Septic shock	30 (2.51)	3 (9.09)	0.7660
Return to OR within 30 days	94 (7.85)	7 (4.90)	0.2050

DVT deep venous thrombosis

this technique. However, larger studies specifically focused on complications rates, especially studies which are either multi-institutional or population based, are still largely absent.

While wide application of minimally invasive colon cancer surgery has remained low in the general population, laparoscopic rectal cancer surgery has gained even less traction. Much of this reticence is no doubt related to the observation that pelvic surgery for rectal cancer is often more challenging than colon cancer resections and that rectal cancer surgery is unforgiving if not performed properly at the first attempt. In the present study, there was little difference between the OAPR and LAPR groups with respect to medical problems. Though mean BMIs were different between the groups to a statistically significant degree, both groups had BMIs which were on average below the obese range. The only factors associated with higher odds of undergoing an LAPR were female gender, non-Caucasian race, and a BMI <25, while the numerous patient comorbidities included in NSQIP did not appear to influence the choice of surgery. This information may indicate that patients currently undergoing LAPR are not appreciably healthier or of lesser operative risk than those being offered an OAPR and that the anticipated challenge of a laparoscopic rectal cancer surgery is still the greatest deterrent to LAPR gaining wider acceptance as opposed to few suitable laparoscopic surgical candidates with rectal cancer being available. This would suggest that, in terms of choosing a surgical approach, surgeons currently place a higher weight on the challenge of LAPR as well as the relative lack of cancer-related outcomes for this approach than they do upon the concept that minimally invasive rectal cancer surgery will offer consistent and substantial benefits which are purported with other types of laparoscopic surgeries. This would also suggest that the lack of penetration of laparoscopic rectal cancer surgery in the surgical community represents a lack of confidence among surgeons that LAPR is simply another minimally invasive version of an open surgery, as opposed to surgeons simply being highly selective in who is offered LAPR. This coincides with the present study's findings of great similarity between open and laparoscopic cohorts with respect to demographic information and medical diseases. The NSQIP data presented in this study would strongly suggest that surgeon preference, as opposed to patient factors, serves as the principal impetus in choosing between open and laparoscopic surgery and that the strong preference is still in favor of OAPR.

An area of particular interest in this study was to analyze the effect that preoperative radiotherapy exerted on both the choice of surgical approach and postoperative outcomes.

Table 8 Number of postoperative complications between OAPR and LAPR

Number of complications	OAPR (N=1,197), n (%), p=0.18	LAPR (N=143), n (%), p=0.18
0	789 (65.91)	103 (72.03)
1	258 (21.55)	27 (18.88)
2	89 (7.44)	11 (7.69)
3+	61 (5.10)	2 (1.40)

Table 9 Logistic regression of likelihood of developing postoperative complications with OAPR

Postoperative complication	OR	95% confidence		*p* value
		Lower	Upper	
Surgical site infection	1.23	0.76	1.99	0.3890
Wound disruption	0.63	0.22	1.77	0.3810
Pneumonia	2.38	0.51	11.07	0.2700
Unplanned intubation	0.76	0.18	3.29	0.7140
Pulmonary embolus	0.56	0.05	6.11	0.6350
Ventilator dependence >48 h	0.83	0.15	4.74	0.8330
Renal failure (acute and/or progressive)	3.53	0.32	39.33	0.3050
Urinary tract infection	0.90	0.45	1.80	0.7570
Cardiac arrest and/or myocardial infarction	0.33	0.05	2.05	0.2370
DVT	2.64	0.31	22.81	0.3770
Sepsis	2.51	0.75	8.40	0.1350
Septic shock	0.98	0.24	4.09	0.9800
Return to OR within 30 days	1.41	0.60	3.29	0.4340

DVT deep venous thrombosis

While there was no statistically significant difference between the absolute incidence of preoperative radiotherapy between LAPR and OAPR groups, patients who received neoadjuvant radiotherapy had 40% greater odds of undergoing LAPR, a finding which only approached statistical significance. This finding, while somewhat unexpected, may refer to a subgroup of patients who had more complex disease and who were referred to larger centers which both provide multidisciplinary preoperative care as well as provide the option of a laparoscopic resection. The choice of LAPR in the setting of neoadjuvant therapy may simply be an association and not a cause and effect relationship, since patients requiring neoadjuvant therapy who are referred to larger centers may encounter surgeons who would offer many patients within this group a laparoscopic resection regardless of their need for radiotherapy and not in response to their having undergone neoadjuvant treatment. The data presented does not allow for the inference that neoadjuvant therapy itself prompts the choice of a laparoscopic approach, which would be quite the opposite of what would be expected.

The finding that LAPR patients received preoperative radiotherapy as often as OAPR patients may explain why the incidence of postoperative surgical site infections and urinary tract infections was similar between both groups. With respect to surgical site infections, regardless of a minimally invasive or open approach, the perineal wound remains the same length and has the same higher incidence of infection and poor healing for both groups compared to abdominal wall incisions. The presence of neoadjuvant

Table 10 Logistic regression of likelihood of developing postoperative complications with LAPR

Postoperative complication	OR	95% confidence		*p* value
		Lower	Upper	
Surgical site infection	0.81	0.50	1.31	0.3890
Wound disruption	1.59	0.56	4.48	0.3810
Pneumonia	0.42	0.09	1.96	0.2700
Unplanned intubation	1.31	0.30	5.69	0.7140
Pulmonary embolus	1.78	0.16	19.41	0.6350
Ventilator dependence >48 h	1.21	0.21	6.89	0.8330
Renal failure (acute and/or progressive)	0.28	0.03	3.15	0.3050
Urinary tract infection	1.12	0.56	2.24	0.7570
Cardiac arrest and/or myocardial infarction	2.99	0.49	18.33	0.2370
DVT	0.38	0.04	3.26	0.3770
Sepsis	0.40	0.12	1.33	0.1350
Septic shock	1.02	0.24	4.25	0.9800
Return to OR within 30 days	0.71	0.30	1.67	0.4340

DVT deep venous thrombosis

radiotherapy only serves to augment these risks. Since the perineal wound is the highest-risk surgical site for APR patients due to its location and its exposure to radiotherapy, a laparoscopic approach may not appreciably alter the overall risk of surgical site infections in this group of rectal cancer patients. Additionally, a major driver for postoperative urinary tract infections in APR patients is related to the length of time that bladder catheterization is required and whether urinary retention requires the reinsertion of the catheter. Laparoscopic approaches may, theoretically, provide some advantage in avoiding urologic dysfunction, since pelvic exposure does not involve the placement of open retractors against the pelvic side walls and the sacrum and since high-definition cameras may provide better visualization of pelvic nerves and promote their preservation. However, radiotherapy can create praxis of the pelvic nerves and may potentially, just as was noted with surgical site infections, mitigate what would otherwise be an advantage to a minimally invasive approach. If the centers where LAPRs are preferentially performed are larger-sized, academic centers, which are facilities well represented in the NSQIP database, these hospitals would also tend to be the facilities where patients are referred for treatment of advanced rectal cancers in need of preoperative radiotherapy. Radiotherapy may ultimately be found to lessen the advantages of LAPR to the degree that it may be appropriate to distinguish between LAPR patients who do and do not require neoadjuvant therapy in terms of gauging the alleged advantages usually touted for minimally invasive surgery.

In the present study, the finding that patients undergoing radiotherapy prior to LAPR were 63% less likely to experience a postoperative occurrence must be interpreted carefully, as this particular OR compares LAPRs who do and do not receive radiotherapy as opposed to comparing LAPRs and OAPRs. Selection bias undoubtedly has an influence on this finding. The LAPR group in this study would include those patients who qualify for radiotherapy on the basis of suspected node-positive disease but who may have smaller primary lesions (a smaller T stage), thus constituting higher-stage cancers which are easier to resect than lesions requiring radiotherapy due to bulky disease or an obstructive component. Likewise, the LAPR group would incorporate those patients who had a major response or a complete response to radiotherapy, which could facilitate surgical extirpation depending on the presence or absence of other factors not included in NSQIP, such as the degree of anatomic distortion created by radiotherapy or the severity of radiation-induced proctitis present at the time of surgery. Patients who might have been offered an LAPR but who did not respond favorably to radiotherapy, who are found to have a persistent, large primary cancer, or those who might have required a conversion to an OAPR in the operating room and were thus counted as undergoing open surgery rather than tallied with an intention-to-treat principle also contributed to this finding.

Conclusion

Short-term complication rates between LAPR and OAPR have a similar incidence despite the greater technical challenge of the laparoscopic approach. In particular, surgical site infections were also similar, which may reflect similar rates of perineal wound infections, a problem which would be unaffected by choosing between an open or a laparoscopic approach. Far fewer patients are currently offered LAPR for cancer compared to OAPR, which appears largely due to surgeon preference and not due to consistently identifiable patient factors.

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ORIGINAL ARTICLE

Significance of Thoracoscopy-Assisted Surgery with a Minithoracotomy and Hand-Assisted Laparoscopic Surgery for Esophageal Cancer: The Experience of a Single Surgeon

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Abstract
Background This retrospective study evaluated the surgical learning curve and outcomes of thoracolaparoscopic esophagectomy.
Patients and Methods The study group comprised a series of 92 patients with preoperatively diagnosed resectable thoracic esophageal cancer. Additionally, the surgical outcomes in 79 esophageal cancer patients receiving open esophagectomies were compared. All patients underwent thoracolaparoscopic esophagectomy in the lateral decubitus position. The short- and long-term outcomes were evaluated, and the surgical learning curve was assessed.
Results The total operation time was 477.8±102.2 min, the thoracoscopic time was 157.9±61.3 min, the total blood loss was 554.4±280.5 ml, and the number of retrieved lymph nodes was 34.3±14.3. Postoperative morbidity was observed in 23 patients. After the surgeon's first 40 cases, the surgical technique and short-term outcomes were stable. The 5-year disease-specific survival was 66.6% and the 5-year overall survival was 64.6% in patients receiving R0 thoracolaparoscopic esophagectomy. Comparison of 5-year disease-specific survival rate according to tumor–node–metastasis stage between patients receiving R0 thoracolaparoscopic esophagectomy and conventional open esophagectomy showed that there were no significant differences in survival in any stage between the two groups. Loco-regional recurrence was observed in 6 patients, distant recurrence in seven, and combined recurrence in nine after R0 thoracolaparoscopic esophagectomy. There was no significant difference in the pattern of recurrence between the two groups.
Conclusions Thoracolaparoscopic esophagectomy for esophageal cancer was technically feasible and oncologically satisfactory, according to the surgical learning curve.

Keywords Esophageal cancer · Minimally invasive surgery · Surgical learning curve · Thoracoscopic surgery

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Introduction

Surgical resection is a promising treatment for loco-regional esophageal cancer due to its improved procedure and intraoperative and postoperative management. Ivor-Lewis esophagectomy, the traditional open surgical approach, is now commonly used for esophageal cancer;[1] however, open esophagectomy is associated with high morbidity and

mortality compared with other types of gastrointestinal surgery.[2–5] To overcome this, some specialized centers have developed minimally invasive esophagectomy (MIE),[6–9] which has the advantages of hypothesized lower trauma, earlier postoperative recovery, and reduced pulmonary complications. Moreover, thoracoscopic surgery provides satisfactory mediastinal lymph node dissection with an enlarged fine view.

Some studies have reported equal outcomes of thoracoscopic surgery for esophageal cancer compared with conventional open surgery.[10] In general, it is necessary for a surgeon to perform many esophageal cancer operations in order to achieve a satisfactory level of surgical skills. Moreover, it might be particularly difficult to obtain these skills for thoracoscopic esophagectomy. Although some studies have investigated the surgical learning curve for thoracoscopic surgery, many were based on only a small number of cases.[11,12] We therefore conducted a retrospective study to evaluate the surgical learning curve and to compare surgical outcomes between thoracolaparoscopic esophagectomies and open esophagectomies performed by a single surgeon in a Japanese institute, in order to clarify the validity of this technique.

Material and Methods

The study group comprised a series of 92 patients with thoracic esophageal cancer who underwent thoracoscopy-assisted surgery with minithoracotomy combined with hand-assisted laparoscopic surgery (HALS) with two-field lymph node dissection (that is, complete dissection of the mediastinal and abdominal regional lymph nodes) in the Department of Surgery, Yokohama City University, Japan, from April 2002 to March 2009. This technique was performed in patients as follows: who gave informed consent, who had tumors expected to be curatively resected (R0) irrespective of stage, and who had no intrathoracic inflammatory adhesion as we could not obtain the fine operative view during thoracoscopic surgery in such cases. We preoperatively excluded patients for thoracoscopic surgery who had the pleural thickness on chest X-ray. A single surgeon, who had performed more than 200 open esophagectomies and 30 laparoscopy-assisted gastrectomies, carried out all of the esophagectomies in the present study. Data were retrieved from operative and pathological reports, and follow-up data were obtained from the outpatient clinical database. All subjects were preoperatively confirmed to have esophageal squamous cell carcinoma by analysis of endoscopic biopsy specimens. The male/female ratio was 77:15, and the mean age ± standard deviation (SD) was 64.1±7.6 years (range=37–78 years). Moreover, to compare the operative procedures and survival time between thoracolaparoscopic esophagectomy and open esophagectomies, 79 esophageal cancer patients receiving open esophagectomies with two-field lymph node dissection between April 1999 and March 2009 were also included in this study. The same surgeon performed 79 open esophagectomies.

Preoperative Evaluation

All patients underwent a preoperative evaluation that consisted of a barium swallow study, an endoscopic examination with a biopsy, and computed tomography (CT) scans. The tumor diameter and depth of invasion were measured by both endoscopic examination and a barium swallow study. Lymph node metastasis, depth of invasion, and staging were principally based on the International Union Against Cancer (UICC)/tumor–node–metastasis (TNM) classification.[13] The degree of lymph node dissection was according to the Japanese Classification of Esophageal Cancer.[14] In tumors in the middle thoracic esophagus, cervical paraesophageal lymph nodes (LNs), upper thoracic paraesophageal LNs, recurrent nerve LNs, tracheobronchial LNs, subcarinal LNs, middle thoracic paraesophageal LNs, main bronchus LNs, lower thoracic paraesophageal LNs, supradiaphragmatic LNs, posterior mediastinal LNs, LNs in the esophageal hiatus of the diaphragm, cardiac LNs, LNs along the lesser curvature, and LNs along the left gastric artery were eliminated. In tumors in the lower thoracic esophagus, recurrent nerve LNs, subcarinal LNs, middle thoracic paraesophageal LNs, main bronchus LNs, lower thoracic paraesophageal LNs, supradiaphragmatic LNs, posterior mediastinal LNs, LNs in the esophageal hiatus of the diaphragm, cardiac LNs, LNs along the lesser curvature, and LNs along the left gastric artery were eliminated. Experienced pathologists at the institution participated in the study and ensured the quality of diagnosis.

Of the 92 registered patients, 45 had tumors located in the lower thoracic esophagus, 44 in the middle thoracic esophagus, and 3 in the upper thoracic esophagus. Superficial type tumors (that is, flat or elevated, depressed, and mixed type [elevated plus depressed]) were seen in 37 patients, well-defined-type tumors in 28, and ill-defined-type tumors in the remaining 27.

The pathologic tumor diameter corresponded to the maximum microscopic length of the tumors irrespective of the depth. The patients were classified into three groups ("<30 mm", "≥30 to <60 mm", and "≥60 mm") based on the pathologic tumor diameter: tumors measuring <30 mm were observed in 21 patients, tumors measuring ≥30 to <60 mm in 44, and tumors measuring ≥60 mm in the remaining 27. Histologically, T1 (mucosa, submucosa) tumors were observed in 34 patients, T2 (muscularis propriae) in 10, and T3 in 48. Well-differentiated squamous

cell carcinoma was observed in 28 patients, moderately differentiated squamous cell carcinoma in 48, and poorly differentiated squamous cell carcinoma in 16.

Lymph node metastasis was observed in 46 patients. Of these, 21 were designated as N1, 14 as N2, and the remaining 11 as N3. Among the registered patients, 29 were classified as stage I, 27 as stage II, and 36 as stage III.

Of these 92 patients, 87 patients underwent R0 esophagectomy (94.6%). Comparison of clinicopathological features between patients undergoing thoracolaparoscopic esophagectomy and conventional open esophagectomy revealed that depth of invasion and curability significantly differed (T1/T2/T3, 34/10/48 versus 15/19/45, p=0.0095; R0/R1 or R2, 87/5 versus 62/17, p=0.0017) although there were no significant differences in lymph node metastasis and pathological stage.

Surgical Procedures

We precedingly dissect lower mediastinal lymph nodes as broad as possible by transhiatal approach during abdominal manipulation and subsequently we can concentrate on upper mediastinal lymph node dissection during thoracic manipulation. In this study, two-field esophagectomy was principally employed in patients with tumors in the middle or lower thoracic esophagus.

Abdominal manipulation was performed by HALS with the patient in the dorsosacral position. We employed the HALS technique to shorten the operation time of abdominal manipulation (paragastric lymph node dissection and making the gastric conduit) and to perform the lower mediastinal lymph node dissection satisfactorily by extending the operative field by the surgeon's left hand. Moreover, it is useful to pull up the gastric conduit through the esophageal hiatus retromediastinally into the thoracic cavity by the surgeon's right hand. The HandPort™ system (Smith & Nephew Inc., Mansfield, MA, USA) was introduced through a 6-cm mid-medial incision placed 5 cm to the cranial side of the umbilicus. Three 12-mm trocars (Covidien, Norwalk, CT, USA) were introduced in the following locations: 2 cm left of the left margin of the expanded HandPort™ system (trocar #1), 2 cm to the left of trocar #1 (trocar #2), and in the left hypochondral region in the same longitudinal line as trocar #1 (trocar #3).

The left hand of the surgeon was inserted into the abdominal cavity through the HandPort™ system, and a 0° or 30° 10-mm straight forward video camera was inserted through trocar #1, #2, or #3 according to the operative site; thereby, all trocars were 12 mm. Laparoscopic coagulating shears (5 mm LCS; Johnson & Johnson Corp., New Brunswick, NJ, USA) or a vessel-sealing system (LigaSure™ Atlas or LigaSure™ Advance, Covidien) was inserted through trocar #1 or #2, or occasionally for dissection of lower mediastinal lymph nodes, through trocar #3 (Fig. 1).

The operator stood between the patient's legs, and the assistant surgeon stood on the left side of the operating table. The greater omentum was incised along the greater curvature by the LCS or vessel-sealing system, preserving the gastroepiploic vessels, followed by cutting of the short gastric vessel.

After manipulation of the greater omentum, the stomach was tracted on the ventral side using the left hand, and the gastropancreatic ligament was incised along the suprapancreatic line. The left gastric vein and artery were isolated, ligated, and divided. The lesser omentum was incised along the liver margin to the esophagogastric junction, preserving the root of the right gastric artery and reaching the lesser curvature at the junction. The stomach was resected from the former curvature point to the top of the fornix with Endo-GIA Universal™ (Covidien) through trocar #1, and the gastric conduit was made. In this series, Kocher maneuver was not performed and pyloroplasty was not made in the gastric conduit. After a 6-cm hiatal incision of the diaphragm, the esophagus hiatal, retromediastinal, lower paraesophageal, and supraphrenic lymph nodes were dissected. The mid-paraesophageal lymph node was fully dissected in small patients using the transhiatal approach (Fig. 2). A feeding jejunostomy was made by the Witzel method at the 30-cm anal side from the Treitz ligament using a feeding tube (8.5 Fr).

The thoracoscopic procedure was performed with the patient in the left lateral decubitus position. The right lung was deflated during the thoracoscopic procedure for selective single-lung ventilation using a double-lumen endobronchial tube. During thoracoscopic surgery, four 12-mm trocars were introduced in the following locations: the second intercostal space in the mid-axillary line, the fourth intercostal space in the posterior axillary line, the sixth intercostal space in the posterior axillary line, and the sixth intercostal space in the mid-axillary line. Additionally, a 5-cm minithoracotomy was placed in the fourth intercostal space. The operator stood on the right side of the operating table (behind the patient) and carried out the manipulations either with the graspers used for the laparoscopic procedure or electric scissors, through the posterior axillary trocars. The thoracoscope was usually inserted through the trocar placed in the sixth intercostal space in the mid-axillary line (Fig. 3).

Initially, the arch of the azygos vein was isolated and divided by LigaSure™ with an absorbable clip. The pleura was incised along the right vagus nerve cranially, then subsequently along the right subclavian artery, and finally to the ventral side of the vertebral column. The right

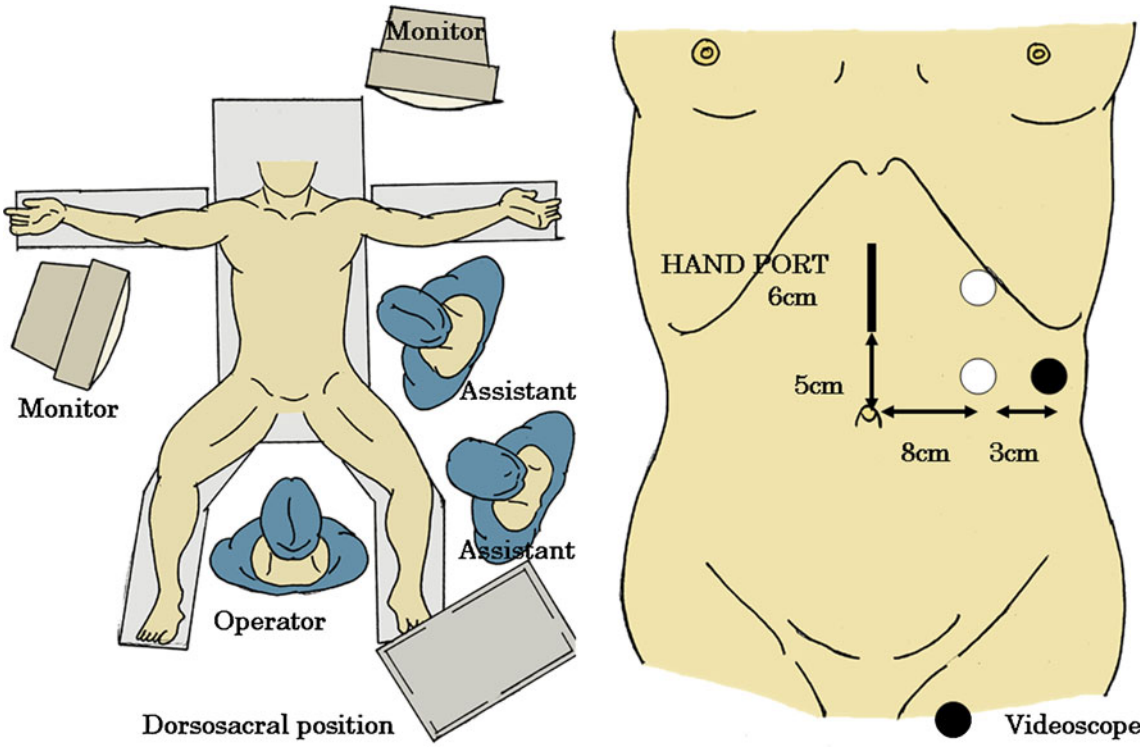

Fig. 1 Abdominal position and port sites for laparoscopy. The *closed circle* shows the 12-mm trocar. A videoscope is mainly inserted through the *black closed circle*

laryngeal recurrent nerve was identified and preserved. Lymph nodes around the nerve were carefully dissected to avoid injury and up to the margin of the right thyroid gland. Subsequent mobilization of the esophagus was initiated by incising pleura both sides of the esophagus to the supradiaphragmatic tissue. During this procedure, the incision line was connected to the dissected line from the transhiatal approach.

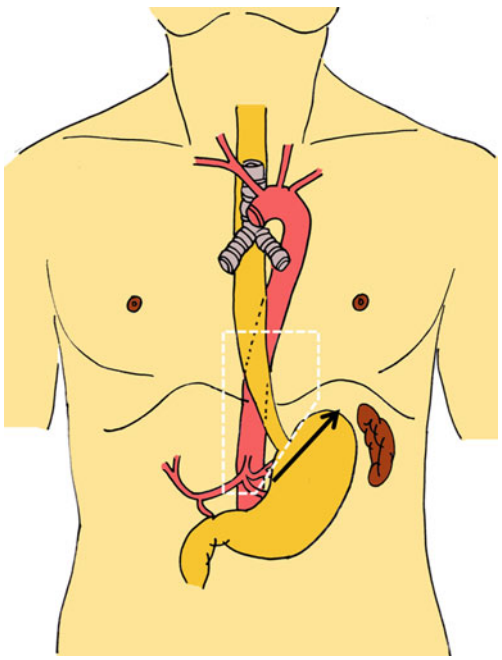

Fig. 2 Abdominal manipulation. The stomach is incised as shown in the *black arrow*. Paragastric and lower mediastinal lymph node dissection are performed within the *white dash square*

After preservation of the right bronchial artery, further mobilization of the thoracic esophagus was continued to expose the descending aorta. Mid-paraesophageal, tracheobronchial, tracheal bifurcation, and retromediastinal lymph nodes attaching to the esophagus were eradicated. The thoracic duct was routinely removed except in patients with liver cirrhosis. Finally, the upper mediastinal lymph nodes were cleared. Lymph nodes along the left laryngeal recurrent nerve were eliminated up into the neck as far as possible, and the node in the infra-aortic arch was eradicated to the level of exposing the right pulmonary artery. The esophagus was resected for subsequent intrathoracic anastomosis 3 cm from the lower margin of the right subclavian artery on the distal side (Fig. 4). The gastric conduit together with a gastric sump tube (10 Fr) was pulled up through the esophageal hiatus retromediastinally into the thoracic cavity, after enlargement of the 5-cm minithoracotomy to an 8–10-cm thoracotomy. Intrathoracic end-to-side anastomosis was completed at the apex of the right chest by an intraluminal stapler (PPCEEA, 21 or 25 mm, Covidien) after opening the intercostal space with a small rib retractor. Initially, anvil head was inserted into the

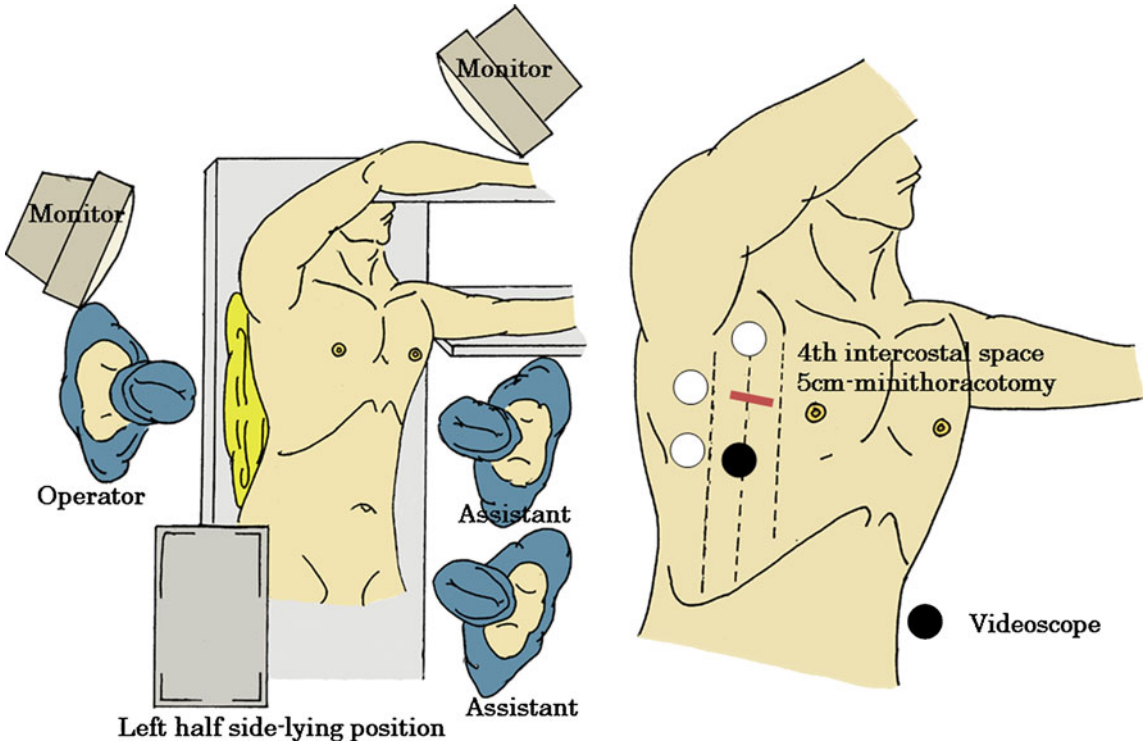

Fig. 3 Thoracic position and ports sited for thoracoscopy. The *closed circle* shows the 12-mm trocar. A videoscope is routinely inserted through the *black closed circle*

esophageal lumen and fixed through the thoracotomy. The PPCEEA was inserted into the gastric conduit by incising the gastric wall of the apex of the gastric conduit and followed by the suction of gastric juice, and an anastomosis was performed at the greater curvature side of the gastric conduit. Gastric stump was sutured by the Endo-GIA Universal™ (Covidien) through the thoracotomy. The gastric sump tube was placed near the anastomotic site to drain sufficiently when the anastomotic leakage was observed. Two chest drainage tubes (28 Fr) were inserted into the thoracic cavity: one was placed at the ventral side and the other was at the dorsal side. A nasogastric tube was orally introduced into the gastric conduit by an anesthesiologist. The hiatal incision was not closed as the gastric conduit fully occupied this space (Fig. 5).

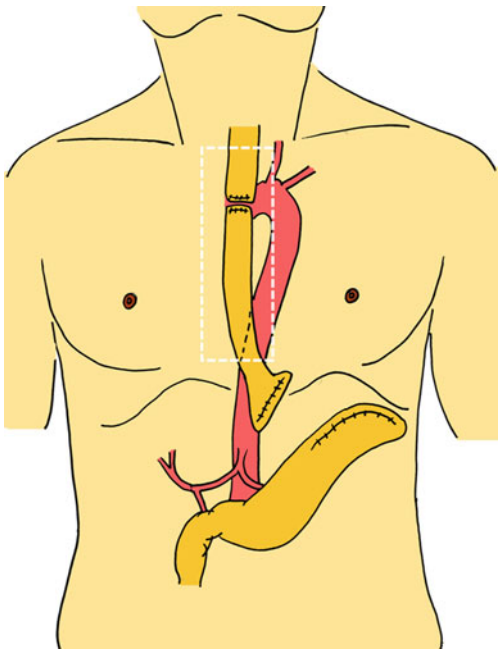

Fig. 4 Thoracic manipulation. Upper and middle mediastinal lymph node dissection are performed within the *white dash square*

Principally, the surgical procedures in patients receiving open esophagectomies were same as compared to those in patients following thoracolaparoscopic esophagectomies. Surgery was performed after all possible alternative procedures or treatments had been explained to the patients, and they had given their informed consent.

Neoadjuvant and Adjuvant Treatments

Neoadjuvant therapy was not employed in these patients, and adjuvant chemotherapy was only administered to those with tumors deeper than the muscularis propria or with lymph node metastasis, after they had given their informed consent. Of patients who met the criteria, 12 patients received adjuvant chemotherapy,

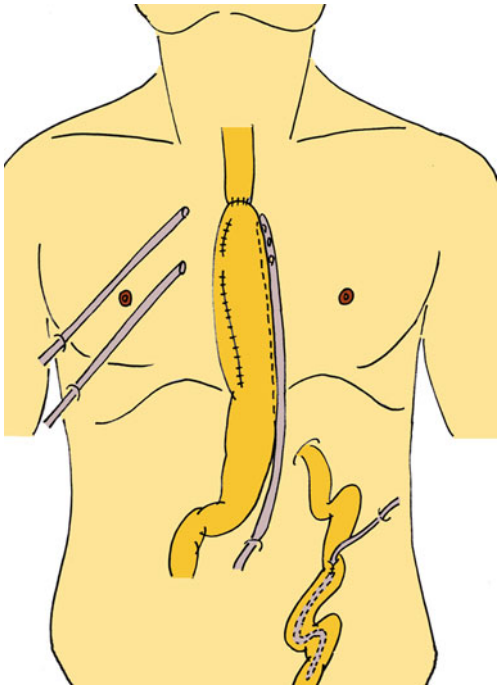

Fig. 5 Completed reconstruction using the gastric conduit. Two chest tubes are placed in the right thoracic cavity for postoperative drainage. An 18-Fr gastric sump tube is placed near the esophagogastric anastomosis. An 8.5-Fr feeding tube is placed in the upper jejunum

consisting of cisplatin (5 mg/m^2 on days 1–5 and 8–12) plus fluorouracil (500 mg/m^2 on days 1–5 and 8–12). This regimen was continued for at least four courses during the first 2 years after surgery.

Indication of Discharge from the Hospital

Eligible criteria for discharge are as follows: no fever (less than 37°C), no inflammation (normal range of C-reactive protein and white blood cell counts), no symptom due to the recurrent nerve palsy, oral intake more than 50% of served solid foods, and expectation of sufficient care from family.

Follow-up Protocol

All patients underwent a blood examination every 3 months, a CT scan every 6 months, and an annual endoscopic examination. If gastrointestinal symptoms were reported, an additional examination was carried out. After the fifth year, patients received an annual check-up at an outpatient clinic. The follow-up time (mean ± SD) was 33.9±28.4 and 36.4±33.2 months between the thoracolaparoscopic group and the open group (p=0.6025).

Definition of Recurrence

Loco-regional recurrence was defined as tumors occurring in lymph nodes in the neck, the mediastinum including the anastomotic site, or the upper abdomen at the site of the initial esophagectomy and lymph node dissection. Distant recurrence was defined as hematogenous metastasis within the solid organ, lymph nodes at the abdominal para-aorta, or peritoneal metastasis. Recurrence was diagnosed histologically, cytologically, and radiologically. Combined recurrence was defined as plural recurrences on initial investigations or subsequent recurrence at another site within 30 days.

Statistical Analysis

SPSS version 10.0 for Windows (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses. The chi-square test or the Fisher's exact test was applied to evaluate differences in proportions, and the Student's t test was used to evaluate continuous variables (data are expressed as the mean ± SD). Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. A probability value of $p<0.05$ was considered statistically significant. The institutional review board of our institute approved this retrospective study.

Results

Patient Characteristics

The patient characteristics are listed in Table 1. In total, 34 patients had preoperative co-morbid diseases: of these, cardiovascular disease was the most frequent, followed by diabetes mellitus and liver dysfunction. Moreover, 11

Table 1 Patient characteristics

Characteristic	
Mean age, years (range)	64.1 (37–78)
Male/female	77/15
Preoperative co-morbid disease	34 (36.9)
Cardiovascular	24 (26.1)
Diabetes mellitus	8 (8.7)
Liver dysfunction	7 (7.6)
Respiratory	5 (5.4)
Cerebrovascular	2 (2.2)
Renal	2 (2.2)
Past history of cancer	11 (12.0)

Figures in parentheses are percentages

patients had a past history of colorectal cancer (n=5), gastric cancer (n=4), tongue cancer (n=1), gingival cancer (n=1), uterine cancer (n=1), or breast cancer (n=1). These cancers had been treated adequately and no recurrence was observed at the time of esophagectomy in every patient.

Intraoperative Factors

The operation time was 477.8±102.2 min, the thoracoscopic time was 157.9±61.3 min, the total blood loss was 554.4±280.5 ml, and the number of retrieved lymph nodes was 34.3±14.3 in patients receiving thoracolaparoscopic esophagectomy. As compared to those in patients following open esophagectomy, significant differences were observed in the operation time (531.4±112.7 min, p=0.0016), the total blood loss (979.2±738.7 min, p<0.0001), and the number of retrieved lymph nodes (29.0±12.2, p=0.0114) (all data are the mean ± SD). The retrieved number of lymph nodes in the caudal side of the middle and the lower mediastinum increased in patients receiving thoracolaparoscopic esophagectomy.

Postoperative Course

The length of intensive care unit (ICU) stay was 6.1± 3.0 days and the postoperative hospital stay was 33.2± 16.5 days (mean ± SD for both). Postoperative morbidity was observed in 23 patients (25.0%). Among these, transient recurrent nerve palsy (11.9%) and anastomotic leakage (8.7%) were the most common followed by chylothorax (2.2%), pneumonia (1.1%), and injury of the trachea (1.1%). Ice massage at the pharynx was performed to improve the transient recurrent nerve palsy, and adequate drainage by the gastric sump tube was continued until the anastomotic leakage improved. Most patients were controllable and recovered gradually after appropriate treatments during their hospital stay. There was no patient required reoperation due to the anastomotic leakage. However, 1 patient suddenly died of arrhythmia (1.1%) on the postoperative 14th day. We have never experienced morbidity due to the HALS technique including hiatal incisional hernia and obstructive ileus at the enlarged hiatus.

Correlation of Intraoperative Factors and Postoperative Morbidities

The operation time, the thoracoscopic time, and the total blood loss were compared between patients with (n=10) and without postoperative morbidities (anastomotic leakage and pneumonia) (n=82). There was no significant difference in the total operation time, the thoracoscopic time, and the total blood loss between the two groups (514.4±66.6 versus 473.3±105.1 min, p=0.2323; 221.4± 91.3 versus 182.0±76.2 min, p=0.1758; 520.2±203.5 versus 551.3±287.5 ml, p=0.7412, respectively) (all data are the mean ± SD).

Comparison of Patient Characteristics According to the Surgical Learning Curve

There were significant differences in gender, preoperative co-morbid disease, and macroscopic tumor type according to the surgical learning curve, whereas there were no significant differences in age, tumor site, tumor size, histological type, depth of invasion, lymph node metastasis, stage, or curability (Table 2).

Comparison of Intraoperative Results According to the Surgical Learning Curve

Significant differences in total operation time were seen as follows: between cases 1–20 and 41–60, 61–80, and 81–92; between cases 21–40 and 41–60, 61–80, and 81–92; and between cases 41–60 and 61–80, and 81–92 (p<0.05). Significant differences in thoracoscopic time were seen as follows: between cases 1–20 and 21–40, 41–60, 61–80, and 81–92; and between cases 21–40 and 41–60, 61–80, and 81–92 (p<0.05).

Significant differences in blood loss were seen as follows: between cases 1–20 and 41–60, 61–80, and 81–92; and between cases 21–40 and 41–60, 61–80, and 81–92 (p<0.05). There were significant differences in the number of retrieved lymph nodes between cases 1–20 and 21–40, 41–60, 61–80, and 81–92 (p<0.05). After the experience of 40 cases, the surgical technique stabilized, and after the experience of 60 cases, it plateaued. Five cases were converted from thoracoscopic surgery to open surgery in this series, although there was no significant difference in the incidence of conversion to open surgery. The reasons for conversion to open surgery were one suspected T4 tumor case and one case of uncontrollable inflammatory adhesion in each of the groups of cases 21–40 and 61–80 and one suspected T4 tumor case in the group of cases 81–92 (Table 3).

Comparison of Postoperative Courses According to the Surgical Learning Curve

There were significant differences in the length of ICU stay between cases 1–20 and 41–60, 61–80, and 81–92 (p< 0.05). Moreover, the length of postoperative hospital stay significantly differed between cases 1–20 and 81–92 (p= 0.0415). Pneumonia and chylothorax were not observed

Table 2 Comparison of patient characteristics according to surgical learning curve

	Cases 1–20	Cases 21–40	Cases 41–60	Cases 61–80	Cases 81–92	*p* value
Age (years)	63.3±5.5	63.5±6.7	62.4±6.9	66.4±8.5	64.1±11.1	
Gender						0.0054
Male/female	18/2	20/0	16/4	17/3	6/6	
Preoperative co-morbid disease	2 (10)	9 (45)	12 (60)	7 (35)	4 (33.3)	0.0219
Tumor site						0.1989
Lower thoracic	10 (50)	8 (40)	12 (60)	6 (30)	9 (45)	
Middle thoracic	10 (50)	11 (55)	8 (40)	12 (60)	3 (55)	
Upper thoracic	0 (0)	1 (5)	0 (0)	2 (10)	0 (0)	
Macroscopic type						0.0288
Superficial	7 (35)	7 (35)	13 (65)	10 (50)	0 (0)	
Well-defined	7 (35)	8 (40)	3 (15)	3 (15)	7 (58.3)	
Ill-defined	6 (30)	5 (25)	4 (20)	7 (35)	5 (41.7)	
Tumor size (mm)						0.9074
<30	4 (20)	7 (35)	5 (25)	4 (20)	1 (8.3)	
≥30 to <60	10 (50)	8 (40)	9 (45)	10 (50)	7 (58.4)	
≥60	6 (30)	5 (25)	6 (30)	6 (30)	4 (33.3)	
Histological type[a]						0.0910
Well diff. sq.	1 (5)	7 (35)	7 (35)	7 (35)	6 (50)	
Mod. diff. sq.	13 (65)	12 (60)	9 (45)	11 (55)	3 (25)	
Por. diff. sq	6 (30)	1 (5)	4 (20)	2 (10)	3 (25)	
Depth of invasion						0.0846
Mucosa, submucosa	6 (30)	6 (30)	12 (60)	8 (40)	2 (16.7)	
Muscularis propriae	2 (10)	0 (0)	3 (15)	2 (10)	3 (25)	
Adventitia	12 (60)	14 (70)	5 (25)	10 (50)	7 (58.3)	
Lymph-node metastasis[b]						0.8239
N0	10 (50)	8 (40)	12 (60)	11 (55)	5 (41.7)	
N1	4 (20)	5 (25)	5 (25)	5 (25)	2 (16.7)	
N2	4 (20)	4 (20)	2 (10)	1 (0)	4 (33.3)	
N3	3 (15)	3 (15)	1 (5)	3 (15)	1 (8.3)	
Stage[c]						0.7322
IA	5 (25)	5 (25)	9 (45)	6 (30)	2 (16.7)	
IB	0 (0)	0 (0)	1 (5)	1 (5)	0 (0)	
IIA	5 (25)	3 (15)	2 (10)	4 (20)	3 (25)	
IIB	2 (10)	1 (5)	3 (15)	2 (10)	2 (16.7)	
IIIA	3 (15)	4 (20)	4 (20)	4 (20)	1 (8.3)	
IIIB	2 (10)	4 (20)	0 (0)	0 (0)	3 (25)	
IIIC	3 (15)	3 (15)	1 (5)	3 (15)	1 (8.3)	
Curability						0.3703
R0	18 (90)	17 (85)	20 (100)	18 (90)	12 (100)	

Figures in parentheses are percentages

[a] Well-differentiated squamous cell carcinoma, moderately differentiated squamous cell carcinoma, and poorly differentiated squamous cell carcinoma

[b] TNM classification

[c] TNM classification

after the experience of 60 cases. Injury of the trachea was only observed in the first 20 cases. However, there was no significant difference in the distribution of postoperative morbidities (transient recurrent nerve palsy and anastomotic leakage) according to the surgical learning curve (p= 0.7779) (Table 4).

Table 3 Comparison of intraoperative results according to surgical learning curve

	Cases 1–20	Cases 21–40	Cases 41–60	Cases 61–80	Cases 81–92
Total operation time (min)	556.1±127.7[a]	526.9±95.0[b]	446.6±62.9[c]	409.1±46.9	398.8±59.5
Thoracoscopic time (min)	270.4±132.1[d]	229.7±50.7[b]	152.4±47.9	143.3±29.4	133.9±43.1
Blood loss (ml)	652.0±236.6[a]	710.7±359.6[b]	413.7±136.5	457.9±174.0	446.9±168.0
No. of retrieved lymph nodes	24.0±11.2[d]	37.2±13.6	38.6±10.7	40.7±16.7	38.9±10.3
Conversion to open surgery	0	2	0	2	1

[a] Significant differences observed between cases 1–20 and 41–60, 61–80, and 81–92

[b] Significant differences observed between cases 21–40 and 41–60, 61–80, and 81–92

[c] Significant differences observed between cases 41–60 and 61–80, and 81–92

[d] Significant differences observed between cases 1–20 and 21–40, 41–60, 61–80, and 81–92

Survival

Twenty-eight patients died after thoracolaparoscopic esophagectomy. Of these, 23 died from esophageal cancer, and the remaining 5 died of other diseases (2 from pulmonary disorder, 1 from bleeding from the gastric conduit, 1 from heart failure, and 1 from urethral cancer). The 5-year disease-specific survival rate of all 92 patients was 59.9%, and the 5-year overall survival rate was 56.4%.

The 5-year disease-specific survival rate and 5-year overall survival rate were compared between patients receiving R0 thoracolaparoscopic esophagectomy (n=87) and open esophagectomy (n=62). A significant difference was observed in overall survival between the two groups (64.6% versus 43.8%, p=0.0236), whereas no difference was observed in disease-specific survival (66.3% versus 49.0%, p=0.0709) (Fig. 6). Comparison of 5-year disease-specific survival rate according to TNM stage between patients receiving R0 thoracolaparoscopic esophagectomy and conventional open esophagectomy showed that there were no significant differences in any stage between the two groups (stage I, 80.0% (n=29) versus 82.5% (n=14), p=0.5960; stage II, 84.0% (n=26) versus 60.7% (n=22), p=0.0553; stage III, 37.2% (n=32) versus 21.5% (n=26), p=0.4286) (Fig. 7).

Overall survival and disease-specific survival were compared between the former 40 patients and the latter 52 patients classified according to the surgical learning curve. There were no significant differences in the overall and disease-specific survival between the two groups (p=0.3393 and p=0.5670, respectively).

Pattern of Recurrence

Loco-regional recurrence was observed in six patients, distant recurrence in seven, and combined recurrence in nine after curative esophagectomy after R0 esophagectomy.

Table 4 Comparison of postoperative courses according to the surgical learning curve

	Cases 1–20	Cases 21–40	Cases 41–60	Cases 61–80	Cases 81–92
ICU stay (days)	8.8±4.7[a]	6.8±2.2	5.6±3.0	5.6±3.1	4.9±2.7
Postoperative hospital stay (days)	35.9±14.0[b]	32.8±14.8	36.9±23.8	31.2±11.5	25.2±7.1
Postoperative morbidity	7 (35)	5 (25)	5 (25)	4 (20)	2 (16.7)
Transient recurrent nerve palsy	3 (15)	2 (10)	2 (10)	2 (10)	2 (10)
Anastomotic leakage	2 (10)	2 (10)	2 (10)	2 (10)	0 (0)
Pneumonia	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)
Chylothorax	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)
Injury of the trachea	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Mortality	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)

Figures in parentheses are percentages

[a] Significant differences observed between cases 1–20 and 41–60, 61–80, and 81–92

[b] Significant difference observed between cases 1–20 and 81–92

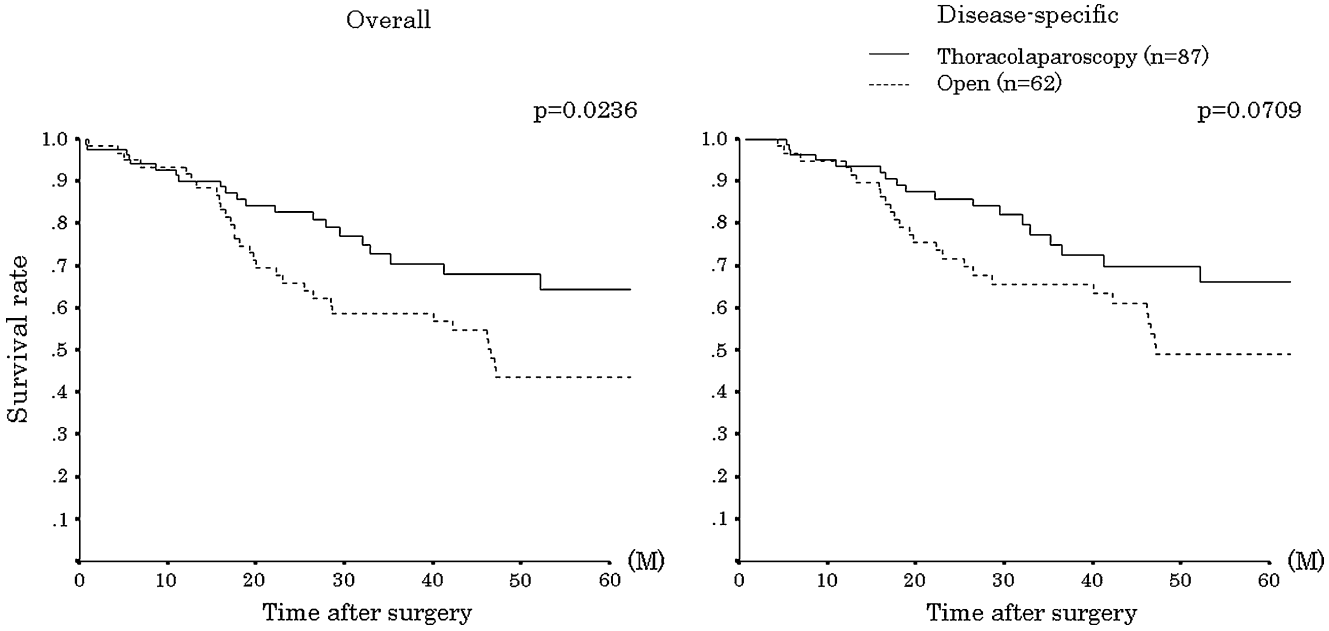

Fig. 6 Comparison of 5-year disease-specific survival rate and 5-year overall survival rate between patients receiving thoracolaparoscopic esophagectomy (n=87) and conventional open esophagectomy (n=62). There was a significant difference in overall survival between the two groups (p=0.0236)

Of the 15 patients with loco-regional and combined recurrences, lymph node recurrences were observed around the left laryngeal recurrent nerve in 6, in the supraclavicular regions in 4, in the mid or lower mediastinal lymph nodes in 3, around the right laryngeal recurrence nerve in 2, and in the paragastric regions in 1. There was no port site recurrence. Moreover, no significant difference was observed in the pattern of recurrence between the thoracolaparoscopic group and the open group (loco-regional/distant/combined, 6/7/9 versus 11/6/9, p=0.5426).

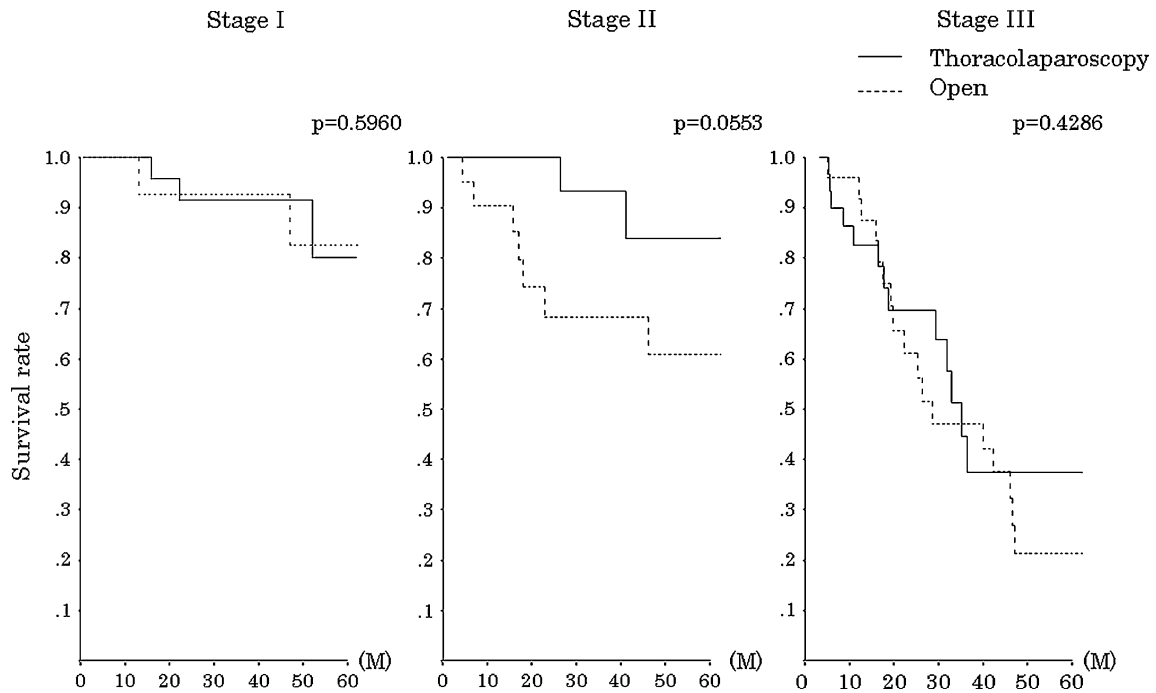

Fig. 7 Comparison of 5-year disease-specific survival rate according to TNM stage between patients receiving thoracolaparoscopic esophagectomy and conventional open esophagectomy. There was no significant difference in any stage between the two groups

Discussion

This study showed that a surgeon must perform at least 40 minimally invasive thoracolaparoscopic esophagectomies for esophageal cancer to achieve stable techniques and progress sufficiently along the surgical learning curve. Although surgical resection is a promising approach for the treatment of loco-regional esophageal cancer,[15–18] a high level of surgical stress is involved, which has resulted in high reported incidences of postoperative morbidity and mortality for esophageal cancer surgery even when performed by experienced surgeons.[2–5] More traditional open transthoracic esophagectomy has been widely performed worldwide, and extended lymph node dissection using this technique has provided satisfactory long-term results.[15–18] Owing to the relatively high incidence of postoperative morbidity, improvements have been made to the surgical approach, technique, and devices and to perioperative treatment and care. In particular, MIE has been adopted by many institutions.[7–9] The advantages of this include fewer wounds; reduced blood loss; easier mediastinal lymph node dissection due to the enlarged, fine operative view; easier mobilization of the esophagus in the deep thorax; earlier postoperative recovery; and reduced postoperative pulmonary complications. The operative procedures of MIE vary widely as follows: thoracoscopy and laparoscopy, thoracoscopy and hand-assisted laparotomy or minilaparotomy, hand-assisted thoracotomy and laparoscopy or hand-assisted laparotomy, and laparoscopic transhiatal or hand-assisted laparoscopic transhiatal. According to a previous study, our method is defined as MIE although minithoracotomy was extended in some cases. In most studies, the esophagogastric anastomosis was performed at the neck with a 4–6-cm collar incision, and therefore, thoracotomy was unnecessary.[6–9] However, we employed intrathoracic anastomosis and so we have to extend the minithoracotomy to 10-cm thoracotomy Therefore, it is necessary to develop a useful method available for intrathoracic anastomosis with a minithoracotomy. A study reported that when one operative procedure (abdominal or thoracic) was conventional open, the method was defined as hybrid minimally invasive esophagectomy.[19] According to this definition, our method is MIE.

In this study, the HALS technique provided the enlarged fine operative view through the esophageal hiatus, and subsequently, the caudal side of the middle mediastinal lymph node dissection was more exactly performed. Moreover, we did not encounter any postoperative complications including wound complications related to the HALS incision. Therefore, this technique may be feasible for thoracolaparoscopic surgery for esophageal cancer.

In our series, patients were placed in a left lateral decubitus position. By contrast, some studies reported the efficacy of videoscopic-assisted transthoracic esophagectomy in a prone position. This was found to offer a fine operative view without lung compression, resulting in reduced postoperative respiratory complications.[20,21] However, the incidence of respiratory complications was both acceptable (2%) and controllable in our series. Therefore, video-assisted thoracoscopy esophagectomy for esophageal cancer in a left lateral decubitus position might provide satisfactory outcomes.

In esophageal cancer surgery, upper mediastinal lymph node dissection is probably the most important procedure due to the high incidence of lymph node metastasis in this region. We therefore performed transhiatal lower mediastinal lymph node dissection using the HALS technique in order to concentrate on upper lymph node dissection in the video-assisted procedure. The inexperienced lymph node dissection in this region results in the recurrent nerve palsy or loco-regional recurrence, and subsequently, patients suffer from these disadvantages. Therefore, it is necessary to realize the anatomy in this region and to acquire steady surgical skills in sufficient number of open esophagectomies prior to the start of thoracoscopic esophagectomy. It will be necessary to compare surgical procedures for upper mediastinal lymph node dissection between the left lateral decubitus position and prone position to clarify which is more favorable for this surgical procedure.

The technique of MIE is associated with a steep learning curve. A previous study reported that postoperative outcomes were stable after a surgeon had performed 34 thoracoscopic esophagectomies,[11] whereas another reported that 14 such surgical experiences were sufficient.[12] In the current study, we found that it was necessary for a surgeon to perform at least 40 thoracoscopic esophagectomies to obtain satisfactory surgical skills. These differences might derive from the number or type of a surgeon's open esophagectomy experiences prior to the thoracoscopic esophagectomy, the degree of lymph node dissection, and differences in surgical procedures.

The surgical learning curve influenced the lengths of postoperative ICU stay and hospital stay and the incidences of pneumonia, chylothorax, and trachea injury, but not those of transient recurrent nerve palsy and anastomotic leakage. A shorter operation time and smaller blood loss might reduce the surgical burden and result in a shorter hospital stay. However, recurrent nerve palsy and anastomotic leakage do not always occur after excessive surgical stress or due to poor surgical skills. Indeed, the performance status and nutritional status of the patient, the degree of co-morbid diseases, and the perioperative management and care all contribute to the incidence of postoperative complications. Moreover, the experience of a sufficient number of open esophagectomies including anastomotic procedure may contribute these outcomes.

In our series, the incidence of postoperative pulmonary morbidities was lower than in many other reports.[9,22] This is probably largely due to the meticulous and intensive pulmonary management, including specific indications for weaning from postoperative mechanical ventilation, a sufficient cough reflex to saline, a partial pressure of oxygen in the arterial blood/fraction of inspired oxygen above 300, and a body weight equal to that preoperatively. Nevertheless, the length of ICU stay in our study was longer than in other reports, although the length of postoperative hospital stay was reduced after surgical experience of 80 cases. In Japan, hospitalization costs are met by government insurance, so patients are often resistant to being discharged on an earlier postoperative day. It is therefore difficult to compare the length of hospital stay between Japan and Western countries.

The long-term survival times in the current series were satisfactory and acceptable and similar to those in other studies focusing on either thoracolaparoscopic or open esophagectomies.[23,24] Lymph node dissection by thoracoscopic esophagectomy might also be sufficient, according to the surgical learning curve.

The pattern of recurrence after thoracolaparoscopic esophagectomy was similar to those reported in conventional open esophagectomies[5,25] as shown in our study. In the current study, lymph node recurrence was commonly observed in cervical lymph nodes and upper mediastinal lymph nodes along the laryngeal recurrent nerve, particularly in the left side of the patient. It is difficult to dissect mediastinal lymph nodes completely, particularly those in the left side, irrespective of the operating method. Technical limitations still exist in thoracoscopic surgery even though this method provides an enlarged and fine operative view. However, the number of dissected lymph nodes and survival time obtained in the current study were oncologically acceptable. Therefore, the technique might be regarded as equivalent to the open method, according to the surgical learning curve.

Conclusion

Thoracoscopic esophagectomy for esophageal cancer was shown to be technically feasible and oncologically satisfactory, according to the surgical learning curve. After the surgeon had the experience of 40 cases of thoracoscopic surgery, the technique appeared to stabilize. It will, however, be necessary to conduct a prospective randomized trial comparing thoracoscopic minimally invasive and open esophagectomy in a large number of patients.

Author Disclosures Drs. Chikara Kunisaki, Takashi Kosaka, Takashi Oshima, Shoichi Fujii, Ryo Takagawa, Jun Kimura, Hirochika Makino, Hirotoshi Akiyama, and Itaru Endo have no conflicts of interest or financial ties to disclose.

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ORIGINAL ARTICLE

Management of Gastrointestinal Leaks After Minimally Invasive Esophagectomy: Conventional Treatments vs. Endoscopic Stenting

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Abstract
Introduction Gastrointestinal leak is a dreaded complication after esophagectomy. Conventional treatments for leak include conservative therapy, surgical reoperation, and even complete gastrointestinal (GI) diversion. The aim of this study was to evaluate the impact of endoluminal stenting in the management of esophagogastric leak after esophagectomy.
Methods Data on 18 (11.3%) of 160 patients who developed postoperative leaks after minimally invasive esophagectomy were reviewed. Indications for esophagectomy included carcinoma (n=14), Barrett's with high-grade dysplasia (n=3), and benign stricture (n=1). Neoadjuvant therapy was used in 57.1% of patients with carcinoma. The first nine patients underwent conventional treatments for leak whereas the latter nine patients underwent endoscopic esophageal covered stenting as primary therapy. There were 5 cervical and 13 intrathoracic anastomotic leaks. Main outcome measures included patient characteristics, types of treatment, length of hospital stay, morbidity, and mortality.
Results Subjects were 16 males and 2 females with a mean age of 66 years. In the conventional treatment group, leaks were treated with neck drainage (n=4), GI diversion (n=2), and thoracoscopic drainage with or without repair or T-tube placement (n=3). In the endoscopy group, all leaks were treated with endoscopic covered stenting with or without percutaneous drainage (n=9). Control of leaks occurred in 89% of patients in the conventional treatment group vs. 100% of patients in the endoscopic stenting group. Three patients in the conventional treatment group (33%) required esophageal diversion compared to none of the patients in the endoscopy group. The 60-day or in-hospital mortality was 0% for both groups.
Conclusion In our clinical practice, there has been a shift in the management of esophagogastric anastomotic leaks to nonsurgical therapy using endoscopic esophageal covered stenting. Endoluminal stenting is a safe and effective alternative in the management of GI leaks.

Keywords Esophageal cancer · Laparoscopy · Thoracoscopy · Anastomotic leaks · Esophageal stent

Introduction

Esophagectomy is a complex gastrointestinal (GI) operation that is commonly performed in high-risk patients. Such patients are often elderly, have poor nutritional status, and have multiple comorbidities that may contribute to the development of postoperative complications. Gastrointestinal anastomotic leak is a dreaded complication after esophagectomy and can lead to significant morbidity and mortality. Conventional treatments for leak depend on the location of the anastomosis and the extent of the leak. Neck anastomotic leak can often be treated conservatively with neck wound drainage and packing; however, a cervical leak also may have intrathoracic manifestations such as tracheoesophageal fistula

This study was presented at the Surgical Forum of the American College of Surgeons 96th Annual Clinical Congress on October 6, 2010, Washington DC, USA.

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or intrathoracic empyema.[1,2] Thoracic anastomotic leak often requires surgical intervention for management, including thoracoscopic or thoracotomy drainage with T-tube placement for control of the leak site or even complete GI diversion in cases of extensive anastomotic disruption.[3]

Recently, there have been multiple reports on the successful use of endoscopic covered stenting in the management of anastomotic leaks after esophagectomy.[4] Endoscopic esophageal covered stenting (ECS) is a less invasive modality that may be used as alternative therapy in the management of leaks. The aim of this comparative study was to evaluate the impact of ECS vs. conventional treatments in the management of gastroesophageal leak after esophagectomy, including efficacy in the control of leaks, length of hospitalization, and preservation of GI continuity.

Methods

The charts of 18 (10.4%) of 160 patients who developed postoperative leaks after minimally invasive esophagectomy were reviewed. There were 5 cervical and 13 intrathoracic anastomotic leaks. Main outcome measures included patient characteristics, type of treatment for leaks, the need for surgical reoperation in the management of leaks, the time interval between the index operation and the diagnosis of leak, treatment success, length of stay, morbidity, and mortality. Surgical reoperation was defined as any return to the operating room for an operation related to a leak. ECS treatment of leaks was not considered a surgical reoperation. Treatment was considered successful if the intervention resulted in the control of a leak and cessation of mediastinal contamination or progression of sepsis. We compared the outcomes of patients who underwent conventional treatments for management of leaks (n=9) to the outcomes of consecutive patients who underwent endoscopic management of leaks using ECS (n=9). This retrospective study was approved by the University of California Irvine Medical Center Institutional Review Board.

Conventional Treatments

Conventional management of anastomotic leak after esophagectomy was dependent on the site and extent of the leak. For cervical leaks, management included opening the neck wound for drainage and wound packing. For thoracic leaks, management included thoracotomy or thoracoscopic intervention, or gastrointestinal diversion with construction of a cervical end esophagostomy. For thoracoscopic management, the patients were intubated with a double lumen endotracheal tube and positioned in the left lateral decubitus position. The right chest was reentered through the previous thoracic trocar sites. A 30° scope was placed and the lung was retracted away from the chest wall. Infected pleural collections were suctioned and a specimen obtained for bacteriology. The lung was retracted anteriorly, exposing the gastric conduit and the esophagogastric anastomosis. The anastomosis and gastric conduit staple lines were inspected for the area of disruption. Intraoperative endoscopy was then performed with air insufflation while the anastomosis was submerged under irrigation fluid. The site of the leak was identified by the presence of persistent air bubbles. Management of the leak then depended on the size of the leak and the presence and degree of conduit ischemia. A small leak (less than 2 cm) was treated by placement of a T-tube into the esophagus at the site of the defect with local drainage.[3] To facilitate the placement of the T-tube, an endoscope was placed intraluminally and an endoscopic grasper was placed through the anastomotic defect into the pleural cavity. A long umbilical tape was inserted transthoracically and positioned for retrieval by the endoscopic grasper. The endoscope was removed through the mouth, pulling the umbilical tape along with it. The umbilical tape was then tied onto the end of the T-tube. The umbilical tape was pulled slowly, under endoscopic guidance, to position the T limb of the T-tube immediately adjacent to the defect. A chest tube and Blake drain were also placed for chest drainage. The T-tube was left in place for 6–8 weeks. The patient was kept nothing per oral (NPO) for 2 weeks after which oral fluid was started. A contrast study was performed with the T-tube in place prior to its removal. At 8 weeks, the T-tube could be removed slowly (1 in. per week), until the entire tube was removed. Another contrast study was performed with the Blake drain in place. If there was no extravasation of contrast into the drain, the drain also could be removed slowly over the next 3 weeks.

In cases of near-circumferential breakdown of the anastomosis or the presence of a large leak (>2 cm) along the anastomosis or gastric conduit staple line, a gastrointestinal diversion with take down of the gastric conduit and cervical esophagostomy was performed. In this scenario, the initial approach was a right thoracoscopy with drainage of the pleural cavity. The gastric conduit was separated away from the esophagus at the level of the disrupted anastomosis. The proximal esophagus was mobilized up to the level of the thoracic inlet in preparation for construction of a cervical esophagostomy. A Blake drain and a chest tube were placed for chest drainage. The patient was then placed in the supine position. The neck and abdomen were prepped. A left neck incision was performed and the entire proximal esophagus was exteriorized through the left neck. An end esophagostomy was constructed lateral to the sternocleidomastoid muscle and positioned at the lateral aspect of the neck wound. Laparoscopy was also performed with retrieval of the gastric conduit intraabdominally. The

esophageal hiatus was closed by approximating the left and right crura with interrupted sutures. The tip of the gastric conduit was removed and a gastrostomy tube was placed within the gastric remnant for postoperative feeding. Once the patient recovered from the septic event, a colonic interposition could be considered to restore gastrointestinal continuity.

Endoscopic Esophageal Covered Stent

In the latter part of our esophagectomy series, anastomotic leaks were treated with endoscopic stenting as the primary therapy irrespective of the size of the leak. An endoscopy was performed to evaluate the site and extent of the leak. If feasible, the scope was then passed through the anastomotic disruption, into the mediastinal cavity for drainage of the adjacent collection. The scope was then passed back into the gastric conduit. The site of the leak was marked using fluoroscopy by external radiopaque markers that were placed to outline the proximal and distal extent of the future stent. An ultra-stiff guide wire was placed into the gastric conduit and its placement confirmed under endoscopic visualization. A covered esophageal stent (Alimaxx-E, Alveolus® Inc., Charlotte, NC, USA or Wallflex®, Boston Scientific Corporation, Natick, MA, USA) was deployed over the guide wire and positioned between the two radiopaque markers (Fig. 1a, b). The endoscope was positioned along the side of the stent to ensure optimal positioning of the stent. A completion endoscopy was then performed by passing the scope through the stent to exit into the gastric antrum. A nasogastric tube was then placed through the stent for gastric decompression. The patient was kept NPO with complete nutritional support through a jejunostomy tube. The stent was then removed endoscopically at 6 weeks post-deployment.

Statistical Analyses

All data are expressed as mean ± standard deviation. Analyses of differences between groups for demographic and operative data were performed using two-sample *t* tests or Fisher's exact test for categorical data. Statistical analysis was performed using standardized biomedical software (Statview, SAS institute Inc., Cary, NC, USA). A *P* value of less than 0.05 was considered significant.

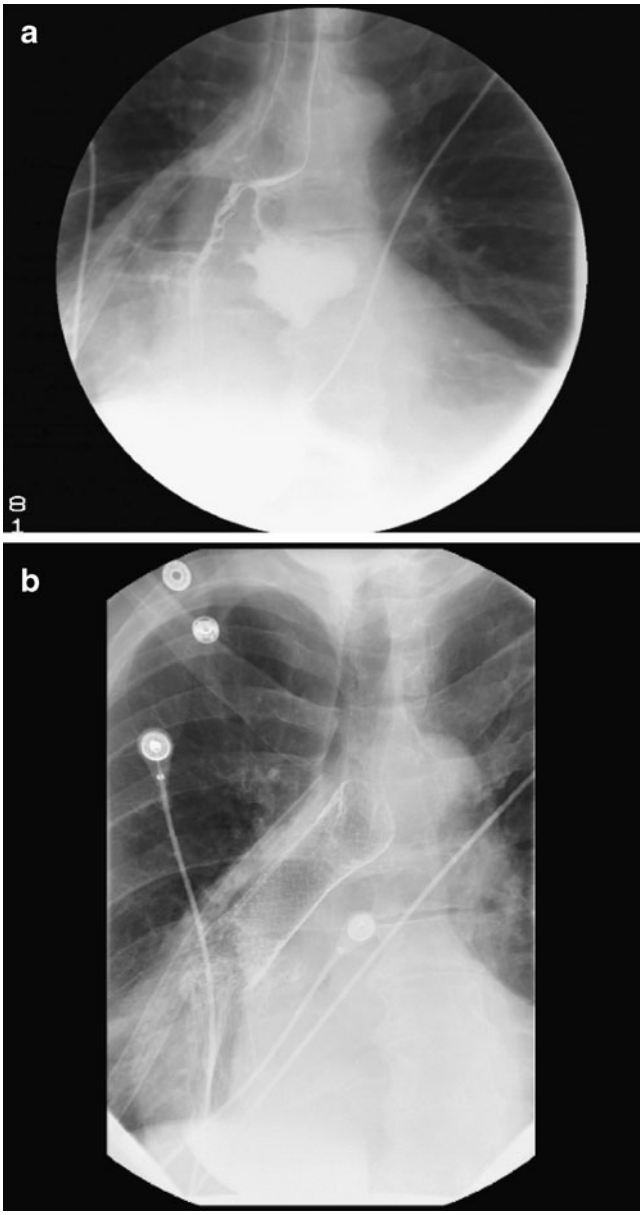

Fig. 1 **a** Upper gastrointestinal contrast study on postoperative day 5 demonstrating an anastomotic leak into a contained mediastinal collection. **b** Chest X-ray following endoscopic drainage of mediastinal collection and deployment of a covered esophageal stent

Results

Subjects included 16 males and 2 females with a mean age of 66 years. Indications for esophagectomy included carcinoma (n=14), Barrett's esophagus with high-grade dysplasia (n=3), and benign stricture (n=1). Neoadjuvant therapy was used in 57.1% of patients with carcinoma. The mean time interval between the index operation and the diagnosis of leak was 9.3 days (range, 2–21 days).

Conventional Treatments

In our early experience, five patients with cervical anastomotic leaks were treated with neck drainage and wound packing (n=4) and with thoracotomy for repair of tracheogastric fistula with GI diversion (n=1). The patient who developed a

tracheogastric fistula had complete anastomotic dehiscence requiring thoracotomy with take down of the gastric conduit, cervical esophagostomy, and buttress repair of the trachea fistula with an onlay muscle flap. The four patients with intrathoracic leaks were treated with thoracoscopic drainage with T-tube placement (n=2), thoracoscopic drainage with primary repair (n=1), and complete GI diversion (n=1). The patient with GI diversion had a large leak at the anastomosis and the staple line of the gastric conduit requiring thoracoscopic take down of the gastric conduit, cervical esophagostomy, and laparoscopic gastrostomy tube placement.

Endoscopic Esophageal Covered Stent

In our recent experience, nine consecutive patients with intrathoracic leaks were treated with endoscopic drainage with or without percutaneous drainage and ECS. Of these nine patients, six patients had a contained leak with a collection within the mediastinum, two patients had a noncontained leak with contamination of the right pleural cavity, and one patient had a tracheoesophageal fistula (Fig. 2a, b). All nine patients successfully underwent esophagoscopy with deployment of a covered esophageal stent. The two patients with noncontained leaks also underwent percutaneous drainage of the right pleural cavity collections (Fig. 3). All stents were removed under intravenous (IV) sedation within our endoscopy suite at 6 weeks after placement. All stent removal procedures were performed successfully without postprocedural complications.

Conventional Treatments vs. Endoscopic Stenting

Characteristics of the 18 patients with anastomotic leaks after esophagectomy are depicted in Table 1. Leak complications were detected in an outpatient setting in 8 (44.4%) of 18 patients. Outcomes of leaks managed by conventional treatments vs. endoscopic stenting are listed in Table 2. Surgical reoperation for management of leaks was required in 55.5% of the patients in the conventional treatment group compared to 0% in the ECS group. Treatment success, defined as an intervention that resulted in the control of a leak and cessation of mediastinal contamination or sepsis, occurred in 88.9% of patients in the conventional treatment group vs. 100% of patients in the endoscopic stent group. One of nine patients who underwent conventional treatment for leaks had continued leakage and subsequently required a third operation with GI diversion and cervical esophagostomy. Although not statistically significant, compared to conventional treatment for leaks, endoluminal treatment was associated with a shorter length of hospital stay (15.9 vs. 22.7 days, respectively) and better preservation of GI continuity (100% vs. 67%, respectively). The in-hospital or 60-day leak-associated mortality was zero for both groups.

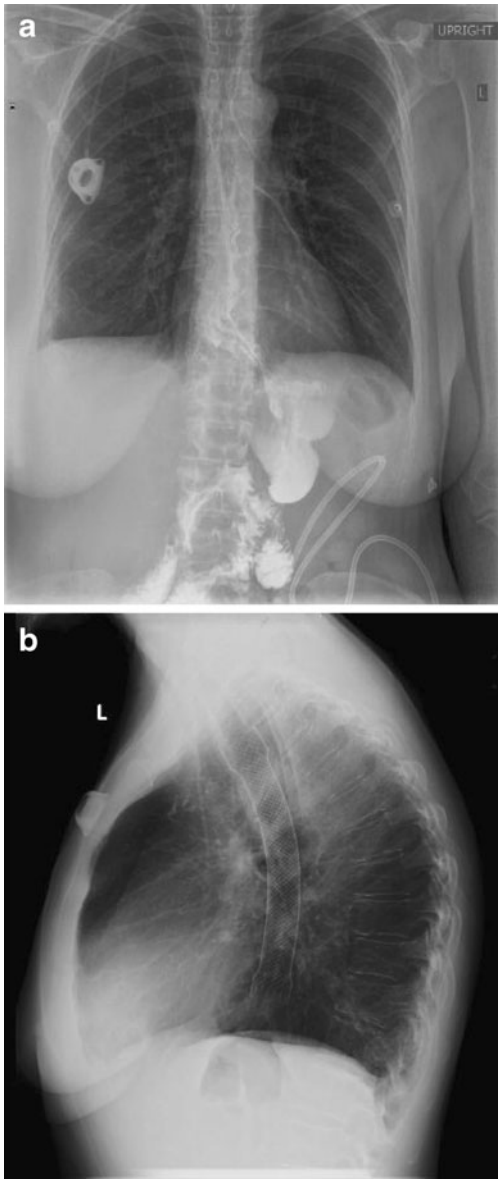

Fig. 2 **a** Upper gastrointestinal study showing tracheoesophageal fistula after minimally invasive esophagectomy. **b** Endoscopic management of tracheoesophageal fistula with deployment of a covered esophageal stent

Discussion

Gastrointestinal leaks after esophagectomy can be associated with significant morbidity and mortality. The management of anastomotic leaks is often selective based on patients' symptoms, site of leak, and extent of leak. Conventional treatments for leak include conservative treatment such as drainage alone, surgical intervention, and in certain cases complete esophageal diversion. More recently, an alternative and less invasive treatment option is endoscopic management with deployment of an esophageal covered stent. The results from this study demonstrate that endoscopic management of

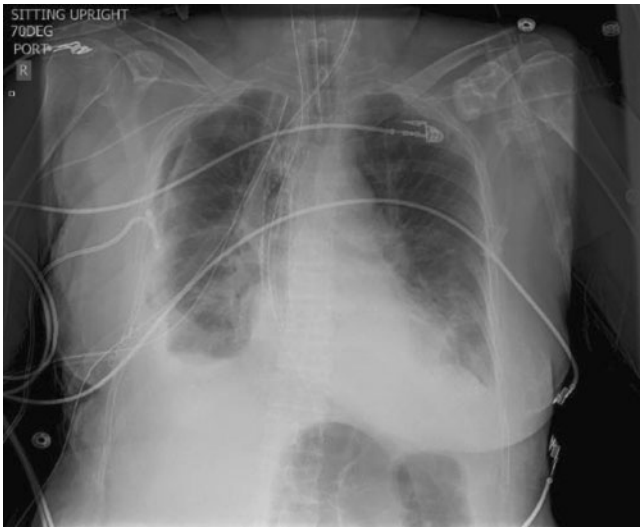

Fig. 3 Management of noncontained anastomotic leak with placement of esophageal stent, percutaneous drainage of the right pleural collection, and decompression of the gastric conduit with a nasogastric tube

anastomotic leak after esophagectomy is feasible, safe, and highly effective in controlling leaks. Although the number of subjects in this study was small, and therefore, the study lacks statistical power to detect significant differences among the outcome variables between the two treatment groups, the observation can be made that compared to convention treatments for leaks, endoscopic stenting trended towards a shorter length of hospital stay, higher rate of treatment success, and higher rate for preservation of gastrointestinal continuity.

Mortality associated with conventional treatments for esophageal leak ranges from 8.5% to as high as 46.2% in selected case series (Table 3).[5–11] Conventional treatments for esophageal leak depend on the location and extent of leakage. Conventional treatments also vary widely and include conservative therapy with percutaneous drainage, thoracotomy or thoracoscopic treatment, and gastrointestinal diversion. The largest study using conventional treatments for leak was reported by Crestanello and colleagues.[9] They reported the outcomes of intrathoracic anastomotic leak in 47 patients, with 27 patients (57.4%) treated conservatively and 20 patients (42.6%) requiring surgical intervention. The overall mortality in their series was 8.5%. Martin et al.[7] reported that the mortality associated with an intrathoracic leak following esophagectomy had decreased in the modern era; the leak-associated mortality between 1970 and 1986 was 43%, which decreased to 3.3% in 1987–2004. Along similar lines, our study showed a leak-associated mortality of 0% in nine patients treated with conventional treatments.

Alternatively, ECS has been reported as a method for management of esophageal leaks (Table 4).[5,12–17] Esophageal stenting is often performed with simultaneous endoscopic or percutaneous drainage of mediastinal fluid

Table 1 Patient characteristics and treatment of post-esophagectomy leaks in 18 consecutive patients (in chronological order)

Pt #	Age (years)	Site of anastomosis	Presentation (days)	Sepsis[a]	Treatment	Treatment success[b]
13	46	Neck	14 (outpatient)	No	Thoracotomy, muscle flap, esophageal diversion	Y
18	60	Neck	4	No	Neck wound drainage	Y
21	83	Thoracic	21 (outpatient)	Yes	Thoracoscopic drainage with T-tube	Y
34	57	Thoracic	7	No	Thoracoscopic drainage with primary repair	No, required esophageal diversion
44	75	Neck	3	No	Neck wound drainage	Y
48	84	Neck	5	No	Neck wound drainage	Y
64	77	Thoracic	8 (outpatient)	Yes	Esophageal diversion	Y
74	75	Thoracic	11 (outpatient)	No	Thoracoscopic drainage with T-tube	Y
84	69	Neck	3	No	Neck wound drainage	Y
98	67	Thoracic	7	No	Stent	Y
109	48	Thoracic	6	No	Stent	Y
121	55	Thoracic	10 (outpatient)	No	Stent	Y
128	77	Thoracic	2	Yes	Stent, percutaneous drain, tracheostomy	Y
144	63	Thoracic	9	Yes	Stent, percutaneous drain	Y
152	55	Thoracic	2 (outpatient)	No	Stent	Y
153	62	Thoracic	14 (outpatient)	No	Stent	Y
157	52	Thoracic	14 (outpatient)	No	Stent	Y
159	72	Thoracic	10	No	Stent	Y

[a] Sepsis was defined as the presence of hemodynamic instability with pulmonary, cardiac, or renal insufficiency

[b] Treatment success was defined as successful if the intervention resulted in the control of leak and cessation of mediastinal contamination or sepsis

Table 2 Perioperative outcomes of patients with post-esophagectomy leak who underwent conventional treatment vs. endoscopic esophageal covered stenting

	Conventional treatment	Endoscopic stent
No. of patients	9	9
Mean age (years)	68.9±13.5	61.2±9.6
Male/female	9:0	7:2
Surgical reoperation for leaks (%)	5 (55.5%)	0 (0%)
Treatment success for control of leaks[a] (%)	8 (88.9%)	9 (100%)
Length of stay after diagnosis of leaks (days)	22.7±12.2	15.9±16.5
Preservation of gastrointestinal continuity (%)	6 (67%)	9 (100%)
Leak-associated mortality (%)	0 (0%)	0 (0%)

[a]Treatment success was defined as successful if the intervention resulted in the control of leak and cessation of mediastinal contamination or sepsis

collections. If successful, endoscopic stenting may obviate the need for a major reoperative intervention in the management of leaks. The mortality associated with endoscopic stenting for management of esophageal anastomotic leak appears to be comparable or lower than that of conventional treatments, ranging between 0% and 15.4%.[5,12–17] The largest study of endoscopic stenting for anastomotic leaks was reported by Dai and colleagues.[17] They found a mortality of 4.5% in 22 patients with anastomotic leak after esophagectomy who underwent esophageal stenting. In our study, we reported a 0% leak-associated mortality for nine patients with intrathoracic leak who underwent esophageal stenting.

Conventional treatments for anastomotic leak vary widely and are based on the patient's symptoms and location and extent of the leak. The keys to management of leak include early recognition and expeditious institution of management. However, the optimal treatment for leak has not been clearly delineated. Most surgeons utilize a selective approach to the treatment of anastomotic leaks. Large leaks with significant contamination of the pleural cavity are often treated with surgical intervention while small contained leak are treated with conservative management including drainage, nothing per oral, IV antibiotic, and jejunostomy nutritional supplementation. Success in the management of leaks using the conventional surgical approaches varies widely as reported in the literature and ranges between 0% and 100%.[5–11] Crestanello et al. reported 20 patients with intrathoracic leaks that were managed by reoperation. All leaks were controlled adequately with only one patient requiring a second reoperation for treatment of an empyema.[9] Alternatively, Alanezi and Urschel reported that all four patients with esophageal anastomotic leaks treated with surgical intervention died.[6] In our series, four (80%) of five patients who underwent surgical intervention for leaks had control of the leak; one patient had failure of a surgical intervention and required a subsequent GI diversion. Similarly, success in the use of conservative therapy in the management of anastomotic leaks varies widely, ranging between 40% and 100% (Table 5).[5–11] In our study, four of five patients with cervical leaks were treated successfully with conservative treatment; however, one (20%) of five patients with cervical leaks required a thoracotomy with drainage and esophageal diversion for tracheoesophageal fistula. Cervical anastomotic leak can also lead to high morbidity and mortality. Turkyilmaz and colleagues reported that 4 of 14 patients with cervical anastomotic leak died from sepsis and multiorgan failure due to fistula.[11] Conservative management

Table 3 Outcomes of selected case series in the management of anastomotic leak after esophagectomy using conventional surgical treatments

Author/year	Number	Location of anastomosis	Overall mortality	Surgical intervention	Treatment success[a]	GI diversion
Hunerbein et al.[5] 2004	10	Thoracic	2/10 (20%)	7 (70%)	5/7 (71.4%)	0/7 (0%)
Alanezi and Urschel[6] 2004	23	Cervical and thoracic	8/23 (35%)	4 (17.4%)	0/4 (0%)	–
Martin et al.[7] 2005	37	Cervical and thoracic	4/37 (10.8%)	13 (35.1%)	11/13 (84.6%)	3/13 (23.1%)
Junemann-Ramirez et al.[8] 2005	14	Thoracic	5/14 (35.7%)	10 (71.4%)	–	–
Crestanello et al.[9] 2005	47	Thoracic	4/47 (8.5%)	20 (42.6%)	20/20 (100%)	2/20 (4.3%)
Page et al.[10] 2005	23	Cervical and thoracic	4/23 (17.4%)	17 (73.9%)	15/17 (88.2%)	14/17 (82.3%)
Turkyilmaz et al.[11] 2009	13	Thoracic	6/13 (46.2%)	3 (23.1%)	–	–
Current study	9	Cervical and thoracic	0/9 (0%)	5 (55.5%)	4/5 (80%)	3/5 (60.0%)

[a] Treatment success was defined as successful if the intervention resulted in the control of leak and cessation of mediastinal contamination or sepsis

Table 4 Outcomes of selected case series on the management of anastomotic leak after esophagectomy using endoscopic esophageal covered stenting

Author/year	Number	Location of anastomosis	Overall mortality	Treatment success[a]	Need for reoperation
Hunerbein et al.[5] 2004	9	Thoracic	0/9 (0%)	8/9 (88.9%)	0/9 (0%)
Schubert et al.[12] 2005	12	Thoracic	0/12 (0%)	11/12 (91.7%)	0/12 (0%)
Langer et al.[13] 2005	13	Cervical and thoracic	2/13 (15.4%)	13/13 (100%)	0/13 (0%)
Kauer et al.[14] 2007	10	Thoracic	2/10 (20%)	9/10 (90%)	0/10 (0%)
Zisis et al.[15] 2008	9	Cervical and thoracic	2/9 (22.2%)	7/9 (77.8%)	2/9 (22.2%)
Tuebergen et al.[16] 2008	22	Cervical and thoracic	2/22 (9.1%)	17/22 (77.3%)	2/22 (9.1%)
Dai et al.[17] 2009	22	Thoracic	1/22 (4.5%)	21/22 (95.4%)	1/22 (4.5%)
Current study	9	Thoracic	0/9 (0%)	9/9 (100%)	0 (0%)

[a] Treatment success was defined as successful if the intervention resulted in the control of leak and cessation of mediastinal contamination or sepsis

also has been utilized for intrathoracic leaks. Crestanello and colleagues reported good success in 26 of 27 patients with intrathoracic leak who were treated nonoperatively.[9] Alternatively, Turktilmaz et al.[11] reported that 6 of 10 patients with thoracic anastomotic leaks died due to fistula.

The success rate for control of anastomotic leak after ECS appears to be similar or better than that of conventional treatments, ranging between 77.3% and 100%.[5,12–17] In our series, all nine patients with anastomotic leaks were treated successfully with ECS and percutaneous drainage in selected cases. These cases were consecutive and the endoscopic option was used irrespective of the size or extent of the leak. None of the patients in this group were treated conservatively, such as with drainage alone. Alternatively, Tuebergen et al.[16] reported success in sealing of fistula in 17 of 22 patients (77.3%) with an intrathoracic leak after esophagectomy. In their series, 9.1% required a rethoracotomy and the leak-associated mortality was also 9.1%.[16] A major advantage of endoscopic stenting in the treatment of anastomotic leak is that a surgical intervention often can be avoided. Using conventional approaches for management of anastomotic leaks, surgical reoperation is often required in 23.1–73.9%.[5–11] Using ECS for management of leaks, none of the nine patients in our series required additional surgical reoperation.

The advantages in the use of endoscopic stenting are difficult to quantify, as a prospective comparative study between conventional treatments and ECS has not been performed. In our study, we noted that the advantages of ECS are that it is highly effective in controlling leaks and may shorten the length of hospitalization. However, the most notable advantage was that none of the patients who underwent esophageal stenting required invasive surgical reoperation or esophageal diversion. Esophageal diversion with end esophagostomy is a major operation performed in extreme cases to control anastomotic leaks. It is a life-saving operation but is associated with poor quality of life and the need for a second major reoperation for gastrointestinal

Table 5 Outcomes of selected case series in the management of anastomotic leak after esophagectomy using conservative therapy only, including observation or percutaneous drainage alone

Author/year	Number	Location of anastomosis	Overall mortality	Conservative intervention	Treatment success[a]
Hunerbein et al.[5] 2004	10	Thoracic	2/10 (20%)	3 (30%)	3/3 (100%)
Alanezi and Urschel[6] 2004	23	Cervical and thoracic	8/23 (35%)	19 (82.6%)	15/19 (78.9%)
Martin et al.[7] 2005	37	Cervical and thoracic	4/37 (10.8%)	24 (64.9%)	–
Junemann-Ramirez et al.[8] 2005	14	Thoracic	5/14 (35.7%)	4 (28.6%)	–
Crestanello et al.[9] 2005	47	Thoracic	4/47 (8.5%)	27 (57.4%)	26/27 (96.3%)
Page et al.[10] 2005	23	Cervical and thoracic	4/23 (17.4%)	6 (26.1%)	4/6 (66.7%)
Turkyilmaz et al.[11] 2009	13	Thoracic	6/13 (46.2%)	10 (76.9%)	4/10 (40%)
Turkyilmaz et al.[11] 2009	14	Cervical	4/14 (28.6%)	14 (100%)	10/14 (71.4%)
Current study	9	Cervical	0/9 (0%)	4 (45.5%)	4/4 (100%)

[a] Treatment success was defined as successful if the intervention resulted in the control of leak and cessation of mediastinal contamination or sepsis

reconstruction at a later date. In our series, the use of endoscopic stenting avoided performance of this drastic procedure. In contrast, esophageal diversion was performed in anywhere from 0% to as high as 82.3% of patients treated with conventional treatments.[5,7,10] In the study reported by Page et al.[10], 14 (82.3%) of 17 patients who underwent surgical reoperation for treatment of anastomotic leak were treated with cervical end esophagostomy. Although we did not analyze the cost differences between conventional treatments vs. ECS, it is likely that endoscopic stenting is associated with a lower cost of treatment by avoiding the need for surgical reoperation and GI diversion. The only other study that compared outcomes of conventional treatments with endoscopic stenting was reported by Hunerbein and colleagues.[5] Their study compared 10 patients who underwent conventional treatments to 9 patients who underwent ECS for management of intrathoracic leaks.[5] They found that immediate leak occlusion occurred in eight of nine patients who underwent endoscopic stenting. Compared with the conventional treatment group, patients who were treated with endoscopic stent had earlier oral intake (11 vs. 23 days, respectively), a less extensive intensive care course (25 vs. 47 days, respectively), and shorter hospital stay (35 vs. 57 days, respectively); in-hospital mortality was 0% in the stent group and 20% in the conventional treatment group.[5] Given these findings, it is very likely that ECS would be associated with significant cost savings over conventional treatments.

Tracheo- or bronchoesophageal fistula is an infrequent complication after esophagectomy. Treatment options include conservative management, or reoperation with take down of fistula and the use of muscle flap.[18–20] In our series, one patient in the conventional treatment group had tracheoesophageal fistula and required GI diversion and placement of a muscle flap. On the other hand, one patient in the ECS group had tracheoesophageal fistulae and was successfully treated with endoscopic stenting without the need for reoperation.

From our experience, ECS is not a treatment option for all locations of leak after esophagectomy. There are two possible sites for leaks with an intrathoracic anastomosis. First, a leak can occur at the esophagogastric anastomosis. Alternatively, a leak can occur along the staple line of the gastric conduit. In this study, all of the patients who underwent ECS had a leak at the esophagogastric anastomosis. The use of ECS might not be feasible with leaks located along the staple line of the gastric conduit because the large diameter of the conduit may prohibit adequate sealing of the leak. The primary mechanism by which ECS promotes healing of an anastomotic disruption is the ability for the stent to divert the gastrointestinal content away from the site of the leak and allow the defective area to heal.

There are some limitations in this study. First, the number of patients in our study was too small to draw any statistical conclusions. This is reflected upon the small number of esophagectomies being performed at most single institutions. The largest published study on the management of esophageal anastomotic leak was reported on only 47 patients.[9] Second, this is a retrospective, comparative study with some of the limitations inherent to a retrospective study. Lastly, the two groups were not comparable as five patients in the conventional treatment group had cervical anastomosis whereas all patients within the ECS group had intrathoracic anastomosis. Despite these limitations, a major strength of this study is that the endoscopic stent treatment was consecutive, which eliminates potential bias based on selection of treatment.

In conclusion, endoscopic management of leaks with esophageal covered stenting is safe, feasible, and highly effective in controlling leaks. ECS is now our first line of therapy in the management of leaks after esophagectomy and may ultimately reduce the morbidity and mortality associated with this dreaded complication.

Conflict of Interest None declared.

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ORIGINAL ARTICLE

Intensive Versus Conventional Insulin Therapy in Nondiabetic Patients Receiving Parenteral Nutrition After D2 Gastrectomy for Gastric Cancer: A Randomized Controlled Trial

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Abstract
Background This study was used to compare the effects of intensive insulin therapy with conventional insulin therapy on postoperative outcomes among nondiabetic patients receiving parenteral nutrition following D2 gastrectomy for gastric cancer.
Method A total of 248 eligible patients were randomly assigned to receive intensive insulin therapy targeting a blood glucose level between 4.4 and 6.1 mmol/l [intensive group (n=125)] or conventional insulin therapy targeting a blood glucose level less than 11.0 mmol/l [conventional group (n=123)] during the postoperative period.
Results Mean blood glucose concentrations were lower in the intensive group than in the conventional group. Severe hypoglycemia defined as blood glucose ≤2.2 mmol/l occurred in eight (6.4%) patients in the intensive group vs one (0.8%) patient in the conventional group (P=0.036). One (0.8%) patient died in the intensive group vs two (1.6%) patients in the conventional group (P=0.620). However, intensive insulin therapy significantly reduced overall postoperative complications rate (from 25.2% to 13.6%, P=0.024). Moreover, both insulin resistance indicated as HOMA-IR and HLA-DR expression on monocytes were improved in the intensive group.
Conclusions Intensive insulin therapy significantly reduced the postoperative short-term morbidity but not mortality among nondiabetic patients receiving parenteral nutrition after D2 gastrectomy. The benefits may be due to the suppression of insulin resistance and improvement of HLA-DR expression on monocytes.

Keywords Intensive insulin therapy · Gastric cancer · Parenteral nutrition · Insulin resistance · HLA-DR · Postoperative complications

Introduction

Although existing evidence indicates gastrectomy with D2 lymphadenectomy was associated with increased postoperative mortality and morbidity compared with D1 gastrectomy,[1,2] D2 gastrectomy is considered the standard treatment for curable gastric cancer in eastern Asia. Current guideline recommends that if a patient is expected to undergo major upper gastrointestinal surgery and enteral nutrition (EN) is not feasible, parenteral nutrition (PN) should be initiated in the immediate postoperative period but should be delayed for 5–7 days.[3] At the same time, PN was considered to be associated with atrophy and disruption of the intestinal mucosa and an increased risk for nosocomial infection, as well as hyperglycemia.[4] Hyperglycemia has been established as a risk factor and predictor for postoperative mortality and morbidity.[5,6] Moreover, most recent studies including both critically ill and noncritically ill identifies PN-associated hyperglycemia as a risk factor for development of infection, cardiac and renal dysfunction, and increased mortality.[7–9]

However, to date, available studies on the treatment for hyperglycemia have yielded conflicting results, therefore

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the efficiency and safety of treatment remain controversial. Van der Berghe and colleagues[5] reported that intensive insulin therapy (IIT) to maintain a blood glucose level no higher than 6.1 mmol/l reduced mortality and morbidity among critically ill patients in the surgical ICU (SICU), regardless of whether they had a history of diabetes. Furthermore, they found that strict normalization of blood glucose level (4.4–6.1 mmol/l), compared with the conventional therapy (maintenance of blood glucose at 11.1 mmol/l or less), significantly reduced morbidity but not mortality among all the patients in the medical ICU.[10] On the contrary, a large, international, randomized trial suggested that a blood glucose target of less than 10 mmol/l led to lower mortality than a target of 4.5–6.0 mmol/l. The lower glucose target was not suggested in critically ill adults.[11] Of note, most existing trials on perioperative glucose control focus mainly on diabetic or nondiabetic patients following cardiac surgery. However, the optimal target of glucose control in nondiabetes patients undergoing major abdomen surgery remains an area of uncertainty and has not been specifically investigated in patients receiving PN.

Thus, a prospective randomized controlled trial was performed to investigate whether the nondiabetic patients receiving PN after radical D2 gastrectomy for gastric cancer will benefit from IIT compared with conventional insulin therapy (CIT). Meanwhile, insulin resistance indicated as homeostasis model assessment (HOMA)-insulin resistance (IR) score and human leukocyte antigen (HLA)-DR expression on monocytes were analyzed to explore the underlying mechanisms of IIT. The primary outcome was postoperative overall complications rate; the secondary outcomes included postoperative mortality, HOMA-IR, and monocytes HLA-DR expression.

Patients and Methods

Patients and Design

This single-center, prospective randomized controlled trial was approved by the ethics committee of the hospital, and written informed consent was obtained from each study patient. The present study was conducted in the Department of General Surgery, Qingdao University Medical School Hospital from January 2005 to December 2010. We screened 550 consecutive adult patients who were to undergo open elective gastrectomy for gastric cancer and required at least 5 days of PN for eligibility. Patients included were aged ranging from 18 to 80 years with a perceived need for PN postoperatively. The exclusion criteria were as follows: (1) diabetes mellitus or impaired glucose tolerance; (2) contraindications for PN or unnecessary to receive PN postoperatively assessed by clinical nutritionist; (3) patients performed palliative surgery; (4) took corticosteroids, steroids, growth hormone, or immunosuppressive drugs within 2 weeks prior to the study; (5) patient received neoadjuvant radiochemotherapy; and (6) patient was diagnosed with gastric stump cancer or recurrent gastric cancer.

After complete preoperative assessment and preparation, the patients were performed with the surgical procedure under general anesthesia by qualified experienced surgeons in our hospital, a large-volume gastric cancer center. The guidelines of the Japanese Research Society for the Study of Gastric Cancer were followed in our study for standard surgical treatment and pathological evaluation.[12] All eligible patients received elective radical gastrectomy (subtotal or total) with D2 lymphadenectomy and were admitted into SICU after surgery.

Upon SICU admission, the eligible patients were randomly assigned to one of the two groups: the intensive group (IG) in which the blood glucose was maintained at a level between 4.4 and 6.1 mmol/l and the conventional group (CG) in which the blood glucose was maintained at a level below 11.0 mmol/l. The Portland protocol of continuous intravenous insulin infusion was adopted in the present study.[13] To ensure the safety of IIT as much as possible, a multidisciplinary team was established for implementing the protocol. The team consisted of well-trained surgeons, diabetologists, and SICU nurses who had extensive experience in blood glucose control and could promptly identify early hypoglycemia and give appropriate intervention. Blood glucose levels were measured, monitored, and adjusted according to our previous study.[14] In brief, regular insulin (50 IU) added into normal saline (50 ml) was administered intravenously using an infusion pump (Smith Medical Instrument CO., Zhejiang, China). Blood levels were measured and monitored with a bedside glucometer (Onetouch Ultra 2, Lifescan) or a laboratory analyzer in routine use. The glucometers were calibrated regularly by the manufacture to ensure the accuracy, reliability, and repeatability. In IG treatment, the insulin infusion was initiated when the blood glucose levels exceeded 6.1 mmol/l; whereas in CG treatment, the insulin infusion was started when the blood glucose levels exceeded 11.0 mmol/l. The insulin infusion was continued until oral intake or enteral nutrition was established. In this study, a blood glucose level of 2.2 mmol/l or less was considered as severe hypoglycemia. And also, the postoperative mean glucose concentration was calculated as the composite average of all the glucose levels from the period immediately after surgery to the end of the protocol.

Nutrition Intervention

PN was administered as “all in one” mixtures which were prepared daily in the clinical nutrition center of our hospital by pharmacists with specific training. PN was given either

by peripheral or central vein for at least 5 days after surgery. PN was initiated on the first day after surgery and terminated when oral or enteral ingestion exceeded 50% of target energy requirements. To restore EN or oral intake as soon as possible, the patients were assessed daily for tolerance to EN or oral intake. The PN regimens were isonitrogeneous (0.2 g/kg/day) and isocaloric (25 kcal/day/kg ideal body weight) PN solutions, delivering 3.0 g glucose and 1.0 g lipid per kg ideal body weight per day. Patients in both two groups received the same solution of lipid emulsion (Lipovenos 20%, Fresenius, Germany), amino acids (Novamin11.4%, SSPC, China), and glucose. Moreover, fat-soluble (Vitalipid) and water-soluble (Soluvit) vitamins as well as trace elements (Addel N; all from Fresenius, Germany) were added daily as required. The TPN solution was infused at a constant (pump-controlled) rate over a period of 16 to 18 h per day.

Outcome Measurements

All included patients were followed up from hospital admission to 28 days after surgery. Demographic and clinical characteristics and intraoperative data of both two groups are summarized in Table 1. The postoperative complications were recorded as wound infection, intra-abdominal infection, sepsis, urinary tract infection, pneumonia, pseudomembranous colitis, as well as anastomotic leakage. Infection complications were identified in line with the definitions of nosocomial surgical site infections of the US Centers for Disease Control and Prevention.[15] The definition of sepsis was described previously elsewhere.[16] When peritonitis (localized or generalized), fluid or purulent drainage from wound or drain, or abdominal abscess were presented, anastomotic leakage was clinically suspected and further confirmed by a water-soluble contrast swallow examination. Besides, days to suture removal, postoperative hospital stay, and duration of antibiotic use were also recorded. The patients were allowed to discharge from the hospital when the patients met the following criteria: ability to manage toilet visits without assistance, no fever, without drains requiring inpatient management, and no intravenous access. Hospital mortality was defined as death from any cause within 28 days after surgery or during the hospital stay.

HOMA-IR Index

HOMA was chosen to assess IR because HOMA-IR strongly correlates with the euglycemic clamp IR which is considered the golden standard method for assessing insulin resistance. Several studies have demonstrated that HOMA-IR can be reliably used in large-scale or epidemiological studies and has shown good reproducibility and consistency.[17,18] The HOMA-IR score is calculated with the following mathematic formula: $\mathrm{HOMA-IR} = \mathrm{FI} \times \mathrm{FG}/22.5$, where FI denotes fasting plasma insulin (in microunits per milliliter), FG denotes fasting plasma glucose (in millimoles per liter), and 22.5 is a constant. In view of a pulsatile type of insulin secretion, the FI value was the mean of three results at 5-min intervals (0, 5, and 10 min samples). Insulin was determined using insulin reaction kits by Elecsys Automatic Electrochemiluminescence Immunoassay Instrument (Roche, German), While blood glucose was detected using automatic chemistry analyzer (Hitachi, Japan).

The blood samples for FI and FG test were collected from the median cubital vein on the morning of preoperative day 1 after overnight fasting (baseline) and on postoperative days 1, 3, and 5 when fluid infusion was ceased at least 6 h. FI and FG analysis was executed immediately. These blood samples were also used to measure the HLA-DR expression on monocytes.

HLA-DR Expression on Monocytes

The percentage of CD14+ monocytes expressing HLA-DR was measured by flow cytometry; 100 μl of whole blood was processed for staining and cell acquisition on flow cytometer (BD FACSAria, BD Biosciences) within 6 h after blood sample collection. Monoclonal antibodies were used according to the manufacture's protocol: fluorescein isothiocyanate-labeled anti-CD14 and phycoerythrin-labeled anti-HLA-DR (both from Multisciences Biotech Co., Shanghai, China). Results were expressed as percentages of HLA-DR-positive monocytes among total monocyte population.

Statistic Analysis

The expected postoperative morbidity of the conventional group was 30% based on the preliminary study. The minimum required sample size was determined by using an appropriate formula, which would provide 80% power to detect a 15% difference in the postoperative complication rate at a 0.05 level (two-sided test). Approximately 121 patients were required to be recruited in each group to fulfill the aim of the study. A simple randomization method (300 random numbers were generated through a computer system) with concealment was used to allocate the patients into different groups. The analyses were performed on an intention-to-treatment basis. The normally distributed data were reported as mean±sd and non-normally distributes variables as median (range), while the qualitative variables were expressed as frequency and percentage. The χ^2 test (or the Fisher's exact test, where appropriate) was used for comparison of proportions, Student's t test of independent samples for comparison of normally distributed data, and the Mann–Whitney U test for non-normally distributed data between two groups. Two-

Table 1 Baseline characteristics and surgical data

	Intensive group (n=125)	Conventional group (n=123)	P value
Gender (m/f)	83/42	79/44	0.790
Age (years)	58.5±8.1	59.9±7.6	0.170
BMI (kg/m^2)	20.8±2.1	21.2±2.1	0.160
FBG (mmol/l)	5.5±0.8	5.3±0.7	0.052
Albumin (g/l)	32.5±3.4	31.8±3.4	0.105
Smoking status [n (%)]			0.222
Nonsmoker	69 (55.2)	73 (59.3)	
<20 cigarettes/day	37 (29.6)	40 (32.5)	
≥20 cigarettes/day	19 (15.2)	10 (8.1)	
ASA (1/2/3) [n (%)]	25/50/17 (27.2/54.3/18.5)	21/52/14 (24.1/59.8/16.1)	0.764
NNISS score (0/1/2) [n (%)]	31/83/11 (24.8/66.4/8.8)	35/75/13 (28.5/61.0/10.6)	0.701
SENIC score (1/2/3) [n (%)]	34/80/11 (27.2/64.0/8.8)	30/85/8 (24.4/69.1/6.5)	0.643
Comorbidity [n (%)]	40 (32.0)	38 (30.9)	0.892
Hypertension	17 (13.6)	18 (14.6)	
Coronary artery disease	4 (3.2)	5 (4.1)	
Cardiac insufficiency	9 (7.2)	6 (4.9)	
Pulmonary disease	5 (4.0)	6 (4.9)	
Neurological disease	2 (1.6)	1 (0.8)	
Renal insufficicency	2 (1.6)	3 (2.4)	
Liver insufficiency	6 (4.8)	7 (5.7)	
Type of operation [n (%)]			0.794
Distal gastrectomy	82 (65.6)	85 (69.1)	
Proximal gastrectomy	19 (15.2)	15 (12.2)	
Total gastrectomy	24 (19.2)	23 (18.7)	
Combined resection [n (%)]	14 (11.2)	12 (8.9)	0.544
Type of anastomosis [n (%)]			0.452
Billroth I	65 (52.0)	59 (48.0)	
Billroth II	17 (13.6)	26 (21.1)	
Roux-en-Y	24 (19.2)	23 (18.7)	
Billroth reverse	19 (15.2)	15 (12.2)	
Length of surgery (min)	142.1±16.8	138.0±15.8	0.049
Estimated blood loss (ml)	377.6±95.4	381.1±81.4	0.759

Data are presented as mean ± sd or number (percent)

BMI body mass index, *FBG* fasting blood glucose, *ASA* American Society of Anesthesiologists classification, *NNISS* National Nosocomial Infection Surveillance System, *SENIC* Center for Disease Control Study on the Efficacy of Nosocomial Infection Control

sided P<0.05 was considered as statistically significant. Statistical analysis was performed using SPSS Advanced Statistical 13.0 software (SPSS Inc., Chicago, IL).

Results

Demographic and Surgical Data

Among 260 patients randomized, 248 eligible patients were included in the analysis: 125 in the IG and 123 in the CG (Fig. 1). They underwent regular follow-up for 28 days after surgery. There were no significant differences in the main clinical characteristics and surgical data between groups including gender, age, BMI, fasting blood glucose, albumin, smoking status, American Society of Anesthesiologists classification, National Nosocomial Infection Surveillance System, and Center for Disease Control Study on the Efficacy of Nosocomial Infection Control for the risk of infection, comorbidity, type of operation, combined resection, type of anastomosis, location of the tumor, and estimated blood loss (Table 1). However, the mean length of surgery in IG was longer than in the CG (142.1±16.8 vs 138.0±15.8 min, P=0.049).

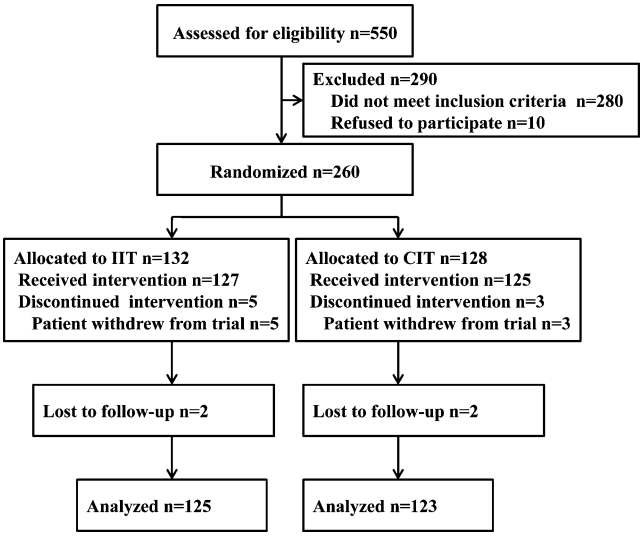

Fig. 1 Flow diagram for the trial. *IIT* intensive insulin therapy, *CIT* conventional insulin therapy

Outcome Measurements

Postoperative mean blood glucose concentrations were lower in IG than in CG (5.25±0.85 vs 10.22±0.93 mmol/l, $P<0.001$). However, based on blood glucose level below 2.2 mmol/l, the occurrence of undesirable severe hypoglycemia in patients receiving IIT was higher than in patients receiving CIT (6.4% vs 0.8%, $P=0.036$). In detail, a total of 19 episodes of severe hypoglycemia occurred in eight patients in the IG were recorded, and 1 event occurred in one patient in the CG. Because of appropriate intervention by the staff in the intensive treatment team, no sequelae of severe hypoglycemia were reported in these patients.

The postoperative short-term outcomes and PN duration are shown in Table 2. Median (range) PN duration were 6 (6–14) and 6 (7–14) days for IG and CG, respectively ($P=0.106$). With regard to hospital mortality, 1 of 125 patients (0.8%) in IG died vs 2 of 123 patients (1.6%) in CG ($P=0.620$). The one death in IG was due to renal failure with severe sepsis, whereas the two deaths in CG were due to acute cardiac failure and respiratory failure due to pulmonary infection, respectively. Overall, IIT reduced the short-term morbidity rate from 25.2% to 13.6% ($P=0.024$). Furthermore, the percentage of patients receiving therapeutic antibiotics, days to suture removal, and postoperative hospital stay were also evaluated; all of them had significant differences between the two groups.

HOMA-IR and HLA-DR Expression on Monocytes

To investigate the effect of intensive glucose control on insulin resistance, the dynamic changes of HOMA-IR scores were observed over time (Fig. 2). HOMA-IR did not differ significantly between groups at baseline. In contrast, IIT decreased the mean HOMA-IR scores on postoperative days 1, 3, and 5 (3.37±0.50 vs 4.03±0.85, $P<0.001$; 3.01±0.58 vs 4.01±0.88, $P<0.001$; 2.47±0.56 vs 3.30±0.59, $P<0.001$; respectively, for IG vs CG). Figure 3 presents the percentage of monocyte HLA-DR expression at different time points in both groups. There was no significant difference at baseline and on postoperative day 1 between the two groups. It differed significantly on postoperative days 3 and 5 (66.2±10.9 vs 53.1±10.4, $P<0.001$, and 71.7±12.7 vs 57.6±10.4, $P<0.001$, respectively, for IG vs CG).

Table 2 Outcomes after surgery in intensive and conventional groups

	Intensive group ($n=125$)	Conventional group ($n=123$)	P value
Postop hospital mortality [n (%)]	1 (0.8)	2 (1.6)	0.620
Postop overall complications [n (%)]	17 (13.6)	31 (25.2)	0.024
Type of complications [n (%)]			
Wound infection	5 (4.0)	13 (10.6)	
Anastomotic leakage	1 (0.8)	1 (0.8)	
Intra-abdominal infection	3 (2.4)	10 (8.1)	
Pneumonia	4 (3.2)	6 (4.9)	
Urinary tract infection	4 (3.2)	3 (2.4)	
Sepsis	2 (1.6)	4 (3.4)	
Pseudomembranous colitis	1 (0.8)	2 (1.6)	
PN duration (days) [median (range)]	6 (5–11)	6 (6–12)	0.106
Patients with therapeutic antibiotics [n (%)]	8 (6.4)	19 (15.4)	0.022
Days to suture removal (days) [median (range)]	7 (6–14)	8 (7–14)	<0.001
Postop hospital stay(days) [median (range)]	8 (6–26)	10 (7–28)	<0.001

Data are shown as number (percent) or median (range). Some patients had more than one complication

Postop postoperative, *PN* parenteral nutrition

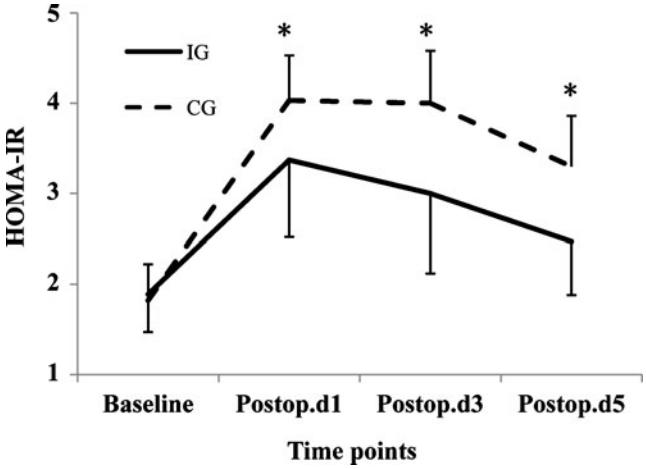

Fig. 2 Comparison of baseline and postoperative HOMA-IR score between intensive and conventional group. *IG* intensive group, *CG* conventional group, *HOMA-IR* insulin resistance of homeostasis model assessment, *Postop* postoperative. *$P<0.01$ vs conventional group

Discussion

In this prospective study, we investigated the effects of IIT in a homogenous population without diabetes receiving PN after elective radical gastrectomy for gastric cancer. Although IIT (maintenance of blood glucose at a level between 4.4 and 6.1 mmol/l), compared with CIT (maintenance of blood glucose at a level of less than 11.0 mmol/l), had no significant effect on hospital mortality, it strikingly reduced the postoperative short-term morbidity rate. Unfortunately, IIT was associated with the increased occurrence of undesirable hypoglycemia. Moreover, we have demonstrated that the mechanism underlying the clinical benefits from IIT is likely linked with suppression of insulin resistance and improvement of HLA-DR expression on monocytes.

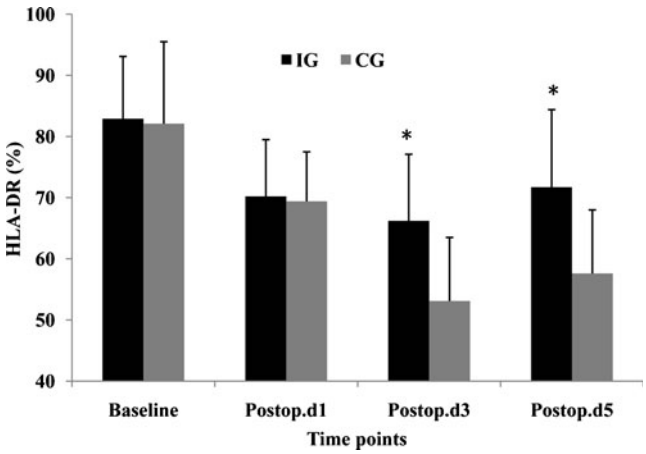

Fig. 3 The percentage of monocytes expressing HLA-DR during perioperative period in two groups. *HLA-DR* human leukocyte antigen-DR. *$P<0.01$ vs conventional group

PN plays an important role in SICU patients undergoing major abdominal surgery such as D2 gastrectomy for gastric cancer because in these patients, EN or oral intake may be not feasible due to compromised function of gastrointestinal tract or goal calories may not be achieved through EN. However, recent studies have shown that hyperglycemia in patients receiving PN is associated with increased complication and mortality in both critically ill and noncritically ill.[19,20] A current guideline issued by the American Society of Parenteral and Enteral Nutrition suggests glucose monitoring every 6 h upon initiation of PN and at least three times daily within days 3–9 until the blood glucose has reached less than 11.0 mmol/l.[3] However, there is much controversy over the optimal target of blood glucose levels in critical patients so far. Several studies indicated that IIT improved the clinic outcomes in different clinical settings.[10,21,22] By contrast, a recent meta-analysis of 34 randomized trials including 1,358 patients demonstrated that tight glucose control was not associated with significantly reduced hospital mortality but was associated with an increased risk of hypoglycemia in critically ill adult patients.[23] We had to point out that the ICU or critically ill patient is not a homogeneous population, therefore the heterogeneity of study patient may interweave the effects of IIT. In the present study, we focused on a homogeneous subpopulation without diabetes receiving PN following elective radical gastrectomy. In this subpopulation, hyperglycemia is a result of comprehensive function of surgical stress and PN. We found that intensive glucose control in this subgroup reduced the risk of postoperative short-term complications. Furthermore, intensive glucose control shortened the days to suture removal and postoperative hospital stay, and lessened the percentage of patients receiving antibiotic therapy after surgery.

Severe hypoglycemia is considered as the major barrier to IIT because severe hypoglycemia, if not treated promptly, is linked to serious neurologic events ranging from seizures to coma. The occurrence of severe hypoglycemia in patients undergoing intensive glucose control is quite variable and ranges between 0.8% and 18.7%.[5,10] In the present study, 0.8% of patients in CG vs 6.4% of patients in IG had severe hypoglycemia; intensive glucose control significantly increased the risk of severe hypoglycemia. Fortunately, there were no short- and long-term sequelae in these patients because of appropriate intervention. Importantly, severe hypoglycemia mainly occurred during the period within 24 h after surgery. It is speculated that early clinical signs and symptoms may be masked by various factors, including administration of sedatives, analgesics, and anesthetics, which reminds that physicians should pay more attention to the patients undergoing IIT during this period. Additionally, a multidisciplinary team formed in this study, including well-trained surgeons, diabetologists, and SICU nurses, was

responsible for monitoring blood glucose, adjusting the infusion rate of insulin, and giving prompt intervention for hypoglycemia. The team played a vital role in achieving the desired target of blood glucose levels and ensuring the safety of ITT in postoperative patients.

It is important to note that extensive nursing workloads are required to achieve the optimal target blood glucose levels, involving frequent monitoring of blood glucose levels and the implementation of the complex intensive insulin infusion protocol. Findings from the study of Aragon indicated that financial costs and time allotment associated with intensive insulin therapy in critical care were considerable, although most nurses endorsed tight glycemic control.[24] Additionally, the cost effectiveness of intensive insulin therapy in different patient populations has been described in several existing studies. A post hoc analysis of healthcare resource utilization demonstrated that intensive insulin therapy in surgical ICU setting was associated with substantial reductions in overall medical care costs.[25] Krinsley et al. reported that intensive insulin therapy in critically ill adult patients had substantial beneficial effects on patient morbidity and mortality. Meanwhile, they found that substantial annualized savings, conservatively estimated at US $1,339,500, or US $1,580 per patient, were due to decreases in all major categories of resource utilization.[26]

Insulin resistance is a central characteristic of the postoperative metabolic response to surgery and critical illness, leading to stimulated glucose production, impairment of glucose utilization, and development of hyperglycemia finally.[27] Past and very recent studies suggest that insulin resistance during surgery is a marker of surgical stress with a clear association with poor clinical outcomes in particular infections.[28,29] Few studies were performed to investigate the change of insulin resistance in nondiabetic patients receiving parenteral nutrition after major abdominal surgery. As shown in Fig. 2, all patients had increased HOMA-IR scores after surgery, implying that postoperative insulin sensitivity was decreased in varying degrees compared to baseline in this population. Insulin resistance was common after radical gastrectomy, although IIT suppressed the severity of insulin resistance and improved the insulin sensitivity.

The mechanism of hyperglycemia underlying poor clinical outcomes involves the immune system, inflammation mediators, and vascular responses.[8,30–32] Acute hyperglycemia may alter the activity of phagocytes due to impairment of neutrophil and monocyte functions including adherence, chemotaxis, and phagocytosis; reduce coronary collateral blood flow leading to increase in infarct size; and induce cardiac myocyte death via apoptosis. HLA-DR molecules, expressing on the professional antigen-presenting cells, play an important role in the specific immune response to infections. HLA-DR expression on monocytes was decreased significantly after trauma and major surgery.[33–35] It is generally accepted that the reduced HLA-DR expression on monocytes is closely related to postoperative infection complications and development of sepsis.[36] The effect of IIT on HLA-DR expression on monocytes is not well known yet. We found that monocyte HLA-DR expression declined strikingly after surgery in both groups, indicating that monocyte function was impaired. However, intensive glucose control enhanced the monocyte HLA-DR expression compared with conventional glucose control.

The present study has several limitations. First, it was designed as a single-center trial on safety ground. Secondly, it could not be strictly blinded because of the nature of this study. However, to minimize this bias, the staff responsible for implementing the protocol of intravenous infusion insulin was not aware of the clinical decision making, primary and secondary outcomes measurement. Thirdly, since this study included only nondiabetic patients receiving parenteral nutrition after D2 gastrectomy for gastric cancer, the results might not be directly extrapolated to other populations such as patients requiring no parenteral nutrition after gastrectomy for gastric cancer due to potential patient selection bias. Finally, PN support was not tailored to the individual patient. But we focused mainly on a homogeneous population receiving certain intervention, which may make our results more powered than other studies on a heterogeneous population of critically ill patients.

In conclusion, on one hand, intensive insulin therapy targeting a blood glucose level between 4.4 and 6.1 mmol/l reduced the postoperative morbidity rate in nondiabetic patients receiving parenteral nutrition after D2 gastrectomy, but the effect on morbidity was not found. On the other hand, severe hypoglycemia rate was higher when blood glucose levels were controlled intensively, however no severe short- and long-term sequelae caused by brief hypoglycemia were observed due to appropriate intervention. Moreover, these benefits from IIT may be due to the suppression of insulin resistance, improvement of HLA-DR expression on monocytes, or a combination of all these factors. Up to now, there are no standard protocols or guidelines regarding PN-associated hyperglycemia in this population. Therefore, large prospective, well-designed, multicenter, double-blind, randomized controlled trials are needed to confirm these results and explore the optimal target of blood glucose in this population.

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Conflict of interest There is no potential and real conflict to any third party.

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ORIGINAL ARTICLE

Evaluation of Postoperative Pancreatic Fistula After Total Gastrectomy with D2 Lymphadenectomy by ISGPF Classification

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Abstract
Introduction Postoperative pancreatic fistula (POPF) is a serious complication of total gastrectomy (TG) with D2 lymphadenectomy (D2). However, the actual incidence and risk factors are not yet completely understood, due in part to the absence of the widely accepted criteria for POPF following gastrectomy.
Patients and methods One hundred and four patients who underwent TG with D2 between March 2007 and December 2009 were included in this study. The incidence and severity of POPF were evaluated according to the International Study Group on Pancreatic Fistula (ISGPF) classification. In addition, risk factors for POPF of ISGPF grade B or higher were investigated.
Results POPFs of ISGPF grade B or higher were observed in 23 patients (22.1%). Univariate analysis found that sex, body mass index, and amylase concentration of drainage fluid (D-AMY) on the first postoperative day (1POD) were significant predictors of POPF grade B or higher. The appropriate cutoff level of D-AMY on 1POD was calculated as 3398 IU/l. Multivariate analysis showed that D-AMY ≥3,398 IU/l on 1POD was the only independent risk factor.
Conclusions High D-AMY on 1POD (≥3,398 IU/l) can predict a grade B or higher POPF, and this value may be useful in the early detection of POPF following TG with D2.

Keywords POPF · Total gastrectomy · D2 lymphadenectomy · ISGPF

Introduction

At present, surgical resection is the mainstay of the treatment for gastric cancer.[1] For advanced gastric cancer located in the upper third of the stomach, total gastrectomy (TG) with D2 lymphadenectomy, which generally includes splenectomy, is a standard treatment in Japan. However, it has been shown that splenectomy in TG is associated with high morbidity rates.[2–7]

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Among such morbidities, postoperative pancreatic fistula (POPF) is one of the serious complications after TG, and it is sometimes life-threatening. Although POPF following TG has been investigated before, the incidence and risk factors are not completely understood, due in part to the absence of widely accepted criteria for POPF. Accordingly, different definitions of POPF have been used, resulting in highly variable reported rates of POPF, ranging from 5.3% to 49.7%,[8–16] thus making it impossible to even accurately estimate the incidence of POPF.

In 2005, the International Study Group on Pancreatic Fistula (ISGPF) formulated an objective definition of POPF.[17] Although this classification has been well accepted for pancreatic surgery, its validation for POPF following gastrectomy is yet to be fully investigated and still remains unclear.

Therefore, the aim of this retrospective study was to clarify the actual incidence of POPF after TG with D2 lymphadenectomy using the ISGPF classification. Risk factors for POPF, including the appropriate cutoff level for

Table 1 International Study Group on Pancreatic Fistula classification with examples[14]

No POPF	D-AMY on or after 3POD is not three times more than the upper normal serum amylase level.
Grade A	No specific treatment is required, although D-AMY on or after 3POD is three times more than the upper normal serum amylase level.
Grade B	Requires a change in management or adjustment of the clinical pathway. For example, antibiotics, total parenteral nutrition or enteral nutrition, and repositioning of drainage tubes are included in this grade.
Grade C	Requires a major change in the clinical pathway. Clinical intervention is aggressive, and often in the ICU setting.

POPF postoperative pancreatic fistula, *D-AMY* drainage amylase level, 3*POD* third postoperative day, *ICU* intensive care unit

the amylase concentration of the drainage fluid (D-AMY) to predict POPF, were also investigated.

Methods

Patients

Between March 2007 and December 2009, 256 patients underwent TG at the Shizuoka Cancer Center, Shizuoka, Japan. Patients were excluded if they met any of the following criteria: (1) patients who underwent combined resection of pancreas, (2) patients who received neoadjuvant chemotherapy, (3) patients who underwent non-curative surgery, and (4) patients with remnant gastric cancer. Among the remaining 194 patients, 110 patients underwent TG with D2 lymphadenectomy. Six patients, in whom D-AMY was not examined on or after the third postoperative day (3POD), were excluded from the analysis; thus, the remaining 104 gastric cancer patients were included in the present study. The patients' clinical, surgical, and pathological records were collected from the database of our hospital.

In this retrospective study, the pathological data were recorded according to the 7th edition of the TNM Classification.[18] Macroscopic type, histologic type, and the number of lymph node stations were determined according to the Japanese Gastric Cancer Association classification (2nd English edition).[19]

Definition of D2 Lymphadenectomy for Upper Third Gastric Cancer

If the primary lesion is located only in the upper third part, the perigastric lymph nodes, suprapancreatic lymph nodes [along the celiac axis (station 9), the common hepatic artery (station 8a), the left gastric artery (station 7), and the splenic artery (station 11)], and splenic hilar lymph nodes should be dissected for D2 lymphadenectomy. If the primary lesion invaded the middle third part, lymph nodes along the proper hepatic artery (station 12a) should be dissected. For the patients with invasion of primary lesion to lower third part, lymph nodes along the superior mesenteric vein (station 14v) should be dissected additionally.

Amylase Concentration of Drainage Fluid

During surgery, one to four drainage tubes were placed. Each drain was connected to a bag through an extension tube. The amylase concentration of the fluid from each drain was evaluated on the first postoperative day (1POD) and on or after 3POD in all patients. In patients with two or more drains, the highest amylase value was taken as the representative value on that day.

Definition and Severity of POPF

In this study, we defined and classified POPF using the ISGPF criteria. The grades of POPF severity, determined by the ISGPF classification, are summarized in Table 1.

Table 2 Clavien–Dindo classification with examples[21]

Grade 0	No complications
Grade I	Deviation from normal hospital course, no need for medication or intervention. Allowed therapeutic regimens are drugs such as antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy
Grade II	Requires pharmacological treatment with drugs other than those allowed for grade I complications. For example, antibiotics, blood transfusions, and total parenteral infusion are included in this grade.
Grade IIIa	Requires intervention not under general anesthesia. For example, exchange of drainage tube or insertion of a new drainage tube is included in this grade.
Grade IIIb	Requires intervention under general anesthesia
Grade IVa	Readmission to ICU—single organ dysfunction (including dialysis)
Grade IVb	Readmission to ICU—multiorgan dysfunction
Grade V	Postoperative mortality

ICU intensive care unit

Using the ISGPF criteria, patients with D-AMY on or after 3POD of three times more than the upper normal serum amylase level were defined as having POPF. We classified patients as grade A when no specific treatment was needed. Grade B required a change in management or adjustment in the clinical pathway, for example, repositioning of drainage tubes or administration of antibiotics. In grade C, a major change in clinical management was required. Patients in this grade were managed in the intensive care unit because of sepsis or organ dysfunction.

In patients with POPF of ISGPF grade B or higher, we also classified their POPF severity by the Clavien–Dindo classification to obtain a more precise grading. This classification also consists of therapy-oriented objective criteria and contains seven severity grades (Table 2). ISGPF grade B or higher is equivalent to Clavien–Dindo grade II or higher, and this condition is considered potentially fatal. In this study, therefore, we focused on POPF with an ISGPF grade of B or higher (Clavien–Dindo classification of grade II or higher).

Statistical Analysis

In order to identify clinicopathological variables that affect the development of POPF, variables were compared between patients with and without POPF of ISGPF grade B or higher. The chi-square test was used for categorical variables, and the Student's *t* test or Wilcoxon test was used for numerical variables as appropriate.

A multivariate logistic regression model was used to adjust for potential confounding factors. Variables achieving a probability value <0.05 in the univariate analysis were subsequently introduced in a multivariate analysis.

The receiver operating characteristic (ROC) curve of D-AMY on 1POD was used to identify an appropriate cutoff level to detect grade B or higher POPF.

All statistical analyses were performed with JMP software, version 8.0 (SAS Institute, Cary, NC). Values of *P* values <0.05 were considered statistically significant, and all tests were two-sided.

This study was approved by the Human Ethics Review Committee of the Shizuoka Cancer Center.

Results

Patient Characteristics

The clinicopathological features of the 104 patients included in the study are summarized in Table 3. Over two thirds of cases were male, and the mean age was 65.8 years.

Table 3 Clinicopathological characteristics of all eligible patients

	No. of patients (n = 104)
Age (years)[a]	65.8 (9.0)
BMI[a]	21.7 (3.6)
Total protein (g/dl)[a]	6.9 (0.8)
Sex	
Male	76 (73.1)
Female	28 (26.9)
Blood loss (ml)[b]	547.5 (70–2,103)
Operation time (min)[b]	239 (153–399)
Macroscopic type	
0	25 (24.0)
1	11 (10.6)
2	24 (23.1)
3	33 (31.7)
4	11 (10.6)
Histological type	
Undifferentiated	55 (52.9)
Differentiated	49 (47.1)
pT	
1	8 (7.7)
2	17 (16.3)
3	39 (37.5)
4a	36 (34.6)
4b	4 (3.8)
pN	
0	30 (28.8)
1	26 (25.0)
2	15 (14.4)
3a	12 (11.5)
3b	21 (20.2)
pStage	
IA	6 (5.8)
IB	11 (10.6)
IIA	17 (16.3)
IIB	21 (20.2)
IIIA	4 (3.8)
IIIB	21 (20.2)
IIIC	24 (23.1)
IV	0 (0)

Values in parentheses are percentages unless indicated otherwise

BMI body mass index

[a] Values are mean (standard deviation)

[b] Values are median (range)

The proportion of patients with early gastric cancer (pT1) was 7.7%. Nodal metastasis was detected in 74 patients (72.2%). The median operation time was 239 min (range, 153–399 min), and median blood loss was 547.5 ml (range, 70–2,103 ml).

Incidence and Severity of POPF

The overall incidence of POPF was 55.8% by the ISGPF criteria. ISGPF grade A and B POPF were observed in 33.7% and 22.1% of patients, respectively. No patient was classified as ISGPF grade C. Perioperative mortality was not seen. The median postoperative hospital stay for patients with no POPF, grade A POPF, and grade B POPF was 16, 14, and 25 days, respectively (Table 4).

Patients with grade A do not need any specific treatment and resolved. All 23 patients, who were classified as grade B POPF, received antibiotics. Of these patients, 16 patients underwent repositioning of drainage tubes, one patient underwent insertion of a new drainage tube, and another patient underwent both repositioning and insertion of a new drainage tube. All 23 patients with grade B resolved after these treatments. Fistulography was performed in 18 patients of grade B, and communication with the main pancreatic duct was not confirmed in any of these patients.

Using the Clavien–Dindo classification, five patients who only received antibiotics were classified as grade II POPF. Eighteen patients who underwent repositioning of a drainage tube or insertion of a new one, in addition to the administration of antibiotics, were classified as grade IIIa. The median postoperative hospital stay for patients with grade II and grade IIIa POPF was 16 and 28 days, respectively (Table 4).

Appropriate Cutoff Level of D-AMY on 1POD

The median D-AMY on 1POD was 1,755 IU/l (range, 124–133,380 IU/l). In order to identify the appropriate cutoff level of D-AMY on 1POD for detecting POPF of ISGPF grade B or higher, we used a ROC curve (Fig. 1). This analysis revealed that 3,398 IU/l on 1POD was the best cutoff value. The sensitivity, specificity, and positive predictive value of the amylase concentration for POPF of ISGPF grade B or higher were 72.7%, 76.7%, and 54.3%, respectively.

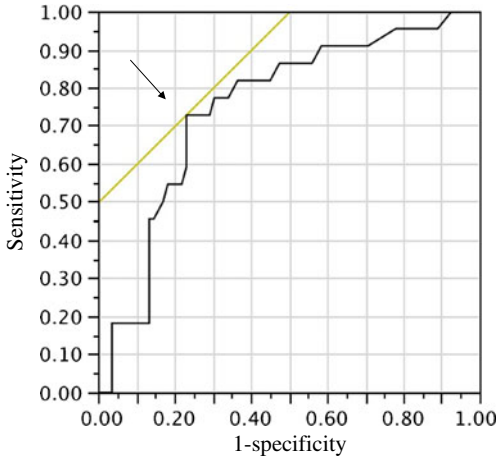

Fig. 1 ROC curve of drainage amylase levels on the first postoperative day, for distinguishing postoperative pancreatic fistula of grade B or higher, based on the International Study Group on Pancreatic Fistula classification. The *arrow* shows the best cutoff point. The area under the curve was 0.75

Risk Factors of POPF

Univariate analysis identified several factors which were highly associated with POPF of ISGPF grade B or higher (Table 5). The preoperative factors, sex (male, $P=0.021$) and increasing body mass index ($P=0.036$) had a strong association with the development of grade B or higher POPF. Moreover, the perioperative factor, D-AMY on 1POD (≥3,398 IU/l, $P<0.001$) was also significantly associated with the development of POPF of grade B or higher. However, no pathological factors were associated with the development of grade B or higher POPF.

Multivariate analysis showed that D-AMY on 1POD≥ 3,398 IU/l was the only significant independent risk factor for POPF of ISGPF grade B or higher ($P=0.001$; Table 6), and the odds ratio was 6.03 (95% CI, 2.14–18.44).

Table 4 Incidence and severity of postoperative pancreatic fistula according to the International Study Group on Pancreatic Fistula and Clavien–Dindo classifications

ISGPF classification	No. of patients	Postoperative hospital stay (days)[a]	Clavien–Dindo classification	No. of patients	Postoperative hospital stay (days)[a]
No POPF	46 (44.2)	16 (10–27)			
Grade A	35 (33.7)	14 (10–27)			
Grade B	23 (22.1)	25 (13–87)	Grade II	5 (4.8)	16 (13–33)
			Grade IIIa	18 (17.3)	28 (15–87)
Grade C	0 (0)				

Postoperative hospital stay is shown with respect to each POPF grading. Values in parentheses are percentages unless indicated otherwise

ISGPF International Study Group on Pancreatic Fistula, *POPF* postoperative pancreatic fistula

[a] Values are median (range)

Table 5 Association between patient characteristics and pancreatic fistula severity according to the International Study Group on Pancreatic Fistula classification

Parameters	Pancreatic fistula (no. of patients)		
	No POPF, grade A	Grade B	*P* value
Preoperative factors			
Sex			0.021
Male	56 (73.7)	20 (26.3)	
Female	26 (92.9)	2 (7.1)	
Age (years)[a]	65.3	67.7	0.276
BMI[a]	21.2	23.3	0.036
Total protein (g/dl)[a]	6.9	7.1	0.181
Perioperative factors			
Blood loss (ml)[b]	524	629	0.479
Operation time (min)[b]	238.5	248	0.796
Amylase concentration			<0.001
<3,398 (IU/l)	63 (90.0)	7 (10.0)	
≥3,398 (IU/l)	19 (55.9)	15 (44.1)	
Pathological factors			
Macroscopic type			0.881
0, 1, 2	47 (78.3)	13 (21.7)	
3, 4	35 (79.6)	9 (20.4)	
pT			0.692
T1, T2	19 (76.0)	6 (24.0)	
T3, T4	63 (79.7)	16 (20.3)	
pN			0.577
N0, N1	43 (76.8)	13 (23.2)	
N2, N3	39 (81.2)	9 (18.8)	
pStage			0.510
I, II	42 (76.4)	13 (23.6)	
III, IV	40 (81.6)	9 (18.4)	
Histological type			0.252
Differentiated	41 (74.6)	14 (25.4)	
Undifferentiated	41 (83.7)	8 (16.3)	

Values in parentheses are percentages unless indicated otherwise

POPF postoperative pancreatic fistula, *BMI* body mass index

[a] Values are mean

[b] Values are median

Discussion

The overall incidence of POPF grade B or higher after TG with D2 lymphadenectomy was 22.1%. In addition, we revealed that a high value for D-AMY on 1POD (≥3,398 IU/l) was the only independent predictor of grade B or higher POPF.

Table 6 Multivariate analysis of association between patient characteristics and postoperative pancreatic fistula of grade B or higher, classified by the International Study Group on Pancreatic Fistula definitions

Variables	Odds Ratio (95% CI)	*P* value
Sex (male)	3.73 (0.90–25.64)	0.072
BMI	5.90 (0.31–135.14)	0.240
D-AMY on 1POD (≥3,398 IU/l)	6.03 (2.14–18.44)	0.001

CI confidence interval, *BMI* body mass index, *D-AMY on 1POD* drainage amylase concentration on the first postoperative day

The extent of lymphadenectomy in gastric cancer surgery remains controversial, and D2 lymphadenectomy has not been performed routinely in Western countries. However, the Dutch Gastric Cancer Study Group recently showed that D2 lymphadenectomy is associated with low locoregional recurrence and gastric cancer-related death rates than D1 surgery after a median follow-up of 15 years.[20] Furthermore, clinical guidelines of the European Society of Medical Oncology referred to D2 lymphadenectomy as the standard treatment for advanced gastric cancer in 2010.[21] D2 lymphadenectomy is considered to be an important role for the local control of advanced gastric cancer, and it may be performed more widely in Western countries. Thus, it is important to comprehend complications after D2. In such complications, intra-abdominal infection which is often induced by POPF is potentially fatal, and so early detection of POPF and appropriate management is essential after D2. This is why we

investigated the risk factors of POPF for early detection in this study.

In the past, there have been some reports concerning pancreatic-associated complications after gastrectomy.[8,15,16,22–24] In these reports, however, the authors developed their own definition of POPF, and POPF after TG has rarely been analyzed using a set of widely accepted objective criteria. Sano et al.[8] defined POPF as a condition in which D-AMY was more than three times the normal serum amylase concentration for more than 7 days. On the other hand, the report of Katai et al.[22] describes pancreas-related abscesses, which they diagnosed when purulent fluid containing turbid necrotic debris drained from the peripancreatic area for more than 7 days. There have also been other definitions of POPF in previous studies.[15,16] To solve this problem, we used the ISGPF classification which is a therapy-oriented objective classification. It was first proposed for pancreatic surgery and has been validated in this situation and has become widely accepted in recent times.[17,25] However, validation of this classification after gastrectomy has not been fully investigated to date. Recently, Obama et al.[23] reported POPF after laparoscopic gastrectomy using the ISGPF classification. However, in their report, they used an additional definition of POPF to allow for missing data for D-AMY on 3POD, which was not the original ISGPF definition. As far as we know, our present study is the first study in which POPF after TG with D2 lymphadenectomy was evaluated by the original ISGPF classification as the objective criteria.

The ISGPF definition of POPF is objective and prevents down-rating because it is based on data that are usually well documented and easily verified. This kind of standardized and reproducible method allows comparison among different centers. However, this classification consists of only three severity groups. Thus, grades B and C may include a very wide range of patients' medical conditions. Accordingly, we also classified patients with grade B or higher POPF by the Clavien–Dindo classification for further investigation. The Clavien–Dindo classification allows the identification of most complications, and it also has gained widespread acceptance.[26–29] This classification consists of seven severity grades, including two subgroups for grades III and IV. In the current study, ISGPF grade B was divided into Clavien–Dindo grades II and IIIa, and more detailed grading could be performed. Anyhow, we considered a complication which needed some sort of intervention as potentially life-threatening. Thus, we analyzed the risk factors for POPF of ISGPF grade B or higher (Clavien–Dindo grade II or higher).

In our study, over half of the patients were diagnosed as POPF: 33.7% and 22.1% of all patients were classified with POPF of ISGPF grades A and B, respectively. It must be noted that total POPF rate after TG with D2 by ISGPF classification becomes high. These rates are higher than those reported after pancreatic surgery.[25] This can be explained by the soft quality of the pancreas in patients with gastric cancer. In fact, soft pancreas density was reported to be a significant risk factor for POPF in pancreatic surgery. Furthermore, resection of pancreatic capsule in D2 may be associated with POPF.

It is true that the frequency of POPF (55.8%) seems to be high, but 33.7% of all patients were ISGPF grade A. We consider that ISGPF grade A is not clinically important because they have only abnormal data and do not need any treatment. Additionally, the origin of high D-AMY cannot be specified exactly, and this amylase-rich fluid in grade A may be from disrupted lymphatic vessels, not from the damaged pancreas itself. This is why we focused on ISGPF grade B or higher as a potentially fatal condition in this study. We compared our incidence of POPF with past some reports (Table 7). Most of the definitions in past reports may approximately correspond

Table 7 Summary of the literatures about POPF after total gastrectomy

First author	Year	No. of patients	Extent of lymph node dissection	Incidence of POPF (%)	Definitions of POPF
Sano	1997	102	D0–D3	14	D-AMY>3 times more than s-AMY for≥7 days
Furukawa	2000	110	D2 (with vs. without pancreatectomy)	16 vs. 13	D-AMY>500 IU/l for 2 weeks
Ichikawa	2004	258	D1–D3	5.8	D-AMY>1,000 IU/l for ≥7 days
Okabayashi	2005	317	Not described	9.5	D-AMY and D-lipase >3 times more than s-AMY and s-lipase, drainage volume >10 ml/day
Kunisaki	2006	147	D2–D3 (with pancreatosplenectomy)	49.7	Dirty appearance, skin redness, D-AMY>1,000 IU/l, bacterial infection, and enhancement of abscess cavity
Nobuoka	2008	740	D1–D3	18	Purulent discharge for ≥7 days
Tanaka	2009	191	D1–D2	19.4	d-AMY between POD1 and POD3>3 times more than s-AMY, drain tube≥2 weeks, no evidence of anastomotic leakage

d-AMY amylase concentration of drainage tube, *s-AMY* serum amylase concentration, *s-lipase* serum lipase concentration, *POD* postoperative day

to ISGPF grade B or higher, and the incidence of POPF in those past reports were about 10–20%. Accordingly, our incidence of ISGPF grade B (22.1%) is not so high rate, considering that the extent of lymph node dissection was specified to D2 in our study.

The results of this study showed that high D-AMY on 1POD (≥3,398 IU/l) was the only statistically significant predictor of POPF, graded B or higher. This is meaningful as this cutoff value can be used in clinical practice. For example, this value can be used as a reference for the early removal of drains, or early preventive management for infection. In their previous report, Sano et al.[8] described that D-AMY on 1POD>4,000 IU/l was the best cutoff value. However, they did not use objective therapy-oriented criteria. Furthermore, the extent of lymphadenectomy was not specified in their study. In fact, standard D2 lymphadenectomy was performed in about half the patients, and the rest of the patients underwent D1 or D3 lymphadenectomy in their report. Thus, we consider D-AMY of approximately 3,000 IU/l on 1POD as a more appropriate cutoff value after TG with D2 lymphadenectomy. At present, there is no definite clinical guideline for the treatment of POPF. We consider that early preventive management by antibiotics or drainage tube placement for the long term may be beneficial for patients whose D-AMY on 1POD is higher than 3,000 IU/l.

In conclusion, the incidence of grade B or higher POPF after TG with D2 lymphadenectomy was 22.1% according to the ISGPF classification. A high D-AMY on 1POD (≥3,398 IU/l) was the only significant predictor of POPF grade B or higher. This cutoff value may be useful in the early detection of patients likely to develop POPF after TG with D2 lymphadenectomy, allowing for the appropriate management of these patients in a timely fashion.

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ORIGINAL ARTICLE

Percutaneous Transhepatic Biliary Drainage and Occlusion Balloon in the Management of Duodenal Stump Fistula

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Abstract
Background Duodenal stump fistula (DSF) after gastrectomy is a complication with a high mortality rate. We report a series of patients with postoperative DSF treated with percutaneous transhepatic biliary drainage and occlusion balloon (PTBD-OB). The aim of this study is to explore the feasibility and efficacy of PTBD-OB in the treatment of DSF.
Patients and Methods Six patients developing DSF underwent PTBD-OB because of high DSF output and because medical and surgical management was unsuccessful. In these patients, an occlusion balloon was percutaneously inserted into the common bile duct and a biliary drain was positioned above the balloon to obtain external drainage of bile.
Results In all cases, percutaneous access to the biliary tree was achieved. Patients maintained the PTBD-OB for a median of 43 days. In all patients, DSF output decreased after PTBD-OB placement from a median of 500 to 100 ml/day (p=0.02). The DSF resolved in three patients and three patients died of sepsis, but in two of them, death was related to other digestive fistulas that developed before PTBD-OB placement.
Conclusions This paper presents the first published series on DSF management with PTBD-OB and shows that it is a feasible and safe procedure which reduces DSF output.

Keywords Duodenal stump fistula · Complications of gastrectomy · Percutaneous transhepatic biliary drainage · Occlusion balloon

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Introduction

Duodenal stump fistula (DSF) after gastrectomy is a potentially devastating complication with a high morbidity, a very long period of hospitalization and an overall mortality rate of about 20% due to sepsis and multiple organ failure.[1] High intraluminal duodenal pressure has been postulated as one of the possible causes of DSF and a reason for healing failure.

Percutaneous transhepatic biliary drainage (PTBD) can successfully reduce duodenal pressure and fistula output by removing bile, pancreatic and duodenal juice accumulating in the duodenal stump,[2,3] while the addition of an occlusion balloon in the biliary tree blocks the biliary flow, thereby avoiding its passage into the intestinal lumen.[4] The aim of the balloon is to avoid contact between bile and the fistula

and promote the healing process by shortening the healing time of the fistula.

We report on a single institution series of patients with postoperative DSF after gastrectomy for malignant disease who were treated with percutaneous transhepatic biliary drainage and occlusion balloon (PTBD-OB). The aim of this study was to explore the role of PTBD-OB in the treatment of DSF. In an attempt to analyze the feasibility of PTBD-OB in the treatment of DSF, we investigated the success rate of PTBD-OB insertion and the morbidity and mortality linked to this technique. To assess its efficacy, we recorded a decrease in DSF output after PTBD-OB placement and DSF healing.

Patients and Methods

A diagnosis of DSF was made on the basis of the presence of duodenal juice in the surgical drainage or its leakage through the abdominal wall and confirmed by explorative surgery, CT scan and/or fistulography. From March 2005 to June 2010, a total of six patients developing DSF after gastrectomy for malignant disease underwent PTBD-OB at the Interventional Radiology Unit of the Department of Radiology of IRCCS Istituto Clinico Humanitas, Rozzano (MI), Italy. Five patients underwent subtotal gastrectomies and one a total gastrectomy; all duodenal stumps were closed by stapler (GIA). In three patients, the operation was associated with a colectomy, in two cases for cancer infiltration and in one case for a second malignancy. Moreover, an abdominal aortic aneurysmectomy was performed in one patient and hepatic resection for liver metastasis in another.

Patient selection for PTBD-OB was based on a high daily DSF output (median 500 ml, range 300–1,000) and unsuccessful medical (parenteral and enteral nutrition, antibiotics, antifungals, octreotide and percutaneous drainage of abdominal abscesses) and/or surgical treatment. In fact, five of the six patients had required at least one percutaneous drainage of an abdominal abscess (range 1–2) and a median of two operations (range 1–3) for peritonitis and DSF repair, always followed by its recurrence. Furthermore, three patients had developed other digestive fistulas (esophageal, gastric and colic).

Technique Description

Institutional review board approval and patients' informed consent for the PTBD-OB placement were always obtained before performing the procedure. All procedures were carried out with the patient under local anesthesia (lidocaine or Carbocaine) and in some cases combined with a mild sedative based on midazolam and ketorolac. The patient was placed in the supine position and monitoring of vital signs was performed by a registered nurse. The bile ducts were punctured using a right intercostal percutaneous approach under fluoroscopic or ultrasonographic guidance. Since none of the patients had dilated intrahepatic bile ducts, an initial puncture was made with a 22-gauge Chiba needle close to the hilum, where the ducts are bigger. There, a small amount of iodinated contrast was injected to opacify the biliary tree and to allow puncture of a peripheral duct. An 0.18-inch micro guidewire was then advanced through the biliary system and later replaced by a conventional 0.35-inch angiographic guide by means of a micro puncture conversion system (AccuStick, Boston Scientific, Natick, MA, USA). Using an 8-F introducer, a second 0.35-inch guidewire was inserted into the same intrahepatic bile duct. Over a first guide, a compliant balloon specifically designed for vessel occlusion (standard occlusion balloon catheter, 10 or 12 mm depending on the dimension of the bile ducts; Boston Scientific, Natick, MA, USA) was positioned in the common bile duct between the confluence of the cystic duct and the sphincter of Oddi. The balloon was then manually inflated to the size deemed sufficient to stop the bile flow. The volume of inflation was visually evaluated by the operator and the correct maintenance of swelling of the OB was ensured by positioning of a high-pressure stopcock (Smiths Medical Deutschland GmbH, Kirchseeon, Germany) at the free end of the catheter. Later, a drainage catheter (Flexima, Boston Scientific, Natick, MA, USA) was inserted over the second guidewire and positioned above the OB in order to obtain complete external drainage of bile (Figs. 1 and 2).

The catheter was left to gravity drainage and flushed twice a day with 10 ml sterile saline solution. Suspicious OB deflation was checked by cholangiography. When the DSF was clinically healing, we performed cholangiography before PTBD-OB and surgical drainage removal. We defined DSF healing as radiologically and clinically demonstrated definitive fistula closure, at which time PTBD-OB and drainage were removed.

In case of displacement or obstruction of the drain, or deflation of the OB with the persistence of a biliary leak, patients underwent a new procedure to replace the device or to reinflate the OB.

Statistical Analysis

Statistical analysis was carried out using the Stata 10 software (www.stata.com). Data are presented as numbers or median and range. Differences in DSF output before and after PTBD-OB were compared by the Wilcoxon test. A p value of less than 0.05 was considered statistically significant.

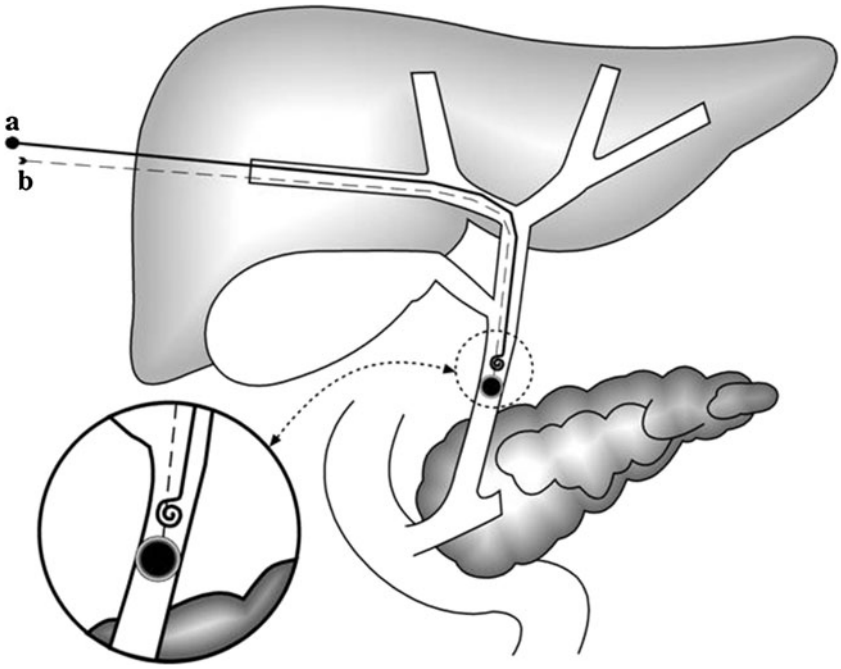

Fig. 1 An occlusion balloon catheter (**b**) is placed into the common bile duct in order to stop the bile flow. A drainage catheter (**a**) is positioned above the occlusion balloon to obtain complete external drainage of the bile

Results

The characteristics of the series are reported in Table 1. In all cases percutaneous access to the biliary tree was achieved without complications. The PTBD-OB was placed at the first attempt in five patients at the second try in the remaining patient after an unsuccessful attempt the day before. Patients kept the PTBD-OB for a median of 43 days (range 20–604), and underwent a median of four (range 2–7) additional interventional radiology procedures after the original PTBD-OB placement (15 tube controls, seven changes of PTBD due to occlusion or kinking of the catheter, one change of OB and one swelling of OB); the PTBD-OB procedures were not associated with any morbidity or mortality. In order to avoid dehydration due to biliary juice loss, all patients were supported by parenteral nutrition, two patients also received enteral nutrition and five patients were treated with octreotide. All patients stopped oral feeding until complete healing of the DSF. All patients except one stayed in hospital until DSF healing or death. One patient (patient number 1 in Table 1) stayed in hospital for 167 days while the DSF healed after 623 days. In all patients daily DSF output decreased immediately after PTBD-OB placement (Table 1). There was a significant reduction ($p=0.02$) from a median output of 500 ml/day before PTBD-OB placement to 100 ml/day collected the day after PTBD-OB placement.

DSF healing was achieved in three patients 63, 73 and 621 days since DSF onset, respectively, and 44, 73 and 604 days after PTBD-OB placement. The other three patients died of sepsis 40, 50 and 63 days since DSF onset, respectively and 20, 29 and 42 days after PTBD-OB placement, but the death of two of these patients was related to other digestive fistulas that developed before

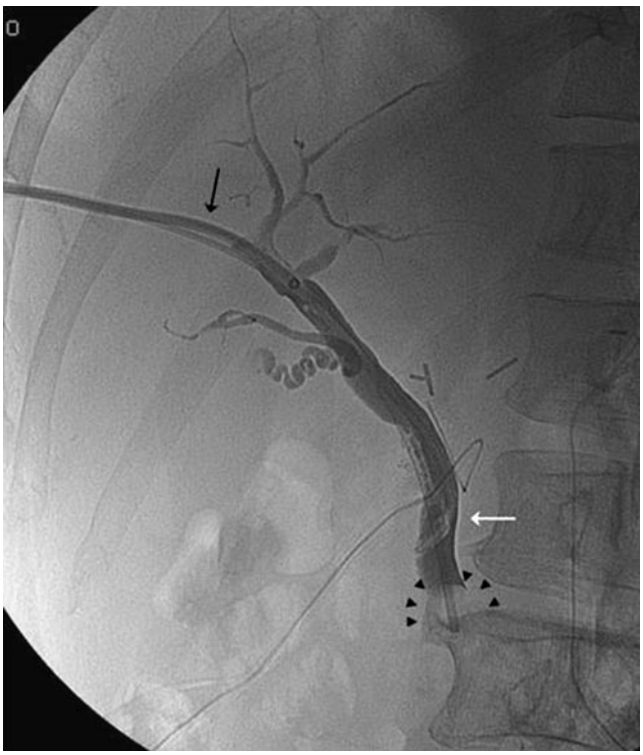

Fig. 2 Technique for total external drainage of bile in a patient with a duodenal stump fistula. Occlusion balloon catheter into the common bile duct (*arrowheads*: profile of the balloon) and drainage catheter (*black arrow*: drainage catheter; *white arrow*: tip of the catheter above the occlusion balloon)

Table 1 Characteristics of patients with DSF treated with PTBD-OB

No.	Age, sex	DSF onset (days)[b]	PTBD-OB placement (days)[c]	DSF output before PTBD-OB (ml/day)	DSF output after PTBD-OB (ml/day)	Days of disease[d]	Outcome
1	79, F	2	17	300	50	621	Recovery
2	68, M	10	0	1,000	900	73	Recovery
3[a]	81, M	4	20	1,000	100	40	Death
4[a]	66, M	5	21	500	300	63	Death
5	75, F	7	21	500	100	50	Death
6[a]	51, M	22	19	300	100	63	Recovery

M male *F* female, *DSF* duodenal stump fistula, *PTBD-OB* percutaneous transhepatic biliary drainage and occlusion balloon

[a] Patients with other digestive fistulas

[b] Days after surgery

[c] Days since DSF onset,

[d] Days of disease (DSF) until recovery or death

PTBD-OB placement. Only a one patient having only DSF died.

No DSF recurrence was observed after its closure, and no surgery or percutaneous drainage of abdominal abscesses was needed after PTBD-OB placement.

Discussion

Our report shows that PTBD-OB converts a high-output DSF into a low-output DSF, reducing the intraluminal duodenal pressure and allowing the fistula to close. The technical difficulty of PTBD-OB is to place a catheter into a non-dilated biliary system, but previous papers on similar cases reported a success rate of about 90% and respectively a complication rate of 9%.[5,6] In our series we obtained a 83% success rate at the first attempt and 100% at the second.

Since placement of an OB compresses the wall of the bile duct into which it is inserted, the balloon could theoretically cause pressure necrosis of the duct or surrounding tissues. However, to the best of our knowledge no data on such complications have been published and we did not observe them in any of our patients.

The small diameter of the catheter and biliary sludge played a role in causing obstruction, but flushing the catheter with saline solution and replacing it with a larger-caliber catheter can prevent or resolve obstruction. A PTBD-OB can stay in situ for a long time without any medical problems, although additional radiological procedures are needed about every ten days to check its function.

PTBD-OB placement can be an effective alternative to surgery (duodenostomy tube or oversewing of the duodenal stump).[7] In fact, surgical management of postoperative DSF poses challenges to the surgeon because patients are often septic or malnourished, may have a hostile abdomen, and duodenal re-leakage after reoperation is fairly frequent.[1,7–9]

In 1997 Villar reported the first experience with percutaneous transhepatic biliary/duodenal drainage in the management of DSF[2] in one patient after failure of surgical repair. In 2008 Zarzour reported on two patients with DSF who were successfully treated with PTBD[3] and more recently an Italian multicenter study reported four cases.[1] In our paper we present the first series reported in the literature of DSF treated by PTBD-OB. PTBD-OB differs from PTBD in that PTBD drains bile, pancreatic and duodenal juice accumulating in the duodenal lumen but is not occlusive, while PTBD-OB blocks the biliary flow, thus preventing its mixture with duodenal and pancreatic juices. Furthermore, in contrast to PTBD, with PTBD-OB the risk of cholangitis decreases because duodenal juice and enteric bacteria do not rise into the biliary tree.

Conclusions

PTBD-OB is a feasible and safe procedure and seems to effectively reduce DSF output. Moreover, PTBD-OB reduces the number of reoperations and the need for percutaneous abscess drainage and could change the prognosis of severe DSF. Further studies on larger series should be done to explore the indications for and timing of PTBD-OB placement. In fact, better results can be expected if PTBD-OB is placed before the clinical situation gets critical. In our series 50% of the patients recovered despite having major negative prognostic factors such as repeatedly unsuccessful surgical treatment of DSF and multiple previous percutaneous drainages of abdominal abscesses[1] before the decision to place a PTBD-OB. The next step should be to improve patient selection by including only

those patients with DSF alone, because the impact of PTBD-OB on survival in patients with other digestive fistulas may be unsatisfactory. Another step could be to move the indication for PTBD-OB placement closer to the onset of DSF in order to prevent the development of intra-abdominal sepsis or other digestive fistulas.

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ORIGINAL ARTICLE

Expression and Clinical Significance of L-Plastin in Colorectal Carcinoma

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Abstract
Introduction L-plastin, an actin-binding protein, is upregulated in many tumours, including colorectal carcinoma. This study evaluated the expression of L-plastin in plasma and colorectal tumour tissue and analysed the correlation between clinicopathological staging and prognosis.
Materials and Methods Enzyme-linked immunosorbent assay was used to detect L-plastin in the plasma of 120 colorectal carcinoma patients and 40 control subjects. Immunohistochemistry analyses were also used.
Results The rate of positive L-plastin expression was significantly higher in colorectal carcinoma patients than in control subjects, and was significantly higher in tumour tissues than in the tissues surrounding the tumour. L-Plastin expression also is correlated with tumour grade and size, and lymph node metastasis. However, there was no correlation with the extent of tumour invasion or distant metastasis.
Conclusion L-Plastin may be a useful marker for screening colorectal carcinoma and determining the prognosis of patients with colorectal carcinoma, and for genetic therapy and targeted therapy of colorectal carcinoma.

Keywords L-plastin · Colorectal carcinoma · Tumour marker · Carcinoembryonic antigen · Tumour grading · Clinical significance

Introduction

According to the World Health Organization, it is anticipated that there will be a total of 15 million cancer patients by 2020, and colorectal cancer (CRC) will be the second most common cancer. The rates of CRC recurrence and survival are closely related to histological type, grading and staging of the tumours. Consequently, much research is focused on increasing the efficiency of early screening, prognosis and treatment.

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L-Plastin, also known as lymphocyte cytosolic protein 1 (LCP1), is an actin-binding protein expressed at low levels in haematopoietic cells. Recently, it has been shown to be overexpressed in CRC cells. However, the relationship between its expression and the pathology, metastasis and prognosis of colorectal tumours is unknown. Therefore, we analysed the expression of L-plastin in plasma and tumour tissue by using enzyme-linked immunosorbent assay (ELISA) immunohistochemical analysis in order to determine the relationship between L-plastin expression and the clinical course of CRC patients.

Methods

Patients

This study involved 120 CRC patients and 40 control individuals at Ruijin Hospital, Shanghai, China, from June 2009 to December 2009. None of the cancer patients received neoadjuvant therapy or colorectal surgery. Control subjects had a normal chest radiograph, abdominal ultrasound and

haematological analysis. The control group was composed of 20 males and 20 females, 43–75 years old (median 63 years). The tumour group comprised 61 males and 59 females, 31–86 years old (median 61 years). The distribution of TNM staging results in the tumour group were: tumour grade—differentiated (75 cases) and undifferentiated (45 cases); extent of the tumour—T_1 (three cases), T_2 (20 cases), T_3 (70 cases) and T_4 (27 cases); lymph node metastasis—N_0 (54 cases), N_1 (38 cases) and N_2 (28 cases); and distant metastasis—M_0 (104 cases) and M_1 (16 cases).

Eighty patients were randomly selected from the tumour group and 5 control patients for immunohistochemical analysis.

Sample Collection

Blood samples (2 mL) were collected from all patients after overnight fasting. EDTA was used as an anticoagulant. Within 3 h after collection, the plasma was isolated by centrifuging at 4,000 rpm for 10 min, and then stored at −20°C, while serum carcinoembryonic antigen (CEA) and CA19-9 were being tested with the same procedure. The colorectal tumours and adjacent normal tissues were collected during operation, fixed in 4% formaldehyde solution, and then frozen in liquid nitrogen and stored at −80°C.

Enzyme-linked Immunosorbent Assay

First, the standards were set, and the diluted samples were injected. Then, samples were injected and incubated in room temperature for 120 min, and the primary antibody was added as working liquid then incubated for another 60 min. Substrate was added as working liquid and dark reaction for 5–8 min. We injected terminated liquid and measured absorbance for 450 nm. We took standards and contrast the OD values of the samples, and measured it for two times. With standard 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 ng/ml of OD values made the standard curve, draw curves with the software CurveExpert 1.3 and got the density of L-plastin for two times, taking the mean value.

Immunohistochemistry

Colorectal tissues were extracted and fixed in formalin, paraffin embedded and sectioned at 5 μm. The paraffin-embedded sections were dissolved in xylene and rehydrated in a graded ethanol series to water. The tissue samples were incubated with L-plastin monoclonal antibody (1:30 dilution) at room temperature overnight. Then 50 μL MaxVision™ reagent obtained from Sengxiong Industrial Company (Shanghai, China) was added to the samples, followed by incubation at room temperature for 15 min. Subsequently, 100 μL 3,3′-diaminobenzidine (DAB) was added to stain the samples. Afterwards, the samples were rinsed with water, counterstained with haematoxylin and washed with PBS. Finally, sections were dehydrated with a graded alcohol series, xylene and neutral gum sealing.

Slides were viewed with an Olympus BX41 microscope and photographed with an Olympus DP71 digital camera. PBS buffer was used as the negative control, while known colorectal tumour samples served as the positive control. Positive cells were identified by the presence of brown granular precipitate in the cytoplasm. Two independent pathologists scored the slides by the percentage of positive cells and the colour. Specifically, the scores corresponding to the percentage of positive cells were: 0 (≤5%), 1 (5–25%), 2 (25–50%), 3 (50–75%) and 4 (≥75%). Likewise, the scores corresponding to the colours were: 0 (uncoloured), 1 (light yellow), 2 (yellow) and 3 (brown). Finally, both scores were added and categorized into three groups: negative (−) (≤3), weakly positive (+) (4–6) and strongly positive (++) (>6).

Statistical Analysis

Data was analysed with Student's *t* test, analysis of variation (ANOVA) and chi-square tests using the SAS software package and receiver operator characteristic (ROC) curves were calculated with SPSS software. The cutoff *P* value for statistical significance was $P \leq 0.05$.

Results

Plasma Concentration of L-Plastin

As shown in Table 1, there was no difference in the median age of patients in the normal or tumour groups ($P=0.3173$). The plasma concentration of L-plastin in the normal group was 3.758 (3.333) ng mL^{-1} (mean (SD)), 95% CI 2.663–4.854 ng mL^{-1}. In contrast, the plasma concentration of L-plastin in the tumour group was 36.127 (30.800) ng mL^{-1} (mean (SD)), 95% CI 30.559–41.694 ng mL^{-1}. Two measurements in the normal group were omitted because they were outliers (>2 SD). This statistical method has been evaluated by a statistician. The difference in plasma concentration of L-plastin in these two groups was statistically significant ($P<0.01$) (Table 1).

Receiver Operator Characteristic Curve Analysis

The plasma concentrations of L-plastin in 120 patients and 40 control individuals were analysed by an ROC curve (Fig. 1). This curve shows that the ideal threshold was 8.85 ng mL^{-1}, sensitivity was 90.0%, specificity was 87.5%, likelihood ratio (LR)=7.2, Youden index=0.775, AUC=0.930, standard deviation=0.029 and $P<0.01$. Compared with the CEA marker (AUC=0.660, data not shown), L-plastin has better

Table 1 Plasma concentration of L-plastin

Group	Number of patients	Median age	Plasma L-plastin (ng mL^{-1}) mean (SD)	95% CI (ng mL^{-1})
Normal	38[a]	62	3.758 (3.333)	2.663–4.854
Tumour	120	61	36.127 (30.800)	30.559–41.694
P value		0.3173	0.0001	

[a] Two outlying results were omitted (see text for details)

sensitivity and specificity for CRC. In addition, although the sensitivity of CEA alone was only 44.2%, the sensitivity of CEA and L-plastin was 94.2% ($P<0.01$). This shows that using two tumour markers significantly improves the sensitivity of detecting CRC.

Plasma Concentration of L-Plastin and Clinical Features

In addition to analysing the plasma concentration of L-plastin, we also collected information about the clinical features of patients in the tumour group, such as age, gender, tumour location, size, differentiation, extent of the tumour (T), lymph node metastasis (N) and distant metastasis (M). The results showed that the plasma concentration of L-plastin is related to tumour differentiation, tumour size and lymph node metastasis (Table 2).

Immunohistochemical Staining

The immunohistochemical staining of L-plastin in 80 samples of normal tissues adjacent to tumours and five samples from control patients was negative (Fig. 2). Among these 80 samples, the combined scores for 14 were negative and 66 were positive. As a result, the sensitivity was 82.5% (66/80).

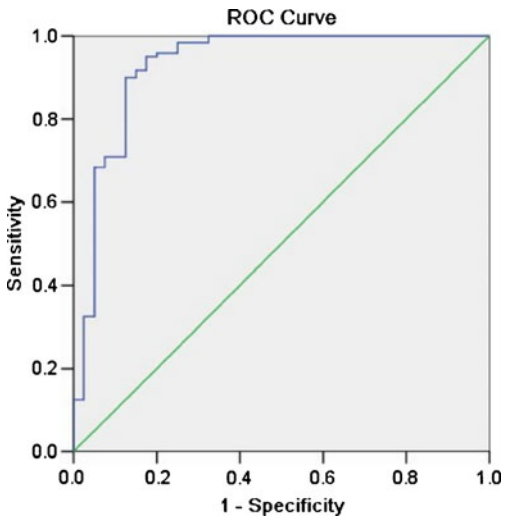

Fig. 1 Receiver operator curve (ROC) curve of L-plastin plasma concentration

Table 2 Plasma concentration of L-plastin and clinical features of cancer patients

Clinical feature	Number of patients	Plasma concentration of L-plastin mean (SD) (ng mL^{-1})	*P* value
Age			
≤60	58	39.990 (31.825)	
>60	62	32.513 (29.610)	0.1851
Gender			
Male	61	34.239 (33.786)	
Female	59	38.078 (27.530)	0.4972
Tumour location			
Colon	58	34.583 (31.210)	
Rectum	59	37.596 (30.826)	
Multiple	3	37.083 (31.511)	0.087
Differentiation			
Differentiated	75	28.445 (23.322)	
Undifferentiated	45	48.929 (37.184)	0.0015
Tumour size			
≤2 cm	8	20.906 (18.352)	
2–5 cm	74	31.089 (26.153)	
>5 cm	38	49.142 (36.920)	0.004
Extent of tumour			
T_1	3	53.953 (20.882)	
T_2	20	29.572 (23.798)	
T_3	70	39.382 (32.648)	
T_4	27	30.563 (30.585)	0.314
Lymph node metastasis			
N_0	54	27.956 (26.226)	
N_1	38	49.195 (35.206)	
N_2	28	34.150 (27.466)	0.0039
Distant metastasis			
M_0	104	34.221 (28.417)	
M_1	16	48.517 (42.333)	0.2087
Dukes stage			
Stage A/B	53	28.376 (26.294)	
Stage C	51	40.294 (29.506)	
Stage D	16	48.517 (42.333)	0.0307

And the immunoprecipitate was in the cytoplasm. There was a significant difference between the expression of L-plastin in colorectal carcinoma tissue and normal tissue ($P<0.01$) (Figs. 2 and 3). Specifically, differentiated tumour cells had weakly positive scores and light yellow deposits (Fig. 3a). In contrast, undifferentiated cancer cells had strongly positive scores and dark brown deposits (Fig. 3b, c, d).

Expression of L-Plastin in Tumour Cells and Clinicopathological Features

In 80 CRC samples, the expression of L-plastin was not related to age, gender, tumour location, extent of the

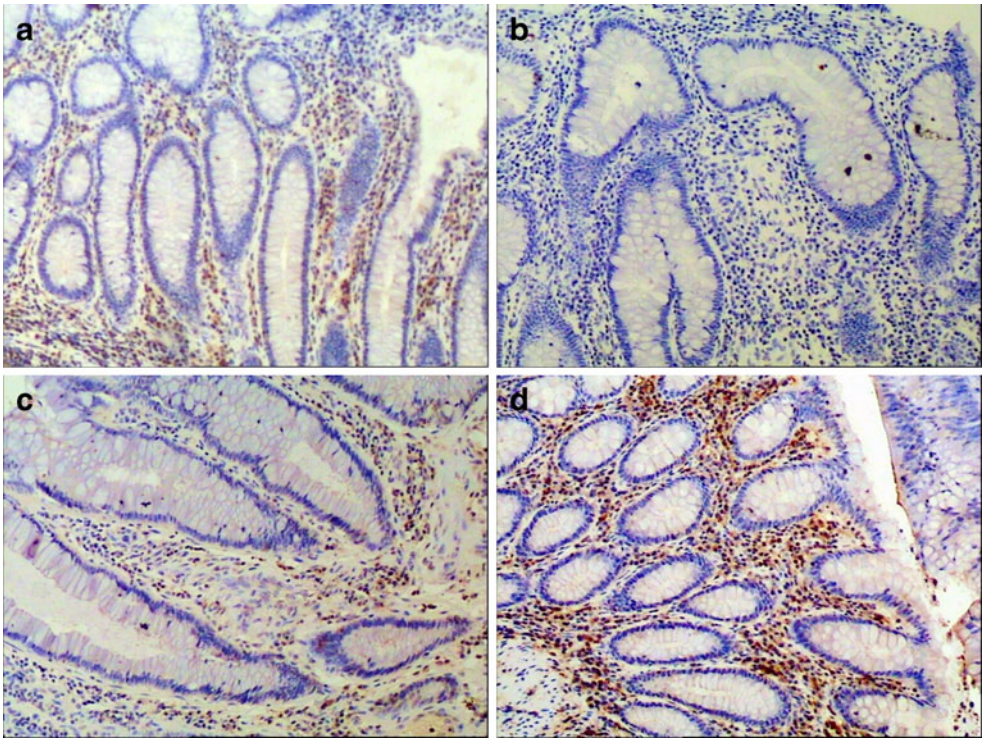

Fig. 2 Normal colorectal tissues (×100). **a**, **b** control individuals; **c**, **d** CRC patients normal intestinal glands were lined, without any brown sediment in epithelial cells. Some mesenchymal cells had *brown deposits*. (*Negative*)

tumour, distant metastasis or plasma CEA and CA19-9 levels. However, it was related to tumour differentiation, size, lymph node metastasis, Dukes stage (Fig. 4) and plasma L-plastin level ($P<0.05$) (Table 3).

Discussion and Conclusion

Metastasis is a complex process. First, tumour cells detach from the primary tumour, migrate into the surrounding tissue

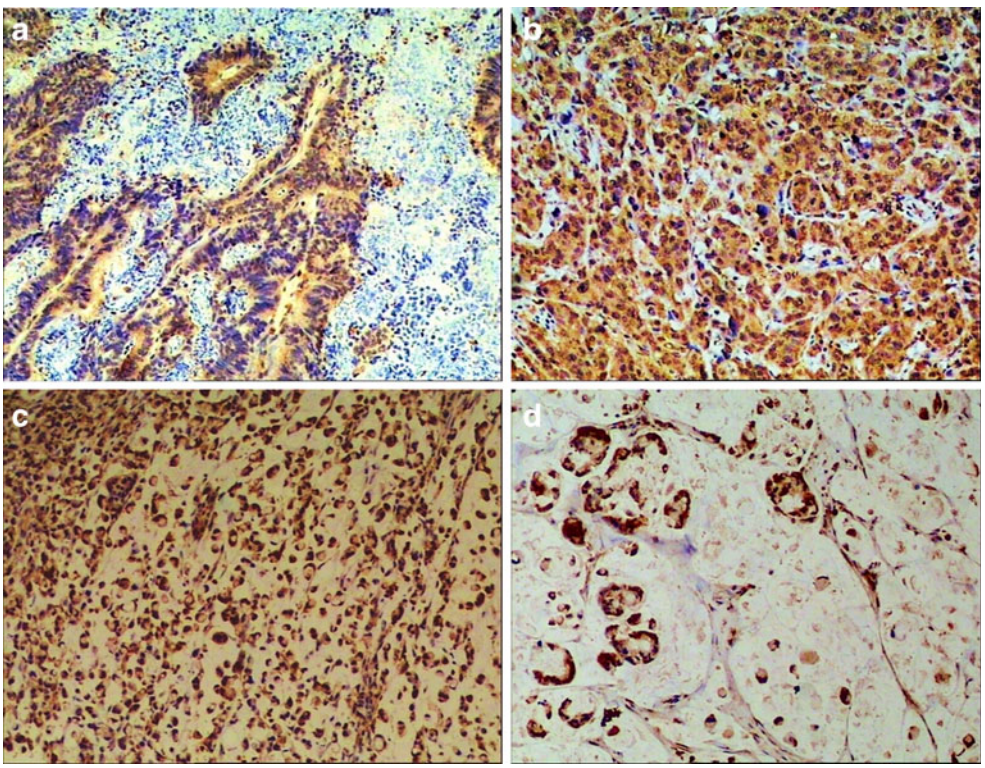

Fig. 3 Colorectal tumours. **a** Differentiated adenocarcinoma (*weakly positive*) (×100). **b**, **c** and **d** Undifferentiated adenocarcinoma (*strongly positive*) (×100). **c** Signet ring cell cancer (×100). **d** Mucinous adenocarcinoma (×100)

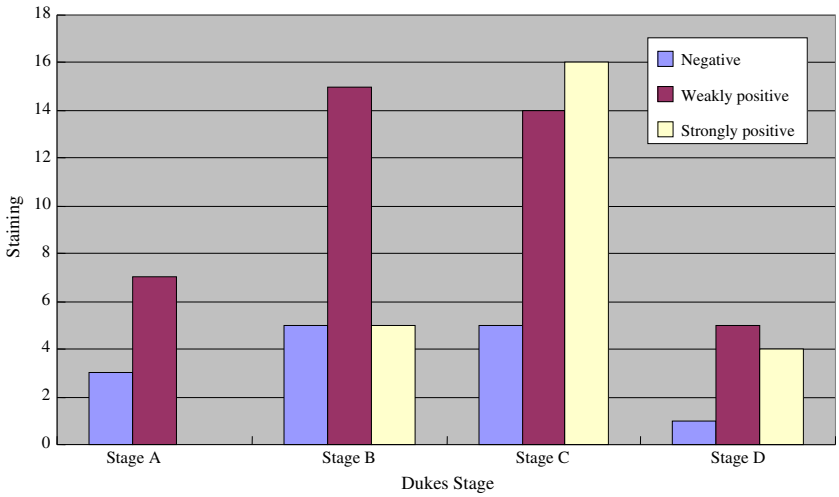

Fig. 4 Immunohistochemistry of L-plastin and Dukes stage in colorectal tumour cell

and invade blood vessels and the lymphatic system. Once they adhere to the endothelium, they can migrate to other parts of the body and form metastases.[1–3] The invasiveness of tumour cells involves hydrolysis of the basement membrane and disruption of cellular adhesion. Adhesion between cells is important for establishing and maintaining cell morphology and function. Abnormal adhesion can interfere with normal growth and cause cells to dedifferentiate and proliferate and spread uncontrollably. Since the actin cytoskeleton is important for regulating cell migration and adhesion, actin-binding protein, such as α-actinin, filamin and plastin, have been investigated as potential tumour markers and drug leads for targeted cancer therapy.[4,5]

There are three types of human plastin—T, L and I. T-Plastin is expressed in epithelial and mesenchymal cells. I-Plastin is expressed in small intestine, colon and kidney cells.[6,7] L-Plastin is expressed at low levels in the cytoplasm of granulocytes. Recent studies show that L-plastin regulates cell motility by binding actin and is overexpressed in tumour cells.[8–12]

In humans, the L-plastin gene is located on chromosome 13q14.3. Lin et al. reported that 68% of epithelial tumours and 53% of mesenchymal tumours expressed the L-plastin gene.[9] L-Plastin is overexpressed in many tumours, including ovarian, breast,[10] colorectal, prostate and nasopharyngeal carcinomas,[11] and melanoma.[12] The molecular weight of L-plastin is 67 kDa. It has two actin-binding domains and two calcium-binding EF hand domains. L-Plastin is regulated by phosphorylation, which may be disrupted during tumour invasion and metastasis.[13,14] L-Plastin also regulates integrin-mediated leukocyte adhesion and activation.

A model of colon cancer metastasis was first proposed by Leibovitz et al.[15] who isolated the SW480 cell line from a primary colorectal tumour and, subsequently, the SW620 cell line from the same patient with lymph node metastasis. L-Plastin is upregulated in SW620 cells cultured in vitro. Since expression of the L-plastin gene is closely related to the progress of tumour, it may be a potential tumour marker.[16] This study also demonstrated that its expression is related to lymph node metastasis and tumour grade. Foran et al.[17] showed that L-plastin induces metastasis, including proliferation, migration and invasion, and reduces expression of E-cadherin. When E-cadherin, an epithelial-specific tumour suppressor, is downregulated, it induces dedifferentiation, invasion and metastasis.[18] Cytochalasin B, an endocytosis inhibitor, prevents this effect, showing that the mechanism involves endocytosis. Furthermore, Hao et al.[19] showed that a plasma L-plastin antibody is expressed in many tumours, including CRC, which is consistent with our results. L-Plastin has been discovered to have correlation with tumour expression and CRC progression by using immunohistochemical analysis or cultured tumour cells in vitro. In this study, we evaluated the expression of L-plastin in plasma and colorectal tumour tissue by using ELISA and immunohistochemical analysis to discover the correlation L-plastin expression and tumour pathology, especially Dukes stage. Thus, L-plastin may be a potential tumour marker for screening or follow-up. Recently, the value of L-plastin and several other proteins as a screening tool for CRC through fecal samples has been reported. But the detection method is not as convenient or widely used as ELISA. And our study found the high sensitivity and specificity between L-plastin and tumour grade, size, lymph node metastasis. Besides, plasma is always available due to patients with or without symptoms usually requiring haematological examination.

The plasma concentration in the tumour group which was much higher than in the normal group leads to the fact that the measure of dispersion in the tumour group was much larger than that in the normal group. Since the scarcity of the availability in collecting normal samples, we only collected five samples from control patients by endoscopic biopsy. And the immunohistochemical staining expression was negative. As shown in Fig. 2a, b, we had stated that L-plastin expression in plasma was

Table 3 L-Plastin expression and clinicopathological features of tumours

Clinical pathological features	Number of cases	Expression of L-plastin			*P* value
		Negative	Weakly positive	Strongly positive	
Total	80	14	41	25	
Age (years)					
≤60	40	8	18	14	
>60	40	6	23	11	0.8711
Gender					
Male	39	6	23	10	
Female	41	8	18	15	0.6582
Tumour location					
Colon	41	11	18	12	
Rectum	36	3	21	12	
Multiple	3	0	2	1	0.2621
Differentiation					
Differentiated	41	7	31	3	
Undifferentiated	33	7	10	22	0.0018
Tumour size					
≤2 cm	6	3	2	1	
2–5 cm	41	11	21	9	
>5 cm	33	0	18	15	0.0004
Extent of tumour					
T_1	1	0	1	0	
T_2	13	3	9	1	
T_3	48	6	23	19	
T_4	18	5	8	5	0.6964
Lymph node metastasis					
N_0	38	9	22	7	
N_1	23	2	12	9	
N_2	19	3	7	9	0.0335
Distant metastasis					
M_0	70	11	37	22	
M_1	10	3	4	3	0.4998
Dukes stage					
Stage A	10	3	7	0	
Stage B	25	5	15	5	
Stage C	35	5	14	16	
Stage D	10	1	5	4	0.0094
Plasma CEA					
Elevated	31	7	13	11	
Normal	49	7	28	14	0.9303
Plasma CA19-9					
Elevated	17	5	4	8	
Normal	63	9	37	17	0.7927
Plasma L-plastin					
Elevated	70	10	36	24	
Normal	10	4	5	1	0.0318

examined at the same time as known biomarkers CEA and CA19-9. Meanwhile, the other biomarkers such as CA724, CA125, CA50, CA242, CA153, TU M2-PK, Ca^{3+} and Fr-PSA have also been verified its effectivity by combination detecting. However, we only chose CEA and CA19-9 for relatively high sensitivity and economy

because testing the other biomarkers individually had been shown inefficiently.

Targeted cancer therapy is an appealing way to enhance the specificity and selectivity of cancer treatment, while avoiding the indiscriminate effects, toxicity and resistance associated with traditional chemotherapy.[20] For example, tumour-specific monoclonal antibodies can induce tumour cell apoptosis, and block tumour cell signaling.[21]Our study demonstrated a statistically significant relationship between colorectal tumour pathology and L-plastin. Further study is needed to determine whether an L-plastin monoclonal antibody can be used safely and effectively in humans. Including an L-plastin antibody in targeted and gene therapy has been effective in clinical trials, so it may be widely used in the near future.[22]

In conclusion, we identified correlations between L-plastin and tumour pathology, particularly tumour grades and lymph node metastasis. We also used an ROC curve to determine the ideal threshold of L-plastin for accurate diagnosis of colorectal carcinoma and showed that it may be a potential tumour marker. The rate of positive L-plastin expression was significantly higher in colorectal carcinoma patients than in control subjects. L-Plastin expression also is correlated with tumour grade and size, and lymph node metastasis. However, there was no correlation with the extent of tumour invasion or distant metastasis. The accurate mechanism has not been shown clearly yet. Further study is needed to determine its diagnostic or clinical efficacy.

Reagents

Anti-human L-plastin antibody was purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA; product code: monoclonal antibody sc-133218, sc-133219; polyclonal antibody sc-16657). L-Plastin was expressed and purified by Shanghai Yinji Biotechnology Company (Shanghai, China). All other materials were obtained from Sengxiong Industrial Company (Shanghai, China).

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ORIGINAL ARTICLE

Single-Incision Laparoscopic Colorectal Surgery, Experience with 50 Consecutive Cases

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Abstract
Background Single-incision laparoscopic surgery (SILS) is one of the most recent developments in laparoscopic surgery. Having proven its effectiveness in cholecystectomy and appendectomy, the feasibility of SILS in more advanced surgery, such as hemicolectomy and low anterior resection, is now a point of discussion.
Methods This study reports on the results of the first 50 SILS colorectal operations at our institution. Twenty right hemicolectomies, 16 sigmoid resections, 9 low anterior resections, and 5 total colectomies were performed. Nineteen patients were operated for benign colonic diseases, 31 for malignant disease.
Results Mean operative time was 130 min, and the median duration of postoperative hospital stay was 6 days. None of the procedures needed conversion to a laparotomy, but four patients were converted to a multiport laparoscopy. In one case, an anastomotic leakage occurred, which was treated by creating a diverting ileostomy laparoscopically. Minor complications were four wound infections and two incisional hernias.
Conclusion SILS colectomy is a safe and feasible procedure even in more complex cases. Comparative studies are needed to demonstrate advantages over traditional laparoscopic surgery.

Keywords Laparoscopy · Minimally invasive · SILS · Single incision · Colorectal surgery

Introduction

Minimally invasive techniques are currently the standard in gastrointestinal surgery. Reducing the surgical trauma leads to faster postoperative recovery, reduced wound-related complications, and improved cosmesis.[1,2] The most recent development in laparoscopic surgery has been single-incision laparoscopic surgery (SILS).

This new technique was initially used for appendectomy and cholecystectomy, proving to be feasible, safe, and cosmetically superior when compared to the standard laparoscopic technique.[3–6]

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More recently, SILS was introduced for advanced laparoscopic procedures. Theoretically, the reduction of the number of abdominal incisions could improve postoperative recovery. In 2008, the SILS approach was first described for a right hemicolectomy[7,8], and in 2010, the first single-port sigmoidectomy for diverticular disease was described in case reports.[9,10] Various small case series demonstrate the feasibility of the SILS technique for colorectal surgery.[11–16]

Our clinic started with SILS cholecystectomies in the beginning of 2009. We demonstrated that the SILS technique was a safe and feasible procedure when performed by an experienced laparoscopic surgeon. Complication rates were comparable to those in conventional laparoscopic surgery. With a learning curve of around 10 to 15 procedures, operative times approached those of conventional LC.

After experience with the SILS technique had increased, it was applied in colorectal surgery as well. The aim of this report is to describe our initial experience with the SILS technique for colorectal surgery.

Methods

Patient Selection

Between January 2010 and February 2011, 50 patients underwent single-incision laparoscopic colon surgery at our institution. All SILS procedures were performed by a single surgeon (CS). Patients were excluded from consideration if they had a T4 or a rectal tumor, if they had undergone a previous median laparotomy, or if there was an indication for an emergency colectomy. Indications for surgery included both benign and malignant pathology. All patients who were treated for a malignancy underwent a colonoscopy with biopsy of the suspect lesion. When the pathology report confirmed the malignancy, a CT scan of the abdomen and thorax was made for pre-operative staging. None of the patients received pre-operative chemotherapy.

Informed consent was received from all patients. All patients were given the option to undergo either an SILS procedure or a standard multiport laparoscopic procedure. All data were registered prospectively. Patient demographic data as well as body mass index (BMI), ASA score, and prior abdominal surgery were recorded. The surgical data included operative time, conversion rate, and location and type of anastomosis. Operative time was calculated as time from first incision to time of completion of skin closure. Postoperative assessment was focussed on duration of hospital stay, mortality, and morbidity. Furthermore, pathologic characteristics such as resection margin status, number of harvested lymph nodes, and length of specimen were compiled. All patients were treated according to the ERAS protocol.

Surgical Technique

For SILS right hemicolectomy, the patient is placed in supine position and tilted to the left. The surgeon and the assistant stand on the left side (the assistant holding the camera at the head of the patient). For SILS sigmoid resection or low anterior resection, the patient is placed in dorsal lithotomy position. The surgeon stands at the head end of the patient; standing on the right side when mobilizing the sigmoid and standing on the left side when dissecting the rectum. No difference was made in the surgical technique between benign and malignant cases.

Following infiltration with bupivacaine 0.25%, the umbilicus is thoroughly disinfected, everted, and opened longitudinally with a 3-cm incision through the skin and fascia. A wound protector is placed, and the SILS port is introduced. After insertion of the trocars, pneumoperitoneum is created. A standard 10-mm 30° laparoscope is used, as well as a straight atraumatic grasper and the 5-mm ligasure (Covidien, Mansfield, MA, USA). All procedures were performed using the SILS port by Covidien (Covidien, Mansfield, MA, USA). This flexible SILS port has three access ports, which can be used for 5- and 12-mm trocars and a separate insufflation attachment. During dissection, the grasper and ligasure device change ports to ensure the best angle.

For a right hemicolectomy, the patient is first placed in reversed trendelenburg. The hepatic flexure is mobilized from medial to lateral by opening the omentum at the proximal colon transversum. Subsequently, the attachments and the lateral peritoneal reflection of the flexure are divided. After this, the patient is placed in trendelenburg and the terminal ileum is lifted. An opening is made in the mesentery and the small bowel is divided using endostaplers (tri-stapling Covidien, Mansfield, MA, USA). The dissection then occurs in a medial to lateral approach. The coecum is lifted and the mesentery is divided up to the basis of the ileocoelic artery. The ileocoelic vessels are divided using ligasure. The retroperitoneal plane is developed until the duodenum is identified. The lateral peritoneum is opened and the mesentery is divided up to the middle colic artery. After complete mobilization of the right colon, both ends of the bowel are grasped and both the port and the specimen are taken out. If necessary, the incision is enlarged to a maximum of 4.5 cm for the externalization of the colon. A hand-sutured side-to-side anastomosis is made using 3.0 PDS (Ethicon, Cincinnati, OH, USA).

For a sigmoid resection, the patient is placed in trendelenburg position. If necessary, the uterus is retracted with a transcutaneous stay suture. In case of a long sigmoid loop, a second suture can be placed to through the sigmoid mesentery lifting the sigmoid to the abdominal wall. The sigmoid is mobilized from medial to lateral. The peritoneum of the mesentery is opened using the ligasure, and the avascular plane is dissected identifying the ureter and the gonodal vessels. The inferior mesenteric artery and vein are dissected at the origin and divided with the ligasure. Next, the lateral peritoneum is opened along the white line of Toldt. Depending on the distance of the tumor from the anal sphincter, the rectum is mobilized, starting with the opening of the peritoneal reflection. The mesocolon and mesorectum are divided using ligasure. After complete mobilization distal to the marked tumor, the bowel is transected using endostaplers. The endostapler is inserted directly through the SILS port without a trocar. If needed, the colon descendens is mobilized up to the splenic flexure to guarantee a tension-free anastomosis. The specimen and the SILS port are extracted and the proximal resection line is marked. In some procedures, the incision was enlarged for retrieval of the specimen to a maximum of 4.5 cm depending on the size of the tumor or mesorectum. The anvil of the circular stapler is introduced in the proximal colon and then the bowel is divided using staplers. The bowel is placed back into the abdominal cavity.

The SILS port is reintroduced, pneumoperitoneum is re-established, and a side-to-end anastomosis is stapled using a 31-mm circular stapler (DST series EEA stapler, Covidien, Mansfield, MA, USA).

The umbilical fascia is closed using interrupted Vicryl sutures (Ethicon, Cincinnati, OH, USA); the umbilicus is restored using Monocryl intracutaneous sutures (Ethicon, Cincinnati, OH, USA).

Results

Patient characteristics are depicted in Table 1. A total of 50 SILS procedures were performed between January 2010 and February 2011. The mean age of all patients was 65 years (range, 21–89), and the population consisted of 18 male and 32 female patients. The mean BMI was 27 (range, 17–35) and 11 patients had a history of previous abdominal surgery.

The results are listed in Table 2. Thirty-one patients were referred for adenocarcinoma of the colon. Sixteen tumors were located in the sigmoid and 15 in the right colon. Eight patients were treated with a sigmoid resection; seven patients underwent a low anterior resection for a distal sigmoid carcinoma. In two cases, a temporary diverting ileostomy was created. Fifteen patients received a right hemicolectomy. One patient with a carcinoma was treated with a total colectomy and ileorectal anastomosis because of Lynch syndrome.

Nineteen patients were referred for benign colon diseases; 8 patients suffered from diverticulitis, 4 patients had a medically uncontrolled colitis, and 7 patients had an endoscopically unresectable polyp. In these patients, eight sigmoid resections, two low anterior, five right hemicolectomies, and four total colectomies were performed. Two patients who underwent a total colectomy were treated with an ileorectal anastomosis without diverting ileostomy.

Table 1 Patient demographics

	n=50
Age (years)	65 (21–89)[a]
Body mass index (kg/m2)	27 (17–35)[a]
Sex	
Male	18
Female	32
Indication	
Malignancy	31
Polyp	7
Diverticulitis	8
Colitis ulcerosa	4
Previous abdominal surgery	11

[a] Values are mean (range)

Table 2 Results

	n=50
Operative time (min)	130 (67–203)[a]
Length of hospital stay (days)	6 (3–30)[b]
Procedures performed	
Right hemicolectomy	20
Sigmoid resection	16
Low anterior resection	9
Total colectomy	5
Additional trocart	4
Perioperative complications	
Wound infection	4
Ileus	2
Anastomotic leakage	1
Hernia	2
Pathology	
T1	2
T2	8
T3	21
Right hemicolectomy	
Tumor size	4.5 cm[a]
Distal free margin	11 cm[a]
Sigmoid/low anterior resection	
Tumor size	4 cm[a]
Distal free margin	4.5 cm[a]

[a] mean (range)

[b] median

The other two patients were treated with an end ileostomy according to patients' wishes.

None of the procedures needed conversion to a laparotomy. Four patients were converted to a multiport laparoscopy. In two cases, the SILS port proved to be too short to bridge the distance between skin and the peritoneal cavity. This resulted in continuous gas leakage from the pneumoperitoneum and dislocation of the SILS port while dissecting. In these cases, two additional trocarts were inserted. In the other two cases, the mesocolon of the sigmoid was too voluminous to allow a safe dissection. An additional 5-mm trocart was inserted.

Mean operative time was 130 min (range, 67–203). Figure 1 shows operative times with regard to the performed procedures. Median duration of postoperative hospital stay was 6 days (range, 3–30). In all patients operated for benign colon disease, the pathology report confirmed the preoperative diagnosis. All resections performed for malignancies in this series had at least 10 lymph nodes harvested with a mean of 14 lymph nodes. The surgical resection margins were all tumor-negative. The majority of the performed procedures for malignancy consisted of T2 or T3 tumors according to the TNM classification (Table 2).

No mortality was seen. One patient developed an anastomotic leakage. A drain was placed in the presacral fluid collection, and a double loop diverting ileostomy was created laparoscopically. The patient recovered rapidly and was discharged 1 week after the reoperation. Three months after the first operation, the ileostomy was reversed.

Apart from this, only minor complications were seen. Four patients developed wound infections, which were treated conservatively. With a mean follow-up of 9 months (range, 3–15), two incisional hernias were seen. Two patients developed an ileus, both treated conservatively, and one patient had a prolonged hospital stay because of a high-output ileostomy.

Discussion

One of the most important advantages of laparoscopic surgery is the reduction of the extent of surgical trauma. Since postoperative recovery is directly related to the amount of trauma, a further improvement in patient well-being postoperatively can be expected with a reduction of the number of incisions. SILS is the logical next step to further reduce surgical trauma. Different pain scores between SILS and classic laparoscopic surgery have been demonstrated,[17] and a superior cosmetic result after SILS has been established.[5]

However, the introduction of SILS in the Netherlands is very slow due to guidelines set by Dutch Endoscopic Association and questions about safety and possible increase of procedure-related complications.[18] Concerns about an increased difficulty are also an important factor for the slow introduction.

We started using the SILS technique in April 2009 for laparoscopic cholecystectomy and showed that it is a safe and feasible procedure with complication rates comparable to conventional laparoscopy. The learning curve was around 10 to 15 procedures. SILS cholecystectomy can however be a challenging procedure and is perhaps not the best SILS procedure to start with.

We started performing SILS colectomy in the beginning of 2010 and started with colectomies for benign disease. We noticed that a SILS colectomy was easier to perform than an SILS cholecystectomy. After performing a right hemicolectomy, we quickly progressed to more extensive procedures, such as total colectomies and low anterior resections.

Our results suggest that SILS colectomy is safe and feasible with reasonable operative times and no increase in complications. The learning curve is included in this number. Figure 1 shows operative times divided for right- and left-sided colectomies. With an increase in experience, operative times decreased. Data published in the literature are mostly feasibility studies and could therefore give a less accurate reflection of operative times. However, three retrospective comparative studies are available, with only one showing an increase in operative times.

Waters et al. published the first comparison between SILS and multiport laparoscopic right hemicolectomy.[12] In this retrospective analysis, 43 patients were analyzed; 16 single-port procedures and 27 multiport procedures. They required no additional ports and morbidity was similar between the two groups. Mean operative time was 106 min in the SILS group and 100 min in the conventional laparoscopic group. These results are comparable to our results for right hemicolectomy. They concluded that the single-port approach can be used safely, efficiently, and effectively; cosmetic outcome was not mentioned.

Another report of SILS right hemicolectomy was published by Adair et al.[19] Seventeen SILS procedures were case-matched retrospectively with 17 multiport laparoscopic procedures. A total of four different ports were used in this

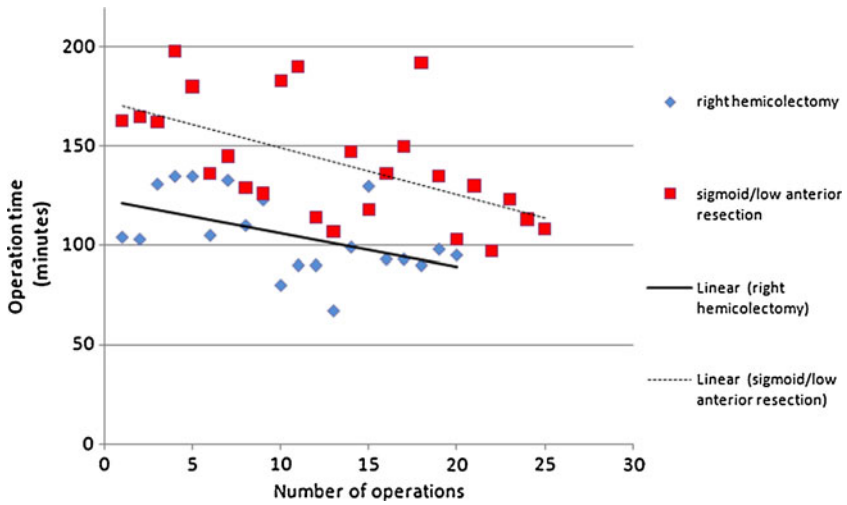

Fig. 1 Operative time divided for right- and left-sided colectomies with *trend lines*

study. In two of the planned SILS cases, an additional port placement was required. Mean operative time was 139 min for SILS colectomy. Complication rates were similar between both groups.

Most of the reports available in literature focus on the use of the SILS technique for right hemicolectomy, a relatively easy procedure. More complex resections appear to be safe as well using the SILS technique.

Champagne et al. reported the first case–control study that also included left-sided colectomies next to right-sided colectomies.[20] Twenty-nine SILS procedures were case-matched with 29 multiport procedures. Operative times in the SILS group were equal to our results. Operative time was significantly less in the multiport group with a difference of more than 30 min. Four patients in the SILS group were converted to a multiport laparoscopy; one patient needed a laparotomy because of a T4 tumor. Only minor complications were seen.

The surgical treatment for diverticular disease is generally considered to be more complex than for malignant disease. Vestweber et al. reported a feasibility study on SILS sigmoidectomy for diverticular disease.[11] A total of ten patients were treated; four patients underwent surgery during an active episode of diverticulitis, six patients were 3 to 6 weeks after the last episode. The procedure was successfully completed in eight of the ten patients. For one patient, conversion to an open procedure was necessary because of adhesions. In another patient, an additional 5-mm port was used. Median operative time was 120 min and no complications were reported, apart from one hematoma.

In our report, eight SILS procedures for diverticular disease are included—none of them during an active episode of diverticulitis; however, two patients had an enterovesical fistula. Two patients needed extra trocars and were converted to a multiport laparoscopy. There were no conversions to open procedures.

Although few data are currently available, the complication rate seems to be low. Besides the apparent cosmetic advantage, all other advantages remain unproven or suspected. Currently, there are only feasibility studies available. Our data shows besides the apparent feasibility also safety of the procedures in more complex resections. Fifty patients were operated and anastomotic leakage was observed in only one patient.

Theoretically, reducing the number of incisions should reduce the number of port-side/incisional hernias. Until now, two port-site hernias were seen with a maximum follow-up of 15 months (4%). This is relatively low when compared with the percentage of hernias seen at the specimen extraction site after laparoscopic colectomy, where a percentage up to 17% has been decribed.[21] Normal port-site hernias after multiport laparoscopic surgery are rare.[22]

Disadvantages of SILS laparoscopy are related to the perceived complexity of the procedure. Handling and freedom of motion for the surgeon are reduced due to the straight instruments parallel to the laparoscope. Various articulating instruments have been developed to improve this; however, in our opinion, these instruments make SILS surgery unnecessarily difficult. Most dissection can be done using straight instruments, and most experienced laparoscopic surgeons can adapt to the limited freedom of motion. In the available literature, few comments are made on the use of stay sutures during SILS colectomy. If needed, carefully placed stay sutures through the mesentery or through the appendix epiploica can be used to retract the sigmoid loop. During right hemicolectomy, no stay sutures were needed.

Leblanc et al. reviewed the current literature and concluded that the limited freedom and the long learning curve presented a challenge for teaching SILS colectomy.[23] Even though the learning curve is relatively short for experienced laparoscopic surgeons, we agree that SILS surgery is a challenge for residents. Currently, more experienced residents start with normal laparoscopic colectomy. They do, however, participate in SILS colectomy and perform part of the dissection.

Conclusion

Our data demonstrate that single-incision surgery can be used for benign and malignant disease of the colon. Even in more advanced procedures such as a low anterior resection or total colectomy, it is a safe technique with acceptable operative times. Whether SILS colectomy has clinical advantages compared to normal laparoscopic surgery remains to be proven.

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ORIGINAL ARTICLE

Experimental Study of Primary Repair of Colonic Leakage with a Degradable Stent in a Porcine Model

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Abstract
Background Anastomotic leakage is a major complication of colon resection. Fecal diversion is necessary in most patients and restoration of intestinal continuity has to be performed several months later. It carries a long treatment time and a considerable financial cost. We have developed a method of primary repair of colonic leakage with a degradable stent.
Methods Thirty pigs were included in this study. Colonic anastomotic leakage model was made successfully by open procedure in 15 pigs and primary repair with a degradable stent was performed 3 days later. Conventional colonic anastomosis was performed in the other 15 pigs without making leakage. Pigs of each group were sacrificed at schedule to evaluate the healing of anastomosis and observe the occurrence of complications.
Results No re-leakage occurred after primary repair, and no anastomotic stricture, peritoneal abscess, or colonic necrosis occurred in either group. No significant difference in bursting pressure or hydroxyproline content was found between the two groups.
Conclusions Primary repair of colonic leakage with a degradable stent is a feasible method in this porcine model.

Keywords Colonic anastomosis · Colonic leakage · Primary repair · Stent

Introduction

Colonic anastomotic leakage is a major complication after colonic surgery, leading to severe infection, sepsis, and sometimes death. The overall leak rate was at 2.4–3.5%.[1–3] Some methods, such as omentoplasty,[4] covering fibrin glue,[5] matrix metalloproteases inhibitors,[6,7] and some exogenous agents,[8,9] had been experimented to decrease leak rate. Reoperation of fecal diversion is necessary in most patients and restoration of intestinal continuity has to be performed several months later. The length of treatment is longer than 3 months and it carries a considerable financial cost. We have developed a method of primary repair of colonic leakage with a degradable stent. Using this method, colonic leakage has been treated by one operation without fecal diversion. Before being used in humans, this method was firstly evaluated in a porcine model.

Methods

Animals

Experimental mini-pigs (ShangHai Multi-Bio-Sci-Tech Co., Ltd., China) of either sex, weighing 12 to 15 kg, were housed one per cage at the Experimental Animal Center at Zhejiang University. They were allowed to become accustomed to the laboratory environment for more than 1 week

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before the start of the experiment. All animals had free access to water and standard food until the day before surgery. The study was approved by the ethic committee of Zhejiang University.

Experimental Design

A total of 30 pigs were included in this study after excluding two pigs of unsuccessful leakage model. Colonic anastomotic leakage model was made successfully by open procedure in 15 pigs, constituting primary repair group (PR group), and primary repair with a degradable stent was performed on these pigs 3 days later. Conventional hand-sewn colonic anastomosis was performed in the other 15 pigs without making colonic anastomotic leakage, constituting conventional anastomosis group (CA group). The timeline of making leakage and repair is described in Fig. 1.

Successful leakage model was defined as presence of leak in anastomosis along with observation of feces spillage, empyema formation, or intraabdominal abscess in reoperation for repair.

Pigs of each group were divided medially into three subgroups and were scheduled to be sacrificed on postoperative day 7, day 14, and month 10 to evaluate the healing of anastomosis. The peritoneal cavity was observed for signs of re-leakage, stricture, colonic necrosis, and so on. Bursting pressure and hydroxyproline content of anastomosis were measured. Pathology evaluation, including hematoxylin and eosin stain and trichrome Masson stain, were performed by the Pathology Department of Sir Run Run Shaw Hospital.

Feature of the Stent

The stent (Fig. 2) is developed and manufactured by the Institute of Polymer Science of Zhejiang University. It is synthesized with 1,3-propanediol, 1,2-propanediol, and sebacic acid and decomposed to carbon dioxide and water ultimately. The relationship of molecular mass and degradation time in vitro had been described in a previous article.[10] In a series of animal experiments relating to this stent in enteric cavity, we found that stents disappeared in the majority of pigs sacrificed in month 1 and in all pigs sacrificed in month 3, and were still in situ in pigs sacrificed on day 14 postoperatively.

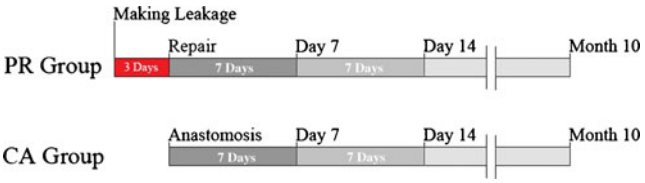

Fig. 1 Timeline of operative and re-operative events

Fig. 2 Degradable stent made of polymers

Making Colonic Leakage

Anastomotic leakage model was made by a laparotomy 3 days before repair. The pigs were without food for 24 h before operation of making anastomotic leakage and were fed with magnesium sulfate (5%) to clean the colonic lumen. Cefazolin sodium was administered intramuscularly before surgery. Pigs were anesthetized by an intramuscular injection of ketamine (6 mg/kg; FuJian Gutian Pharmaceutical Co., Ltd., China) and Sumianxin (0.1 mL/kg; Military Veterinary Institute, Academy of Military Medical sciences, China). Laparotomy was performed via a lower-midline incision for female pigs or a lower-paramedian incision for male pigs. An end-to-end, single-layer colonic anastomosis was constructed using inverting interrupted sutures with one fourth circle of anastomosis unsutured for creating leakage (Fig. 3). Pigs were starved for 24 h with free access to water, and diet started on postoperative day 2.

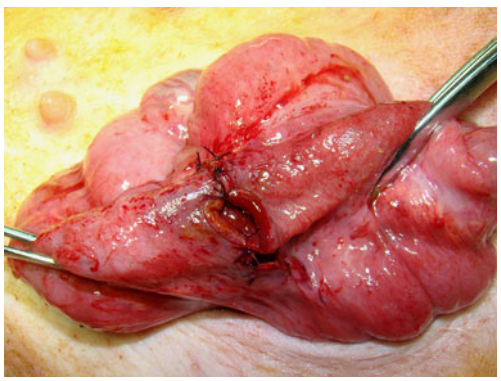

Fig. 3 An end-to-end colonic anastomosis was constructed with one fourth circle of anastomosis unsutured to create a leakage

Primary Repair of Anastomotic Leakage

Repair was performed via the previous incision under anesthesia. Abdominal cavity was inspected firstly to evaluate degree of colonic leakage (Fig. 4) and pigs of unsuccessful leakage model were excluded. Before repair, abdominal cavity and colonic lumen close to anastomosis were lavaged with povidone iodine solution and physiological saline. The necrotic tissue around the leakage was incised and some previous sutures were removed to enlarge the leak (Fig. 5a). Two polyglycolic acid sutures (0 DEXON II, Syneture) were used as binding lines, passing through the colonic mesentery at the site of about 6 to 12 mm to anastomosis on each side. Then a degradable stent was inserted into the colonic lumens through the enlarged leak (Fig. 5b), and the pre-placed polyglycolic acid sutures were tied to fix the colon to the stent (Fig. 5c). The abdomen was closed by two layers of interrupted sutures. The pigs were given free access to water for 24 h postoperatively and were given half of their normal diet on postoperative day 2. Normal diet was resumed on postoperative day 3.

Pigs in the control group underwent a conventional hand-sewn colonic anastomosis without making leakage previously. Briefly, bowel preparation was performed and cefazolin sodium was administered before surgery, a laparotomy was performed under anesthesia, and an end-to-end, single-layer colonic anastomosis was constructed using inverting interrupted sutures. The abdomen was closed as in the PR group.

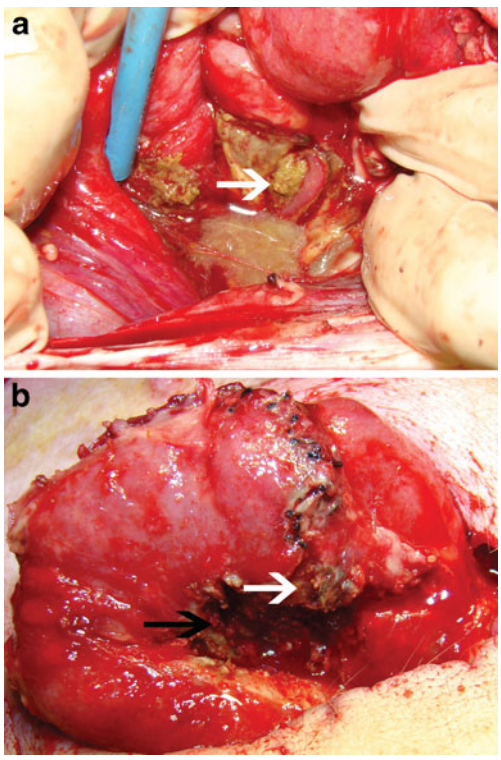

Fig. 4 Anastomotic leaks (*white arrow*) along with feces spillage (**a**) or abscess (**b**, *black arrow*, the abscess had been opened) was observed in reoperation in PR group

Bursting Pressure

Approximately 5 cm of colon with anastomosis was resected, including the surrounding tissues and adhesions, and washed in saline. Intraluminal feces were evacuated. Subsequently, one side of the anastomotic segment was connected to a manometer placed on the same plane, and the other side was closed by hemostatic forceps. The intraluminal pressure was increased gradually by an infusion of saline. Bursting pressure was defined as the maximum pressure the segment resisted or the pressure at the moment the first leakage was observed.

Hydroxyproline Content

The hydroxyproline content was measured using a hydroxyproline assay kit. Tissue specimens were cleared of suture material and weighed 0.03 to 0.05 g. Specimens then were hydrolyzed in sodium hydroxide at 95°C for 20 min. Homogenate was dilated by adding distilled water to a total volume of 10 mL, after the pH value was adjusted to 6.0 to 6.8. Foreign matter was cleared by adding active carbon. The solution was centrifuged, and the supernatant sample was used for analysis. A total of 0.5 mL of chloramine-T (0.05 mmol/L) was added to 1 mL of sample, and the sample was incubated at room temperature for 10 min. Then, 3.15 mol/L of perchloric acid was added, and the sample was incubated for 5 min, followed by the addition of 10% paradimethylaminobenzaldehyde. After incubation at 60°C for 15 min, the absorbency of the solution was measured spectrophotometrically at 550 nm and compared with standard samples for hydroxyproline content.

Statistical Analysis

For statistical analysis, the Mann–Whitney *U* test was used. A *P* value of less than 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS statistical software package (version 13.0, SPSS Inc., Chicago, IL, USA).

Results

No pigs died in the period of colonic leakage and the model was made successfully in all cases in PR group except for two pigs without sign of severe intraabdominal inflammation in reoperation (excluded from this study).

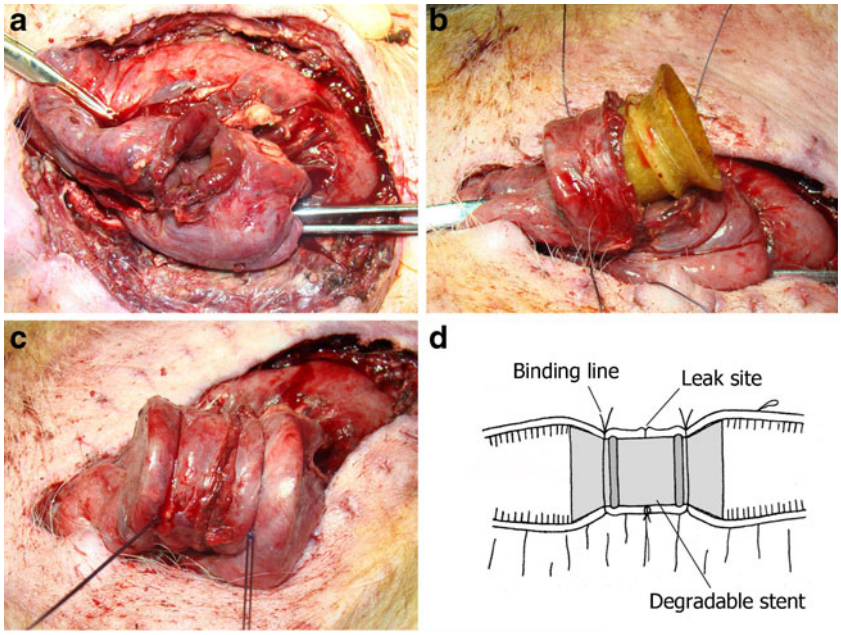

Fig. 5 **a** The necrotic tissue around leakage was incised and some sutures were removed to enlarge the leak. **b** A stent was placed in the colonic lumen. **c** The colon was bound to the stent. **d** Overview of the repair of anastomotic leakage with degradable stent

No re-leakage, anastomotic stricture, peritoneal abscess, or colonic necrosis occurred in the PR group after primary repair. A pig in the PR group was suspected intestinal obstruction for the greatly decreasing diet on postoperative day 8 and reoperation was performed to check the anastomosis. An abscess in proximal colonic wall about 6 cm to anastomosis formed which narrowed the lumen. No significant differences in the bursting pressure and hydroxyproline content were found between the PR and CA groups on postoperative days 7, 14, and month 10 (Table 1).

Stents remained at the site of anastomosis at reoperation on day 7 and day 14. Histopathologic observation of sections stained with hematoxylin and eosin or Masson's trichrome stain revealed that granulation tissue had formed in leak site on postoperative day 7 (Fig. 6). Stents and bind lines had disappeared at reoperation in postoperative month 10. The anastomosis healed well, and no signs of anastomotic hyperplasia were evident in any case.

Table 1 Results of hydroxyproline content and bursting pressure on postoperative days 7, 14, and month 10

	PR group	CA group	*P* value
Hydroxyproline content (mean, mg/g)			
Day 7	1.27	1.43	0.465
Day 14[a]	3.32	2.96	0.005
Month 10	1.07	0.80	0.222
Bursting pressure (mean, kPa)			
Day 7	27	25.4	0.834
Day 14[a]	59	55.6	0.834
Month 10	32.4	35.6	0.421

[a] One pig in PR group, reoperated on day 8 postoperatively for observing sign of gastrointestinal obstruction, was excluded

Discussion

Anastomotic leakage is one of the major complications of gastrointestinal surgery. Because of the high morbidity and mortality associated with anastomotic leakage, effective therapy is important. Repair or revision of the anastomosis without a protective enterostomy frequently results in failure of the procedure.[9] Two operations, fecal diversion and restoration of intestinal continuity, are generally required in these patients. The length of treatment is longer than 3 months and it carries a considerable financial cost. This article had advocates for a method of primary repair of colonic leakage by using a stent to patch the leak and support the anastomosis.

Because of the high re-leakage rate after repair or anastomosis in the environment of peritonitis with sepsis, the conventional method for colonic leakage includes fecal diversion and end-to-end colonic anastomosis to be performed several months after the operation of diversion. End-to-end colonic anastomosis in normal peritoneal environment is regarded as a safe technique and is widely used in colon surgery, so this method was evaluated by comparison with end-to-end colonic anastomosis which was performed in a normal peritoneal environment.

By using this method, the stent occupied the perianastomotic colonic lumen and provided a transit for resistance to intraluminal pressure, and supported the lumen to

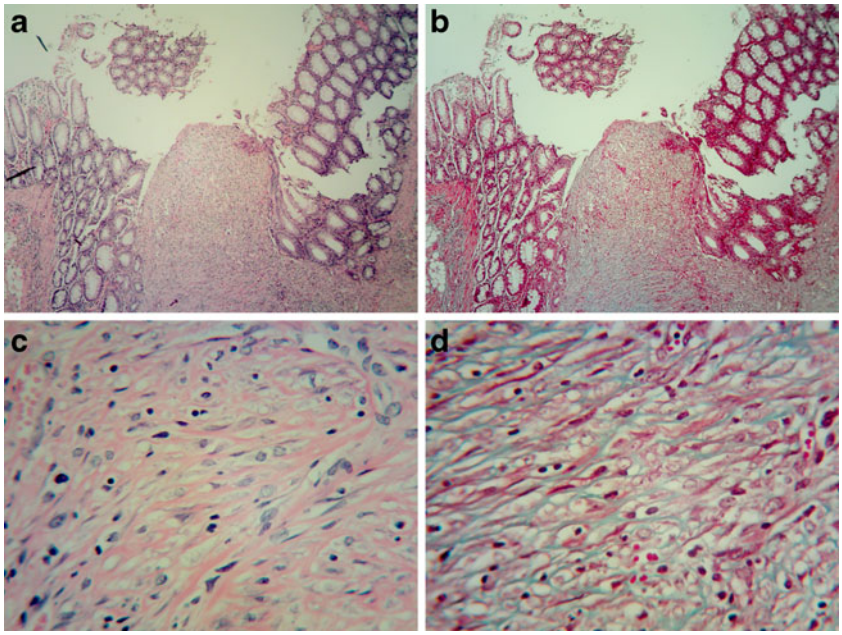

Fig. 6 Hematoxylin and eosin (*left*) and Masson's trichrome (*right*) stains in anastomosis of SA. **a**, **b** Granulation tissue formed (×40) and **c**, **d** collagen (×400) (stained green on slides of Masson's stain) formed in anastomosis on postoperative day 7

prevent anastomotic stricture during the phase of fibroplasia and maturation. The stent isolated the leak and abdominal cavity from colonic content, benefiting healing of the leak and recovery from peritonitis. So the negative presence of re-leakage and anastomosis stricture in PR group may in part be explained by insertion of the stent. In this study, two main indexes for evaluating gastrointestinal healing,[11] bursting pressure and hydroxyproline content, were used to evaluate this method, as well as the occurrence of complications. There is no significant difference in bursting pressure or hydroxyproline content between the PR and SA groups on postoperative days 7, 14, and month 10, and no re-leakage or anastomotic stricture was found in the PR group. The pig, which had intestinal obstruction, had an abscess in the proximal colonic wall about 6 cm to anastomosis that caused an obstruction, while the anastomosis supported by the stent healed well. The abscess node was supposed to be caused by the insufficient clearance of feces in peritoneal cavity during the procedure of repairing leakage. Stent-related obstruction, volvulus, intussusception, and colonic necrosis, were not observed in the PR group. These results indicate that this is a feasible method for repairing colonic leakage, and the strength of anastomosis repaired using this method is even close to the normal colonic anastomosis constructed using traditional hand-sewn method[12] according to the result of bursting pressure.

There is no pig that died during the period of anastomotic leakage while pigs dying had been observed during the period of colonic perforation (<72 h) in the study of primary repair of colon perforation. That may partly be explained by the intestinal preparation before making anastomotic leakage, postoperative fasting of 24 h, and administration of cefazolin sodium which were used to partly imitate a clinical anastomosis leakage. Two pigs were excluded for unsuccessful leakage model according to criteria of leakage mentioned in the part of methods. One pig had adhesion of anastomosis to adjacent abdominal wall and greater omentum that closed the leak, and in the other pig, a fistula between leak and incision had formed and no sign of severe intraabdominal inflammation was observed. Ischemic anastomosis had not been observed in leakage model which is another major cause for anastomosis leakage clinically as well as faulty suture technique, and primary repair in leakage due to ischemic anastomosis would be further studied.

The binding maneuver is the key to this method and two points should be emphasized. Firstly, binding site should have been located in normal colon wall avoiding the inflammatory tissue near leakage; secondly, mesenteric vessels between two binding lines should be conserved to secure a good blood supply to anastomosis. It may be concerned that whether the binding lines would cut the colon wall and further induce colon rupture. As a result of microscopic observation, binding line will induce a gradual atrophy of the intestinal wall and simultaneous hyperplasia of fibrous tissue in the binding site was also observed that made up for the loss of colon wall and maintain intestinal integrity. The line would be absorbed and deposited collagen would be remolded finally, so the binding site could not identified by the evaluation at 10 months.

Conclusions

These results suggested that primary repair of colonic leakage with a degradable stent is a feasible method in a porcine model, and further studies should be done before the method is used clinically.

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ORIGINAL ARTICLE

Roles of VEGF-C and Smad4 in the Lymphangiogenesis, Lymphatic Metastasis, and Prognosis in Colon Cancer

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Abstract
Background/Aims We combined two different signal pathways on transforming growth factor β1 (TGF-β1)-Smad and vascular endothelial growth factor C (VEGF-C)/VEGF receptors for exploring changes in pathway members and their influence on lymphangiogenesis and clinicopathological features.
Materials and Methods Expression of TGF-β1, TGF-βRII, Smad4, VEGF-C, and VEGFR-3 was immunohistochemically evaluated in 147 colon cancer patients who were followed up for 5 years.
Results Lymphatic vessel density in colon cancer tissues was significantly higher than in normal colonic tissues. Smad4 expression negatively correlated with lymphatic vessel count and VEGF-C expression. VEGF-C expression positively correlated with lymphatic vessel count. Analysis using the Kaplan–Meier method indicated that patients with VEGF-C-positive tumors had significantly shorter overall survival and tumor-free survival time than those with VEGF-C-negative tumors. Patients with Smad4-negative tumors had significantly shorter overall survival and tumor-free survival time than those with Smad4-positive tumors.
Conclusions Both Smad4 and VEGF-C are involved in lymphangiogenesis and lymphatic metastasis. Smad4 and VEGF-C expression may be clinically useful indicators for prognostic evaluation in colon cancer patients.

Keywords VEGF-C · Smad4 · Lymphangiogenesis · Colon cancer

Introduction

Colon cancer is one of the most common forms of gastrointestinal malignancies. Although it may spread in a variety of ways, lymphatic vessel invasion and lymphatic metastasis are common in the early stages. Previous studies have shown that vascular endothelial growth factor (VEGF) family members and their receptors (VEGFR) play crucial roles in lymphangiogenesis and lymphatic metastasis of colon cancers. The VEGF-C/VEGFR3 signaling system is regarded as the most efficient pathway in regulating lymphangiogenesis. VEGF-C secreted by tumor cells can specifically act on receptor VEGFR-3 at the surface of lymphatic endothelial cells, thus activating the signaling system for tumor lymphangiogenesis. VEGF-C overexpression in breast cancer cells increases intra-tumoral lymphangiogenesis, resulting in significantly enhanced metastasis in regional lymph nodes.[1] VEGF-C and VEGFR-3 are more frequently expressed in gastric carcinoma tissues than in normal gastric tissues, indicating that the expressions of VEGF-C and VEGFR-3 are associated with lymphangiogenesis, lymph node metastasis, and prognosis.[2] Inhibition of VEGF-C expression using siRNA-mediated gene silencing vectors can reduce lymphangiogenesis and lymph node metastasis, and thus improve survival.[3] All these studies confirmed that VEGF-C/VEGFR-3 signaling plays a key role in tumor lymphangiogenesis and lymphatic metastasis.

Recent studies also demonstrated that the transforming growth factor β1 (TGF-β1)-Smad signaling pathway is

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involved in the progression and prognosis of colon cancer. TGF-β1, a multi-functional cellular factor, can regulate the growth, differentiation, migration, adhesion, and apoptosis of various cells by binding to its receptor I (TβR-I) and II (TβR-II).[4] Following TGF-β1 binding to TβR-II, TβR-II activates TβR-I via phosphorylation. TβR-I then activates Smad2/3 via re-phosphorylation. Smad2/3 and Smad4 then form a heterogeneous complex, which enters cell nuclei and regulates the transcription of TGF-β target genes.

TGF-β1 suppresses the growth of normal colorectal epithelial cells by inhibiting cell proliferation and promoting apoptosis. However, many tumors (including colon cancer) can tolerate TGF-β1-induced growth suppression, while an excessively high dose of TGF-β1 can even facilitate the invasion and metastasis of tumor cells and stromal cells. Smad4, a tumor suppressor gene, is central in the TGF-β1 signal transduction pathway. It suppresses progression and metastasis of colon cancer cells and tumors in mice.[5] Inactivation or mutation of Smad4 may cause TGF-β1 to lose its ability to suppress carcinoma progression.[6] In human tumor cells, the overexpression of Smad4 may recover the functions of TGF-β1 as a signaling molecule and its effects in inducing apoptosis and inhibiting proliferation. Colon cancer patients with low Smad4 expression had a mean survival period of 1.4 years, while patients with high Smad4 had survival time that was 9.3% higher; thus, patients with low Smad4 expression tended to have poorer prognosis. [7] Patients in Duke's stages B and C/D had significantly reduced expression of Smad4 compared with patients in stage A ($P<0.05$), and patients with poorly or moderately differentiated colon cancer had significantly decreased expression of Smad4 compared with those with highly differentiated tumors ($P<0.05$), indicating that the abnormal expression of Smad4 (mutation or decrease in amount) is associated with the level of differentiation and Duke's stage of tumors.[8]

Most previous studies on the lymphangiogenesis and prognosis of colon cancer focused on a single signaling pathway (either TGF-β1-Smad or VEGF-C/VEGFR-3). In this study, by combining these two pathways, we attempted to explore the changes to pathway members and their influences on tumor grading, lymphangiogenesis, lymph node metastasis, and prognosis.

Materials and Methods

Patients

A series of 147 colon cancer patients, who were treated in Harbin Medical University Clinical Hospital (Harbin, China) from March 2003 to March 2004, were enrolled in this study. Specimens were obtained during tumor resection. The patients' characteristics, including tumor location and stage, are shown in Table 1. Formal consent was obtained from patients and approval of the study from the ethics committee. All patients were naive to radiotherapy and chemotherapy before surgery.

Immunohistochemical Analysis

Paraffin-embedded sections (4 μm thick) were deparaffinized with xylene and rehydrated in decreasing concentrations of ethanol. Sections were then incubated with 3% H_2O_2 for 30 min at room temperature. The slides were immersed in 0.01 M citrate buffer (pH 6.0) for 10 min for antigen retrieval and then immersed in phosphate-buffered saline (PBS) containing 15% goat serum. The primary antibodies were rabbit anti-human VEGF-C polyclonal antibody, 1:200 (Zhongshan Biotechnology Inc, Beijing, China), rabbit anti-human VEGFR-3 polyclonal antibody, 1:200 (Abcam), mouse anti-human D2-40 monoclonal antibody, 1:75 (Zhongshan Biotechnology Inc.), rabbit anti-human TGF-β1 polyclonal antibody, 1:200 (Zhongshan Biotechnology Inc.), mouse anti-human Smad4 monoclonal antibody, 1:150 (Zhongshan Biotechnology Inc.), and rabbit anti-human TβRII polyclonal antibody,1:200 (Abcam). After rinsing with PBS, secondary antibodies were added (goat anti-rabbit polymerized HRP-labeled secondary antibody or goat anti-mouse IgG secondary antibody) (Zhongshan Biotechnology Inc.), and the slides placed in a thermostatic water bath at 37°C for 30 min. After rinsing with PBS, the samples were counterstained using diaminobenzidine.

Table 1 Patient characteristics

		Number
Gender	Men	86
	Women	61
Age (24–87)	<40	25
	≥40	122
Location	Sigmoid colon	81
	Ascending colon	22
	Transverse colon	26
	Descending colon	18
Lymph node metastasis	Yes	92
	No	55
Duke's stage	A/B	50
	C/D	97
Adjuvant chemotherapy[a]	Received	113
	Did not receive	34

[a] Chemotherapy was primarily fluorouracil-based with or without levamisole or leucovorin.

Interpretation of Immunohistochemical Results

For each pathological section, ten visual fields (under a high-power microscope (×400)) were randomly selected and independently evaluated by two pathologists who were blind to the patients' clinicopathological data, to determine the staining results and lymphatic vessel density.

An immunohistochemical finding was judged to be positive when the cytoplasm, cell membrane (TβR II), or nucleus (Smad4) was clearly stained brown or yellow. When more than 10% of tumor cells were positively stained in each section, the section was judged to be positive. VEGFR-3 can also be stained inside endothelial cells; a section with >5% positively stained endothelial cells was also judged to be positive.

Antibody D2-40 was used to detect lymphatic vessels: three visual fields were randomly selected in each tumor section (under a microscope (×200)) to determine the mean lymphatic vessel count, which allowed calculation of the lymphatic vessel density.

Statistical Analysis

Each assay was repeated at least twice, and the results were analyzed with SPSS software. Data were expressed as mean±SD, and the means were compared with a chi-square test. The correlations among different factors were analyzed with Pearson's test. Indicators related to the prognosis of colon cancer were screened using Cox's proportional hazards models. Survival was analyzed by the Kaplan–Meier method. A value of $P<0.05$ was considered statistically significant.

Results

Relationship Between D2-40 Expression in Colon Cancer Tissue, Lymphatic Vessel Density Inside Colon Cancer Tissue, and Clinicopathological Parameters

D2-40 was selected as a lymphatic endothelial cell marker to calculate lymphatic vessel density (LVD). Immunohistochemistry showed that D2-40 was expressed in the cell membrane and cytoplasm of lymphatic endothelial cells (Fig. 1a). LVD was 4.38±1.50 vessels/visual field (vessels/VF) in normal colonic tissue and 9.75±2.75 vessels/VF in colon cancer tissues (Table 2). The analysis of the relationship between LVD in colon cancer tissue and clinicopathological parameters in these 147 patients showed that LVD was significantly higher in VEGF-C-positive patients than in VEGF-C-negative patients (11.27±1.94 vessels/VF vs. 7.22±1.95 vessels/VF; $P<0.05$). Patients in Duke's C/D stages had significantly higher LVD than those in A/B stages (10.39±2.56 vessels/VF vs. 8.51±2.71 vessels/VF, $P<0.05$). Smad4-positive patients had significantly higher LVD (8.03±2.24 vessels/VF) than Smad4-negative patients (11.59±1.94 vessels/VF; $P<0.05$). LVD was inversely correlated with Smad4 expression. However, it showed no correlation with TGF-β1 expression. Patients with lymph node metastasis showed significant higher LVD than those without lymph node metastasis (10.49±2.55 vessels/VF vs. 8.53±2.66 vessels/VF, $P<0.05$). Lymph node metastasis was positively correlated with VEGF-C expression and inversely with Smad4 expression (Table 3).

Relationship Between the Expressions of TGF-β1, TβR II, and Smad4 and Clinicopathological Parameters

TGF-β1 was mainly expressed in the cytoplasm of tumor cells; brown-yellow granules could be observed in both cancer cells and cancer nests (Fig. 1b). A small amount of TGF-β1 was also expressed in the inflammatory stromal cells surrounding these tumors; the positive cells were distributed either diffusely or locally. TGF-β1 was expressed in 58.50% (86/147) of normal colon tissue and in 69.39% (102/147) of colon cancer tissue (Table 2). TGF-β1 expression was not associated with any clinicopathological parameter.

Positive staining of TβR-II was found at the membrane and in the cytoplasm of tumor cells (Fig. 1c), with an expression frequency of 48.98% (72/147); it was not associated with any other factor and nor any clinicopathological parameters.

The Smad4-positive granules were stained dark brown. They were expressed in the cytoplasm and nucleus of both colon cancer cells (Fig. 1d) and normal colon epithelial cells. Smad4 expression heterogeneity was observed in tumor. Smad4 was expressed in 74.15% (109/147) of normal colon samples and in 51.70% (76/147) of colon cancer tissues. Smad4 expression showed a negative correlation with lymphatic vessel count, lymph node metastasis (Table 3), VEGF-C expression, and VEGFR-3 expression (Table 4). Patients in Duke's C/D stages tended to have significantly lower Smad4 expression than those in A/B stages; however, Smad4 expression was not correlated with the expressions of TGF-β1 and TβR II (Table 4).

Expressions of VEGF-C/VEGFR-3 in Colon Cancers and Their Relationship with Clinicopathological Parameters

The VEGF-C-positive signal, presented as brown/egg-yellow granules, was expressed in the cytoplasm of colon cancer cells (Fig. 1e). Tumor VEGF-C expression was heterogeneous. Of colon cancer samples, 62.59% (92/147) were positive for VEGF-C; by contrast, only 38.10% (56/147) of normal colon tissues were positive (Table 2).

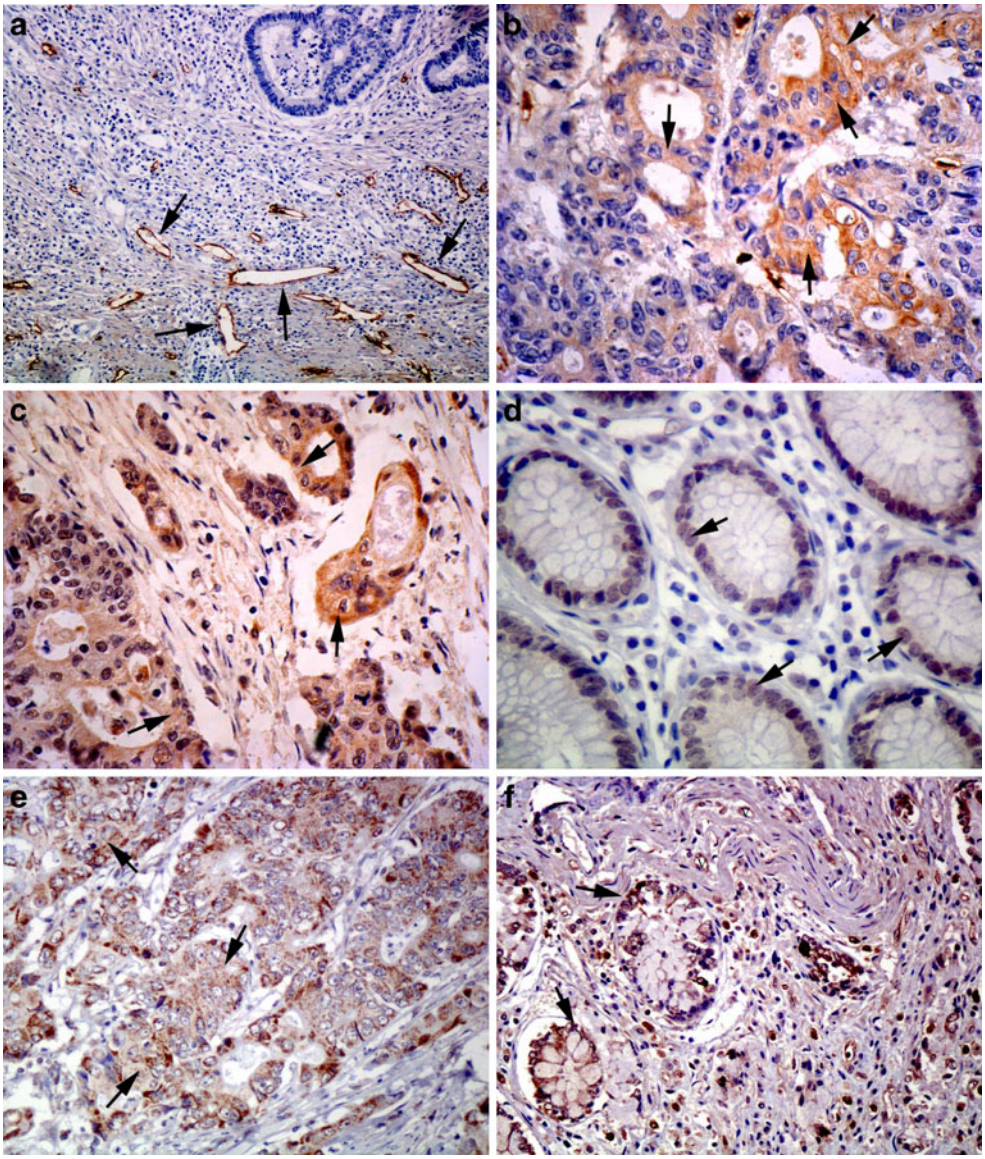

Fig. 1 Immunihistochemical staining of various factors in colon cancer. **a** Detection of lymphatic vessels with D2-40 (*arrow*). **b** Focal expression of TGF-β1 in the cytoplasm of colon cancer cells in tumor nests (*arrow*). **c** Focal expression of TβR-II in the cytoplasm of colon cancer cells in tumor nests (*arrow*). **d** Smad4 expressed in the cytoplasm and nucleu of colon cancer cells (*arrow*). **e** VEGF-C expressed in the cytoplasm of colon cancer cells (*arrow*). **f** VEGFR-3 expressed in the cytoplasm of colon cancer cells in tumor nests (*arrow*) and microvessel endothelium (*V*). Original magnifications: ×100 in (**a**), ×200 in (**b**–**d** and **f**), and ×400 in (**e**)

VEGF-C expression showed positive correlation with lymphatic vessel count, lymph node metastasis, VEGFR-3 expression, and Duke's stages. It was inversely correlated with Smad4 expression and showed no correlation with the expression of TGF-β1 or TβR II (Table 5).

VEGFR-3 protein was expressed in the cytoplasm of colon cancer tissue and the blood vessels and lymphatic endothelial cells surrounding cancer nests (Fig. 1f), with a frequency of 57.82% (85/147). VEGFR-3 expression was positively correlated with VEGF-C expression.

Table 2 Comparison of VEGF-C expression, LVD, TGF-β1 expression, and Smad4 expression between normal colon tissue and colon cancer tissue

		Normal tissue	Cancer tissue	*P*
VEGF-C expression	+	56	92	<0.001
	–	91	55	
LVD values		4.38±1.50	9.75±2.75	<0.001
TGF-β1	+	86	104	0.028
	–	61	43	
Smad4	+	109	76	<0.001
	–	38	71	

Table 3 Relationship between LVD value/lymph node metastasis and clinicopathological parameters

		LVD values	*P*	Lymph node metastasis		*P*	*R*
				Yes	No		
TGF-β1	+	9.73±2.72	0.893	63	41	0.434	
	−	9.80±2.87		29	14		
TβR II	+	9.86±2.36	0.648	50	22	0.081	
	−	9.65±3.10		42	33		
Smad4	+	8.03±2.24	<0.001	38	54	0.001	−0.269
	−	11.59±1.94		38	17		
VEGF-C	+	11.27±1.94	<0.001	72	20	0.001	−0.419
	−	7.22±1.95		20	35		
VEGFR-3	+	10.53±2.56	<0.001				
	−	8.66±2.66					
Duke's stage	C/D	10.39±2.56	<0.001				
	A/B	8.51±2.71					

Relationship Between VEGF-C/Smad4 Expressions and Survival

Univariate analysis of the overall survival rate showed six statistically significant variables: VEGF-C, VEGFR-3, Smad4, lymphatic vessel count, lymph node metastasis, and Duke's stage. Univariate analysis also showed that the tumor-free survival rate was consistent with overall survival rate in terms of statistically significant variables. Multivariate analysis showed that VEGF-C and Smad4 expressions were independent prognostic factors of overall survival rate and tumor-free survival rate (Tables 6 and 7).

Analysis using Kaplan–Meier method showed that patients with VEGF-C-positive tumors had significantly shorter overall survival and tumor-free survival than those with VEGF-C-negative tumors (Fig. 2a). Patients with Smad4-negative tumors had significantly shorter overall survival and tumor-free survival than those with Smad4-positive tumors (Fig. 2b).

To predict the outcomes of the colon cancers more precisely, we divided the patients into three risk groups based on the combination of VEGF-C and Smad4 expressions: a high-risk group (n=66), in which patients had VEGF-C-positive and Smad4-negative tumors; a medium-risk group (n=31), in which patients had VEGF-C-positive and Smad4-positive tumors or had VEGF-C-negative and Smad4-negative tumors; and a low-risk group (n=50), in which patients had VEGF-C-negative and Smad4-positive tumors. Analysis using the Kaplan–Meier method showed that the survival time was significantly shorter in the high-risk group than in the other two groups, and was significantly longer in the low-risk group. The survival time in the medium-risk group was between those of the high-risk group and the low-risk group, and pairwise comparison showed all the *P* values were less than 0.001 (Fig. 3).

Table 4 Relationship between Smad4 expression and clinicopathological parameters

		Smad4 (+)	Smad4 (−)	*P*	*R*
TGF-β1	+	58	46	0.125	
	−	18	25		
TβR II	+	40	32	0.359	
	−	36	39		
VEGFR-3	+	36	50	0.005	−0.234
	−	40	21		
Duke's stage	CD	40	57	<0.001	−0.292
	AB	36	14		

Discussion

Relationship Between VEGF-C Expression and Tumor Lymphangiogenesis/Lymphatic Metastasis

Colon cancer is the third most frequently diagnosed cancer and the second leading cause of cancer deaths in the USA, accounting for more than 50,000 cancer deaths per year.[9] However, factors that regulate its metastasis and prognosis remain controversial. Lymphangiogenesis is a main pathway of tumor invasion and metastasis, and also an important factor that influences tumor growth. VEGF-C is closely related to lymphangiogenesis and also plays a key role in tumor lymphatic metastases. Duff et al. found that the lymphatic vessel count is larger in colon cancer tissue than in normal colonic mucous membrane; at the invading tumor edge with high VEGF-C expression, LVD was even higher. By promoting tumor lymphangiogenesis or by activation of pre-existing lymphatic vessels, high VEGF-C expression enhanced lymphatic metastasis.[10] The amount of lymph node metastasis in VEGF-C-positive patients was significantly higher than that in the negative patients.[11]

Table 5 Relationship between VEGF-C expression and clinicopathological parameters

		VEGF-C (+)	VEGF-C (−)	*P*	*R*
VEGFR-3	+	65	21	<0.001	0.319
	−	27	34		
TGF-β1	+	65	39	0.974	
	−	27	16		
TβRII	+	49	23	0.179	
	−	43	32		
Smad4	+	26	50	<0.001	−0.607
	−	66	5		
Duke's stage	C/D	74	23	<0.001	0.394
	A/B	18	32		

VEGF-C expression was more frequently observed in tumors with nodal metastasis. Moreover, multivariate analysis indicated that VEGF-C expression is an independent predictor of lymph node metastasis.[12] Our research demonstrated that VEGF-C expression was significantly higher in colon cancer tissue than in normal colonic mucous membrane. VEGF-C expression showed a positive correlation with lymphatic vessel count, lymph node metastasis, VEGFR-3 expression, and Duke's stages. However, other studies argued that VEGF-C expression did not increase in tumor tissues, and it was not significantly correlated with the lymph node metastasis. According to Gunningham et al., no significant difference in VEGF-C expression was observed between normal and neoplastic breast tissues. In addition, no association was seen between VEGF-C and either tumor size, tumor grade, or lymph node metastasis.[13] Kazama et al. found that the expression of VEGF-C was significantly correlated with lymphatic involvement, lymph node metastasis, and tumor size but not with venous involvement, liver metastasis, or overall survival rate.[14] These different conclusions may be explained by the presumption that the tumors are located at different sites with different histological features, and that the precursor proteins of VEGF-C secreted by these tumors had different proteolysis levels.

Relationship Between Smad4 Expression and Tumor Lymphangiogenesis/Lymphatic Metastasis

The TGF-β1 signaling pathway is central in tumor angiogenesis; however, little research has been conducted on the roles of the members of this pathway in lymphangiogenesis. TGF-beta inhibited the expressions of lymphatic endothelial cell (LEC) markers, including LYVE-1 and Prox1, in human dermal lymphatic microvascular endothelial cells (HDLECs) and inhibited the migration and cord formation of HDLECs. Moreover, inhibition of endogenous TGF-beta signaling accelerated lymphangiogenesis in a mouse model of chronic peritonitis. Lymphangiogenesis was also induced in pancreatic adenocarcinoma xenograft models inoculated in nude mice.[15] The inhibition of TGF-β1 expression significantly accelerates lymphatic regeneration during wound healing. Increased

Table 6 Analysis of overall survival rate using the Cox's model

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*P*	Hazard ratio	95%CI	*P*
Age	1.404	0.778–2.533	0.260			
Gender	0.930	0.611–1.416	0.736			
Location	0.813	0.535–1.236	0.332			
VEGF-C expression	6.147	3.801–9.940	<0.001	3.038	1.709–5.400	<0.001
VEGFR3 expression	2.112	1.367–3.264	0.001	1.087	0.662–1.783	0.742
Lymph node metastasis	2.587	1.639–4.084	<0.001	1.386	0.307–6.246	0.671
TGF-β1 expression	0.748	0.480–1.164	0.198			
TβR-II expression	0.734	0.481–1.121	0.153			
Smad4 expression	0.106	0.064–1.176	<0.001	0.142	0.078–0.258	<0.001
LVD values	2.967	1.919–4.587	<0.001	1.536	0.924–2.552	0.098
Duke's stage	2.489	1.563–3.964	<0.001	1.384	0.311–6.162	0.670
Adjuvant chemotherapy	1.393	0.880–2.206	0.157			

Table 7 Analysis of disease-free survival rate using the Cox's model

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age	1.376	0.841–2.251	0.204			
Gender	1.024	0.853–1.231	0.797			
Location	0.896	0.622–1.292	0.557			
VEGF-C expression	5.196	3.348–8.064	<0.001	2.603	1.521–4.454	<0.001
VEGFR3 expression	2.139	1.456–3.143	<0.001	1.401	0.932–2.105	0.105
Lymph node metastasis	2.373	1.588–3.548	<0.001	1.214	0.361–4.081	0.754
TGF-β1 expression	0.813	0.551–1.200	0.297			
TβR-II expression	0.768	0.533–1.107	0.157			
Smad4 expression	0.200	0.135–0.297	<0.001	0.355	0.227–0.556	<0.001
LVD values	2.513	1.720–3.672	<0.001	1.211	0.794–1.846	0.374
Duke's stage	2.299	1.522–3.474	<0.001	1.108	0.325–3.774	0.870
Adjuvant chemotherapy	1.455	0.921–2.298	0.108			

TGF-β1 expression inhibits LEC proliferation and tubule formation without changes in the expression of VEGF-C/D, which may be achieved by changing the expression of VEGF receptors or by other mechanisms.[16] Many studies have assessed the relationship between Smad4 and the expression of VEGF-A and angiogenesis. Smad4 suppresses human ovarian cancer cell metastasis, potential through its effect on the expressions of PAI-1, E-cadherin, and VEGF.[17] In vitro experiments showed that Smad4-mediated suppression of angiogenic activity was exerted through two mechanisms: reduction of the major angiogenesis inducer VEGF and induction of the angiogenesis inhibitor TSP-1. In vivo experiments showed that, in nude mice transplanted with Smad4-positive human pancreatic carcinoma cells, the numbers of capillaries were slightly reduced, and densities of medium-sized and large vessels were significantly reduced to 68% and 50% of controls, respectively. Thus, Smad4's effects on VEGF and TSP-1 expression may contribute to reduced tumor growth through diminished vascular supply.[18] Ke et al. noted that Smad4 was expressed at a higher level in a group with tumor lymph node metastasis than in a group without lymph node metastasis.[19] However, few studies have focused on the relationship between Smad4 expression and VEGF-C expression and lymphangiogenesis. Our study found that Smad4-positive colon cancer tissues had smaller LVD and fewer lymph node metastases. Meanwhile, Smad4 expression was inversely correlated with VEGF-C expression. Both VEGF-C and VEGF-A belong to VEGF family, and have highly similar tertiary structures. It is, therefore, presumed that Smad4 may affect the shared promoter of

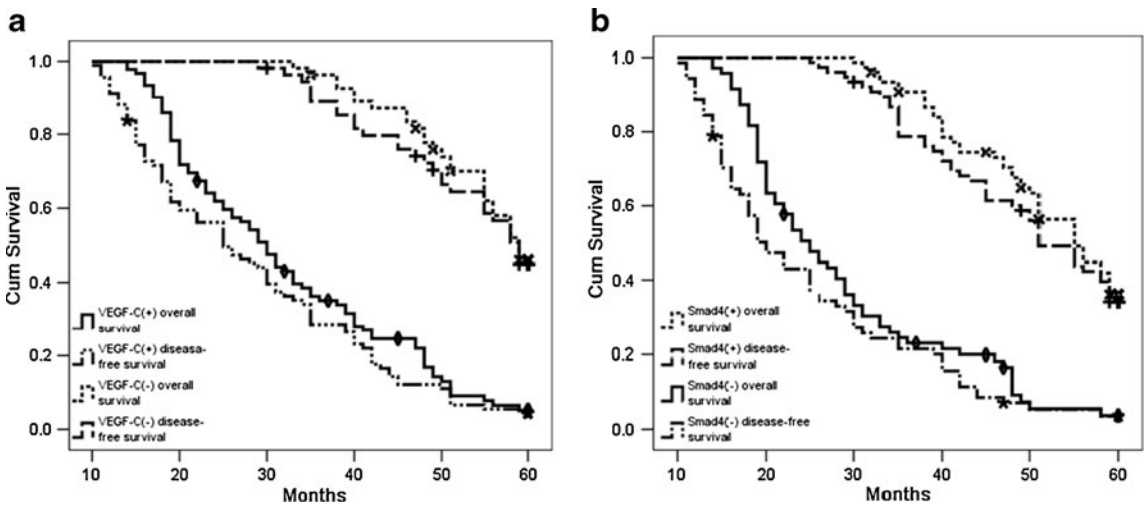

Fig. 2 Kaplan–Meier survival analysis for disease-specific overall survival and disease-free survival depending on VEGF-C expression (**a**) or Smad4 expression (**b**)

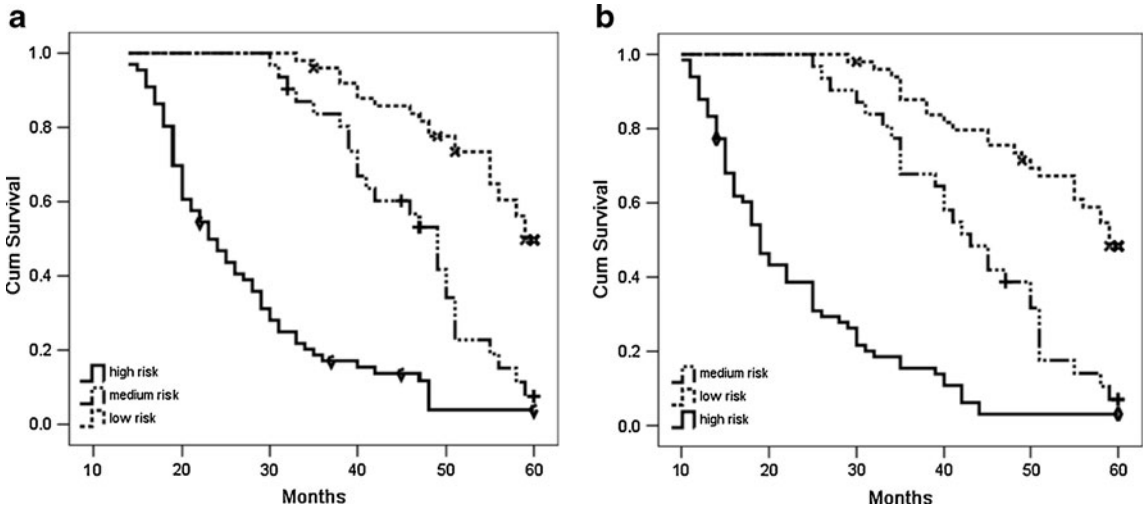

Fig. 3 Disease-specific overall survival (**a**) and disease-free survival (**b**) in risk group

VEGF-C and VEGF-A, and thus further influence lymphangiogenesis and lymphatic metastasis by regulating VEGF-C expression; however, a more detailed analysis of this mechanism requires further research.

Roles of VEGF-C and Smad4 in the Prognosis of Colon Cancer

The neogenesis of blood and lymphatic vessels can be observed in peri-tumor tissues in patients with sporadic colorectal cancer. LVD and microvascular density could be used to predict the metastasis and prognosis of colorectal cancer.[20] Similar findings were also obtained for other tumors, including gastric cancer,[21] melanoma of ciliary body,[22] bladder cancer,[23] non-small-cell lung carcinoma,[24] endometrial adenocarcinoma,[25], and ovarian cancer.[26] Interestingly, our previous study on melanoma of the ciliary body found that lymphangiogenesis was correlated with lymph node metastasis but was not an independent prognostic factor.[27] Similar results were obtained in the present study: despite the fact that neogenesis of lymphatic vessels is found in colon cancer, the LVD was higher in colon cancer than in normal colon tissue. In addition, LVD was positively correlated with lymph node metastasis, but lymphangiogenesis was not correlated with survival rate. In fact, all these studies confirmed the presence of lymphangiogenesis in cancer tissues, while its relationship with clinicopathological parameters remained controversial, which may be due to the difference in LVD measurement methods among different centers. Therefore, it is essential to define a standardized LVD-measuring method.

As shown by previous studies, VEGF-C expression increased in ovarian cancer, it was also related to the prognosis of ovarian cancer, and therefore can be a new indicator for evaluating the prognosis of ovarian cancer.[28] Of the 73 esophageal squamous cell carcinomas patients studied by Liu et al.,[29] the median overall survival of 39 patients who had positive staining for tumor cell VEGF-C and 34 patients who had negative staining were 10.4 and 28.5 months,

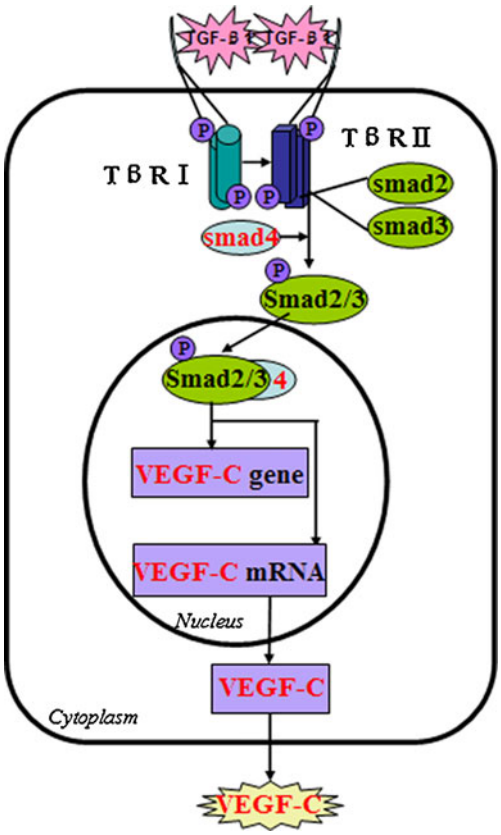

Fig. 4 Proposed mechanism by which Smad4 inhibits expression of VEGF-C in colon cancer. Upon being stimulated by TGF-β1, Smad2/3 becomes phosphorylated by the activated TGF-β receptors and forms a complex with Smad4. This Smad4 translocates into the nucleus, where it affects transcription of the VEGF-C gene

respectively. In multivariate analysis by log-rank test, high VEGF-C expression maintained its independent prognostic influence on overall survival. In patients with adenocarcinoma of the esophagus, there was no correlation between VEGF-C expression and clinicopathological parameters.[30] Similarly, Gou et al. found that VEGF-C expression was not associated with any clinicopathological parameters in 56 patients with gastric adenocarcinoma.[31] However, few studies have reported a relationship between VEGF-C expression and the prognosis of colon cancer. As shown in this study, patients with VEGF-C-positive colon cancer tended to have a lower 5-year survival rate than those with VEGF-C-negative colon cancer; in other words, VEGF-C-positive colon cancer had poorer prognosis. The different findings among different studies may have been influenced by the histological features of tumors and the sample size.

In colon cancers, the tumor suppressor gene Smad4 is located at chromosome 18q21.1. Smad4 gene inactivation was observed in about 30% of invasive colorectal cancers. Patients with Smad4 gene inactivation had shorter survival than those without Smad4 inactivation. Smad4 gene inactivation is associated with poorer prognosis.[32–35] Of 135 patients analyzed by Mesker et al., significant differences in survival rates were observed between the Smad4-positive and Smad4-negative groups: the 5-year survival rate was 7.1% in stroma-high/Smad4-negative group and 80.3% in stroma-high/Smad4-positive group. A high proportion of stroma and Smad4 loss were strongly predictive of poor prognosis.[36] In our study, patients with low Smad4 expression had lower overall survival and tumor-free survival than those with Smad4-positive tumors; however, TβRII expression was not correlated with the prognosis of colon cancer patients. The TGF-β1 signaling pathway has both canonical Smad-dependent pathway and non-Smad-dependent pathways. Our study showed that Smad4 is one of the prognostic factors of colon cancer, and thus further demonstrated the role of the canonical Smad-dependent pathway in colon cancers. However, the effects of the downstream members of this signaling pathway on the prognosis of colon cancer require further research.

Conclusions

Our study demonstrated that Smad4 expression showed a negative correlation with VEGF-C expression, as illustrated in Fig. 4. Expression of Smad4 and VEGF-C is closely correlated with tumor lymphangiogenesis and lymphatic spread to regional lymph node. Smad4 and VEGF-C expression may be clinically useful indicators for prognostic evaluation in patients with colon cancer. They are useful tools for the selection of postoperative management and treatment strategies.

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ORIGINAL ARTICLE

Laparoscopic Colectomy for Carcinoma of the Colon in Octogenarians

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Abstract
Background The incidence of colorectal cancer increases with age; most patients present with resectable disease. Since there is a high morbidity rate in the elderly, the laparoscopic approach, with its lower complication rate, appears to be the ideal choice for treatment of this patient group. In this retrospective study, we aimed to compare the short-term results of laparoscopic (LC) with open (OC) colectomies for carcinoma in patients 80 years of age or older.
Methods The study comprised 93 patients aged 80 years and over who underwent OC or LC between 2005 and 2008. Demographics and clinical data were compared.
Results The LC group included 47, and the OC included 46 patients. No differences were found between the two groups with regard to mean age, comorbidities, and the extent of the resection. The operative time was shorter in the OC (121 vs. 157 min, P=0.001). Hospital stay was shorter in the LC (7.6 vs. 8.8 days, P=0.06). There were more postoperative complications in the OC (35.6%) than in the LC (30.4%), however the difference was not statistically significant (P=0.6).
Conclusions LC in the elderly is safe, with a shorter hospital stay, and carries a short-term benefit for selected patients and could be offered to all elderly patients.

Keywords Colon cancer · Elderly · Laparoscopic colectomy

Introduction

The number of elderly patients in western countries is increasing, along with high incidence of surgically resectable colorectal cancer. In fact approximately 50% of colorectal cancer patients are older than 70 years of age, and in this age group, colorectal cancer is the second most common cause of cancer death.[1,2] Associated comorbidities are mainly responsible for the high postoperative morbidity and mortality rates in elderly patients, especially those aged 80 years or older. Many randomized controlled trials showed that laparoscopic surgery for colon cancer is feasible and safe and has many short-term advantages.[3,4]

The benefits of laparoscopic surgery in comparison with open surgery are decreased morbidity, decreased pain, faster recovery, shorter hospital stay, and possibly reduced immunosuppression.[5] Therefore the laparoscopic approach appears to be the better choice for elderly patients. The aim of this retrospective study was to evaluate the early outcome first 30 postoperative days of patients 80 years old or more who underwent laparoscopic colectomy for cancer, compared with open surgery.

Patients and Methods

The study included patients 80 years old or more who underwent open or laparoscopic colonic resection for colon carcinoma between 2005 and 2008 in the surgery department B, Hasharon Hospital. The full medical records were obtained and collectively reviewed.

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The study excluded patients who were operated on for nonneoplastic colonic lesions, patients with rectal tumors (tumors below 12 cm from the anal verge), and patients with incomplete data. Patients with contraindication to laparoscopy (patients who required emergency operations for perforated or obstructed colonic cancer, and patients who presented with tumor invasion to the abdominal wall or adjacent organs) were also excluded.

All laparoscopic procedures were performed by the same laparoscopic surgeon. The selection of surgical procedure was based on the availability of the laparoscopic surgeon rather than randomization. The preoperative preparation for the patients included mechanical bowel preparation (polyethelene glycol) the day before the operation and prophylactic antibiotics (cefamizine 1 g and metronidazole 500 mg) on the induction of general anesthesia.

Data on patients' demographics and comorbidities were collected. Data of the surgical procedure that were collected included the method of procedure (laparoscopic or open), the type of resection performed, the duration of operation, the rate of conversion from laparoscopic to open procedure, tumor location, and the number of lymph nodes collected in the specimen. Postoperative pain management for all patients included parenteral narcotics (morphine or tramadol) and dypirone or paracetamol administrated orally.

Oral intake of liquid diet of all patients was recorded starting on the morning after surgery for 24 h and subsequently advanced to soft diet. No specific "fast-track" recovery program was applied. Bowel function postoperatively was evaluated with respect to first flatus and bowel movement. Patients were discharged when oral diet was well accepted and no complications were detected. Postoperative complications were defined as general complications (cardiopulmonary, urinary tract infection) or those related to the surgery (wound infection, ileus, intra-abdominal collection or hemorrhage, and anastomotic leak). Operative mortality is defined as postoperative death that occurred within 30 days after surgery. The patients were analyzed as two separate groups according to the procedure: the open colectomy (OC) group and the laparoscopic colectomy (LC) group. The local ethics committee of Rabin Medical Center approved the study protocol and the data collection.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Science software (SPSS Inc. Chicago, IL, USA). The Pearson χ^2 test, Fisher's exact test, and Student t test for equality of means were used when appropriate. Significance was evaluated at the 0.05 level.

Table 1 Demographic characteristics

Variable	OC	LC	*P* value
Number of patients	46	47	–
Age (year)	82.9±2.9	83.6±3.6	NS
Gender, M/F	24/22	25/22	NS
BMI (kg/m^2)	25.3±3.8	24.2±3.2	0.204
Comorbidities			
Ischemic heart disease	20 (43%)	17 (36%)	NS
Other malignancy	6 (13%)	5 (11%)	NS
Diabetes mellitus	21 (46%)	19 (40%)	NS
Chronic lung disease	3 (6.5%)	10 (21%)	0.070
ASA score			
I	3(6.5%)	2 (4.3%)	NS
II	15 (33%)	20 (42%)	NS
III	16 (37%)	19 (40%)	NS
IV	11 (24%)	6 (13%)	NS
Previous colectomy	3 (6.5%)	1 (2.1%)	NS

BMI body mass index, *ASA* American Society of Anesthesiology, *NS* not significant

Results

A total number of 93 patients aged 80 years or more were included in this study. There were 46 patients in the OC group and 47 in the LC group. The mean age was 82.9±2.9 in the LC group and 83.6±3.6 I n the OC group. The two groups were well matched for demographic data, and there were no significant differences in their BMI, comorbidities

Table 2 Operative variables

Variable	OC	LC	*P* value
Type of operation			
Right colectomy	26 (56%)	21 (45%)	NS
Left colectomy	5 (10%)	8 (17%)	NS
Sigmoidectomy	14 (30%)	18 (38%)	NS
Subtotal colectomy	1 (2.2%)	0	NS
Conversion	–	3 (6.3%)	–
Concomitant operations			
Cholecystectomy	2 (4.3%)	3 (6.3%)	NS
TEM	0	2 (4.3%)	NS
Mean operative time (min)	121±33	157±41	0.001
Tumor stage (AJCC)			
I	12 (26%)	17 (37%)	NS
II A	20 (43%)	12 (26%)	NS
III A	2 (4.3%)	2 (4.3%)	NS
III B	12 (26%)	16 (34%)	NS
Number of lymph nodes	11.6±3.8	10.9±4.2	0.237

TEM transanal endoscopic microsurgery, *AJCC* American Joint Committee on Cancer staging (seventh edition), *NS* not significant

Table 3 Number of cases per year

Year	OC	LC
2005	13	13
2006	11	10
2007	11	8
2008	11	16
Total	46	47

including ischemic heart diseases, other malignancy, diabetes, and chronic lung disease. Despite a slightly different distribution of the ASA classes between the two groups, it was statistically nonsignificant (Table 1). No difference was found with respect to tumor location and the preoperative tumor staging.

Table 2 shows the types of surgical resection carried out and the pathological tumor staging. There were no significant differences in the extent of resection and tumor staging between the OC and LC patients.

The number of lymph nodes examined was 11±3.8 in the OC group and 10.9±4.2 in the LC group (P=0.237). In both groups a negative proximal and distal surgical margin of the specimen was obtained. In two (4.3%) patients in the OC group and five (10.6%) patients in the LC group, concomitant operation was performed. Three patients in the laparoscopic group (6.3%) required conversion to open surgery because of adhesions in two of the patients and bleeding in the third. These patients remained in the laparoscopic group.

The mean operative time was significantly longer in the LC group (157±41 min) than the OC group (121±33 min, P<0.001). However, the operative times in the LC group decreased in the last 2 years. Table 3 shows the number of open and laparoscopic colon resection per year performed for octogenarians in the study period.

Patients in the LC group experienced an earlier first flatus (3.2±1.4 days) compared to the OC group (3.6±1.5 days); however, the difference was not statistically significant (P=0.361). Postoperative hospital stay for the LC group (7.6±3.1 days) was shorter than for the OC group (8.8±3.6 days); however, the difference did not reach a statistical significance (P=0.062). No significant difference was found between the two groups regarding the number of patients admitted to the intensive care unit during their hospital stay (Table 4).

Regarding the postoperative complications, there were more complications (general and surgical) in the OC group (35.6%) than in the LC group (30.4%). The difference, however, failed to reach statistical significance (P=0.659). Three patients in the OC group died in the postoperative period in contrast to one death in the LC group; however, this difference was not statistically significant (P=0.361).

Anastomotic leak was diagnosed in two patients in the OC group; they were reoperated. Both underwent laparotomy, drainage, and protective ileostomy. These two patients had multiorgan failure and died. A third patient died in the OC group because of respiratory failure.

Two patients in the LC group were reoperated. One, who had an anastomotic leak, underwent laparotomy, drainage, and protective ileostomy, and died after the intervention. The other had laparotomy and adhesiolysis 10 days postoperatively for small intestinal obstruction.

Of interest was a group of nine patients older than 90 years of age. This subgroup included five patients in the LC group and four in the OC group. Their operative times were similar to their respective groups. No major complications and no death were observed, and the median length of hospital stay was similar to that of their respective groups.

Discussion

In many reports, old age itself is not an independent prognostic factor for colorectal surgery, and the stage-to-stage cancer-specific survival rates are similar to those of

Table 4 Postoperative data

Variable	OC	LC	P value
Mean hospital stay (day)	8.8±3.6	7.6±3.1	0.062
Intensive care unit admissions	12 (26%)	7 (15%)	NS
Complications	16 (35.6%)	14 (30.4%)	0.659
General			
Urinary infection	5 (10.9%)	3 (6.4%)	NS
Pneumonia	4 (8.7%)	3 (6.4%)	NS
Surgical			
Wound infection	2 (4.3%)	0	0.242
Ileus	7 (15.2%)	4 (9%)	NS
Anastomotic leak	2 (4.3%)	1 (2.1%)	NS
Reoperation	2 (4.3%)	2 (4.3%)	NS
Mortality	3 (6.5%)	1 (2.1%)	0.361

NS not significant

younger patients. Therefore, curative intent should be applied in patients with colorectal cancer irrespective of age.[6,7] Over the last decade, the number of surgeries for colorectal cancer in the elderly have increased mainly due to improvements in surgical and anesthesia techniques.[8]

Laparoscopic colectomy is widely accepted for colectomy, and recent data support issues of safety and less operative stress, which can potentially lead to a reduction in postoperative morbidities and faster recovery. Thus short-term benefits should be more evident in elderly patients than in the general population.[3,9]

Many randomized controlled trials demonstrate that laparoscopic surgery for colon cancer has short-term benefits including reduction in perioperative mortality, a lower rate of wound complications, and shorter length of hospital stay,[10] but other studies[11] found only minimal short-term quality of life benefits with LC for colon cancer compared to OC.[11] However, few reports provided information related to the complications and outcome of laparoscopic colectomy in the elderly.[3]

The patients included in our study were those who were operated with the intention to cure and were aged 80 years or older. The age of 80 years was used because it is beyond the normal life expectancy. In fact the life expectancy in Israel is nearly 80 years (83 years for women and 79 years for men).

The differences in the operative times between the two groups are similar to that of other reports.[3] The decrease of the operative time observed in the last 2 years in LC patients and the relatively low conversion rate (6.3%) may reflect more experience gained over time.[12]

The mean length of stay was shorter in the laparoscopic group, which concords with other reports[13,14] that may reflect the earlier recovery of bowel function and less postoperative pain and lower analgesic consumption. For elderly patients, a long hospital stay may be associated with certain complications such as hospital-acquired infection and loss of active daily life. Therefore, for such patients, a short hospital stay and rapid recovery are important issues.

The incidence of postoperative complications has been reported in large LC series to range from 6% to 36%,[4,12] and the postoperative complications were seen to be higher in the OC group.[4,13,15] Other reports provide similar morbidity rates in the two groups.[16] However the differences in morbidity between our two groups were small but we believe clinically relevant and may justify offering LC to all elderly patients with colon cancer.

There were more patients with pulmonary complications in the open colectomy group than the laparoscopic group despite the fact that there were more patients with underlying pulmonary disease in the laparoscopic group. A possible explanation for these results could be that elderly patients may better tolerate the hemodynamic and ventilator changes observed in laparoscopic surgery. In addition, less postoperative pain and lower analgesic consumption, in addition to the shorter hospital stay in the LC group, could have contributed to amelioration of the postoperative respiratory function.

The present study was not a randomized controlled study, and there was an apparent bias. Although the patients in our two groups were similar in terms of tumor staging, the type of resection performed, and the comorbidities, the retrospective nature of the study and the absence of specific selection protocol for laparoscopy were the main limitations and could have skewed the results.

The adequacy of oncologic resection remains a major issue in laparoscopic colectomy procedure. Adhering to standard cancer resection as in open surgery is mandatory. Negative surgical margins and adequate number of harvested lymph nodes in the specimen represent important measurements of the radicalness of colonic resection. A clean surgical margin was obtained in all our patients, and the number of lymph nodes examined was quite similar in both our groups, in accordance with other reports that had shown that the number of lymph nodes harvested was comparable between OC and LC.[17]

Nine patients were nonagenarians, four patients in the OC and five in the LC. They were similar to their respective groups in terms of tumor staging, the type of resection, and the postoperative outcome. This result may draw attention yet again to the principle that whenever possible, curative intent should be applied in patients with colon cancer irrespective of age.[8] Therefore, it might be more appropriate to speak of biological age, which gives a better estimation of the patient's condition than chronological age.

Our results concur with existing data demonstrating that laparoscopic colorectal procedures can be carried out with good results in older patients and may have some advantages over the open approach. Since colon cancer surgery is performed so commonly and since laparoscopic colectomy is increasingly employed for many cancer cases, even a small improvement in outcome can lead to important positive consequences, and these benefits may be more pronounced in the elderly. Laparoscopic colectomy in the elderly is a surgical advancement that appears to be less physiologically stressful than conventional open colectomy, and it should be considered the preferred approach in elderly patients.

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ORIGINAL ARTICLE

Bleeding and Thromboembolic Outcomes for Patients on Oral Anticoagulation Undergoing Elective Colon and Rectal Abdominal Operations

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Abstract
Purpose Patients on chronic oral anticoagulation can be challenging to manage in the perioperative period.
Methods Review of patients on warfarin undergoing elective abdominal colon and rectal operations at a single institution from 2000 to 2006.
Results One forty-six patients underwent 165 abdominal procedures. Mean (±SEM) age was 67±1 years; 59% of patients were men. Median estimated blood loss was 200 ml, and 19% received intraoperative blood products while 19% of patients received a postoperative transfusion. Sixteen patients (10%) experienced bleeding complications (three requiring reoperation). No risk factors for bleeding were identified by multivariate analysis (MVA). Five patients (3%) suffered a postoperative thromboembolic event. Preoperative anticoagulation for cerebrovascular disease was a risk factor for thromboembolism ($p=0.03$). Overall operative morbidity was 30% with no identifiable risk factor in MVA. Mortality was nil.
Conclusion Postoperative bleeding and thromboembolism in patients on chronic anticoagulation are not insignificant (10% and 3%, respectively). Patients on warfarin for cerebrovascular disease are at increased risk for thromboembolic events postoperatively and should be placed on appropriate prophylaxis and monitored.

Keywords Anticoagulation · Warfarin · Thrombosis · Embolus · Bleeding

Introduction

Patients on chronic oral anticoagulation (OAC) with warfarin pose a significant concern for the surgeon. Not only must the surgeon weigh the risk of bleeding due to warfarin and its alternatives in preparation for an operation, but must also consider the thromboembolic risks of withholding anticoagulation in the perioperative period.[1–3] Additionally, data to help guide the clinician's management of perioperative anticoagulation in an evidence-based fashion are sparse.[4,5] The true challenge lies in the heterogeneity of the existing literature.[5–9] We have reviewed our experience to better define the bleeding and thromboembolic risks in this challenging subset of patients specific to elective colon and rectal abdominal procedures.

Methods

With institutional review board approval, the Mayo Clinic Rochester medical and surgical databases were cross-referenced to identify those patients ≥18 years on chronic OAC with warfarin who also underwent an elective abdominal operation performed in the Division of Colon and Rectal Surgery from 2000 to 2006. The medical record was reviewed to collect relevant patient data. Primary outcomes included perioperative bleeding (defined as a drop in hemoglobin requiring a blood transfusion or

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reoperation) and thromboembolic complications as well as postoperative morbidity and mortality. Different strategies for managing anticoagulation in the perioperative period were examined including the duration of time warfarin was withheld and bridging strategies such as the use of low-molecular-weight heparin (LMWH) and unfractionated heparin (UH). Outcomes were assessed in all patients, and subgroup analysis was also completed based on indications for chronic OAC.

Patients not on warfarin prior to their procedure were excluded as well as those patients who were to have their warfarin discontinued immediately postoperatively. We also excluded patients who were not on therapeutic doses of warfarin (defined as an international normalized ratio (INR) of 2–3.5) and those patients on anticoagulant pharmacologic agents other than warfarin. Anti-platelet therapy was not a criterion for exclusion.

Data were analyzed using JMP software (SAS, Cary, NC). Continuous data sets were compared using Student's *t* tests. Nominal data sets were compared using chi-square or Fisher's Exact when appropriate. Those variables with a *p* value ≤0.1 in the univariate analysis were analyzed in a multivariate analysis using a log fit model. Values are expressed as the mean±standard error of the mean unless otherwise stated, and *p* values less than 0.05 were considered statistically significant. In our initial analysis, we observed trends in management strategies based on indications for anticoagulation; therefore, we conducted an additional subgroup analysis looking at outcomes based upon indications for OAC.

Results

One-hundred forty-six patients were identified who met criteria for study and who underwent a total of 165 abdominal procedures (Table 1). The mean age was 67± 1 years. More than half of the patients were male (59%). A history of deep venous thrombosis (DVT) was the most common indication for OAC preoperatively in 45% of patients followed by atrial fibrillation in 36%, a history of pulmonary embolus (PE) with or without a documented DVT in 25%, mechanical heart valve in 16%, treatment of peripheral or cerebrovascular disease in 8%, and other in 5%. Twenty-two patients had more than one indication for OAC, and 11 patients had a known hyper-coaguable disorder.

Warfarin was withheld in all patients a mean of 8.0± 0.4 days prior to their procedure. Patients were bridged with LMWH for 30% of the procedures starting a mean 6± 0.5 days preoperatively; 12% received UH as an inpatient for a mean 4.0±0.6 days preoperatively. In the remaining 58% of patients, no bridging therapy was used. An INR was checked within 24 h of the procedure in 84% of cases, and the mean INR was 1.1±0.02.

Malignancy was the most common indication for an operation (53%) followed by stoma reversal (16%), inflammatory bowel disease (15%), diverticular disease (13%), and other (3%). Eighteen percent of cases were performed laparoscopically. The median estimated blood loss (EBL) obtained from the anesthesia record was 200 ml, and 19% of patients received blood products intraoperatively. Of these 32 patients receiving intraoperative blood transfusions, 15 (47%) were for an EBL >500 ml; the other 17 patients were transfused for a low starting hemoglobin and significant cardiac co-morbidities. Of those patients transfused for intraoperative blood loss, seven (47%) were also transfused with clotting factors.

Postoperatively, all patients were continued on sequential compression devices which had been placed on both lower extremities prior to induction of anesthesia. Prophylactic subcutaneous UH was given to 41% of patients starting a mean 0.2±0.1 days postoperatively. Warfarin was restarted at a mean 5.0±0.3 days postoperatively. Full-dose LMWH was used as a bridge in 18% of patients and was started at a mean 4±1 days postoperatively, and full-dose intravenous UH was used as a bridge in 30% of patients starting at a mean 2±1 days postoperatively. Twenty-seven percent of patients had a therapeutic INR (>2.0, or >2.5 if they had a mechanical heart valve) at dismissal, and 23% were dismissed on therapeutic LMWH; the remaining 50% were dismissed on warfarin alone.

There were 16 (10%) bleeding complications three of which required reoperation. No risk factors for bleeding with univariate or multivariate analyses were identified. Five patients had a thromboembolic event: one DVT and four cerebrovascular accidents. Each event occurred within the 30-day postoperative period. Of those patients with a bleeding complication, 12 of the 16 (75%) received a transfusion of packed red blood cells only. Only one patient received clotting factors in conjunction with the blood transfusion. A total of 30 patients were transfused packed red blood cells postoperatively; 18 (60%) were for chronic anemia with significant cardiac co-morbidities, and these were not felt to be related to a bleeding complication.

Univariate analysis identified known cerebrovascular disease (p=0.06), the use of LMWH preoperatively (p= 0.06), and a preoperative evaluation by a thrombophilia specialist (p=0.04) approached or achieved statistical significance as risk factors for a postoperative thromboembolic event (Table 2). However, multivariate analysis found that only a history of cerebrovascular disease was a significant risk factor for postoperative thromboembolism (p=0.03).

Overall operative morbidity (including bleeding and thromboembolism) was 30%. Wound infection was the most common complication (8.5%) aside from bleeding,

Table 1 Encounter characteristics

	Atrial fibrillation, *N*=54 (%)	Mechanical heart valve, *N*=23 (%)	DVT, *N*=34 (%)	PE, *N*=37 (%)	Vascular disease, *N*=15 (%)	Total, *N*=165 (%)
Mean age (years)	76±1	68±2	62±3	61±3	77±2	67±1
Male sex	33 (61)	15 (65)	16 (47)	18 (49)	8 (53)	94 (57)
Mean days off warfarin	9±1	6±1	8±1	7±1	8±1	8±0.4
LMWH preop	5 (9)	10 (44)	13 (38)	16 (43)	5 (33)	51 (31)
Mean days prior	8±2	5±1	6±1	5±1	7±2	6±1
UH preop	2 (4)	11 (48)	1 (3)	2 (5)	3 (20)	19 (12)
Mean days prior	3±2	4±1	2	6±2	3±1	4±1
Indication for operation						
Malignancy	36 (67)	11 (48)	15 (44)	12 (32)	9 (60)	87 (59)
Stoma reversal	4 (7)	2 (9)	7 (21)	8 (22)	1 (7)	26 (16)
IBD	1 (2)	1 (4)	6 (18)	12 (32)	0 (0)	24 (16)
Diverticular disease	7 (13)	5 (22)	5 (15)	3 (8)	3 (20)	22 (15)
Other	6 (11)	4 (17)	1 (3)	2 (5)	2 (13)	6 (4)
Median EBL (ml)	150	200	200	200	100	200
Intraoperative transfusion	12 (22)	5 (22)	4 (12)	8 (22)	2 (13)	32 (19)
Mean days to restarting warfarin	5±0.5	4±0.9	5±0.6	5±0.7	6±1	5±0.6
LMWH postop	4 (7)	6 (26)	6 (18)	13 (35)	2 (13)	32 (24)
Mean days to restart	5±1	6±2	3±1	4±1	7±2	4±1
UH postop	10 (19)	19 (83)	6 (18)	9 (24)	6 (40)	49 (31)
Mean days to restart	5±3	1±0.2	1±0.4	1±0.5	1±0.3	2±1
Therapeutic INR at dismissal	10 (19)	9 (39)	11 (32)	10 (27)	5 (33)	45 (27)
Outpatient LMWH	5 (10)	11 (48)	11 (32)	8 (22)	3 (20)	38 (23)
Bleeding complication	6 (11)	3 (13)	4 (12)	2 (5)	2 (13)	16 (10)
Thromboembolic complication	2 (4)	1 (4)	0 (0)	1 (3)	2 (13)	5 (3)
Postop morbidity	16 (30)	10 (44)	7 (21)	6 (16)	7 (47)	49 (30)

LMWH low-molecular-weight heparin, *UH* unfractionated heparin, *IBD* inflammatory bowel disease, *EBL* estimated blood loss, *INR* international normalized ratio

followed by ileus/small bowel obstruction (6%), a cardiac complication (4%), supratherapeutic INR requiring treatment (2%), and anastomotic leak (1%). Other complications accounted for 5%, and nine patients had more than one complication. There were several significant predictors by univariate analysis; however, none remained significant on multivariate analysis (Table 2).

We observed differences in perioperative anticoagulation management among patients based on their primary indication for chronic anticoagulation (Table 3). Patients with atrial fibrillation were less likely to have an evaluation by a thrombophilia specialist preoperatively (13%) compared with patients anticoagulated for a mechanical heart valve (35%), DVT (38%), or PE (57%; $p \leq 0.03$). This same

Table 2 Overall primary outcomes multivariate analysis

Primary outcomes	Yes, percent (*N*=5)	No, percent (*N*=160)	*p* Value
	Thromboembolism		
History of cerebrovascular disease	40	8	0.03
Thrombophilia consultation	0	36	0.2
Preoperative full-dose LMWH	0	32	0.3
	Postoperative morbidity		
History of PE	12	27	0.1
Preoperative full-dose UH	18	9	0.4
Postoperative full-dose LMWH	33	14	0.1
Outpatient full-dose LMWH	35	18	0.4

PE pulmonary embolus

Table 3 Comparison among groups

	Atrial fibrillation, percent (N=54)	Mechanical heart valve, percent (N=23)	DVT, percent (N=34)	PE, percent (N=37)	Vascular disease, percent (N=15)	p Value
Mean age (years)	76±1	68±2	62±3	61±3	77±2	<0.001
Male sex	61)	65	47	49	53	0.4
Mean days off warfarin	9±1	6±1	8±1	7±1	8±1	0.2
LMWH preop	9	44	38	43	33	<0.001
UH preop	4	48	3	5	20	<0.001
Malignancy	67	48	44	32	60	0.1
Median EBL (ml)	150	200	200	200	100	0.5
Intraoperative transfusion	22	22	12	22	13	0.5
Mean days to restarting warfarin	5±0.5	4±0.9	5±0.6	5±0.7	6±1	0.8
LMWH postop	7	26	18	35	13	0.04
UH postop	19	83	18	24	40	<0.001
Therapeutic INR at dismissal	19	39	32	27	33	0.3
Outpatient LMWH	10	48	32	22	20	0.004
Bleeding complication	11	13	12	5	13	0.9
Thromboembolic complication	4	4	0	3	13	0.5
Postop morbidity	30	44	21	16	47	0.1

group of patients was also less likely to be bridged with LMWH compared with the other groups ($p \leq 0.02$). Patients with a mechanical heart valve were more likely to receive inpatient intravenous UH preoperatively (46%) compared with patients with atrial fibrillation (4%), DVT (3%), and PE (5%; $p < 0.001$). While the number of patients having an inferior vena cava filter placed was too small for valid statistical analysis, the only patients who received a filter were those with a history of DVT or PE.

Postoperatively, the use of LMWH was more common in patients with a history of DVT (35%), but it only reached significance compared with those patients with atrial fibrillation (7%; $p=0.002$). Patients with a mechanical heart valve were more likely to receive full-dose intravenous UH (83%) compared with the other groups ($p \leq 0.004$), and this group of patients was also more likely to be dismissed on outpatient LMWH. Patients with a mechanical heart valve or cerebrovascular disease had longer durations of stay (mean 11±1 and 12±days, respectively) compared with patients with atrial fibrillation (9±1 days), DVT (7±1 days), and PE (8±1 days; $p \leq 0.03$).

Subgroup Analysis

There were six bleeding complications in the atrial fibrillation group (11%). We identified the use of LMWH postoperatively (33% vs. 0%) and LMWH on an outpatient basis (postoperatively, 67% vs. 4%) as risk factors for a bleeding complication by univariate analysis ($p \leq 0.03$); however, only the use of LMWH as an inpatient maintained significance by multivariate analysis ($p=0.01$). Two thromboembolic complications occurred in this group as well (4%), although no risk factors were identified. Operative morbidity for all patients with atrial fibrillation was 30%, and no risk factors were identified.

Patients with mechanical heart valves had a 13% bleeding complication rate. The use of full-dose intravenous UH preoperatively (27% vs. 0%) and a preoperative INR ≥1.3 (38% vs. 0%) were risk factors for bleeding by univariate analysis ($p \leq 0.03$). However, significance was not maintained on multivariate analysis. Two patients experienced a thromboembolic complication (4%), but no risk factors were identified. Overall operative morbidity was 44% in this group, and the use of laparoscopy (83% vs. 29%) and postoperative full-dose LMWH (100% vs. 24%) were risk factors for postoperative morbidity by both univariate and multivariate analyses ($p \leq 0.02$).

Patients on anticoagulant therapy for known history of DVT had a 12% rate of postoperative bleeding complications without any thromboembolic complications and an overall postoperative morbidity rate of 21%. No risk factors were identified in this group for either outcome.

For patients with a history of PE, two experienced a bleeding complication (5%) and one experienced a thromboembolic complication (3%). There were no risk factors for bleeding identified. Preoperative full-dose intravenous UH (50% vs. 3%), preoperative fresh frozen plasma for INR reversal (100% vs. 0%), and a postoperative transfusion (20% vs. 13%) were all risk factors for postoperative thromboembolism on univariate analysis ($p \leq 0.04$), but significance was lost on multivariate analysis. Overall operative morbidity was 16%, and no risk factors were identified.

Of patients on chronic anticoagulation for peripheral or cerebrovascular disease, two had a postoperative bleeding complication (13%). The use of outpatient, full-dose LMWH was associated with a higher rate of postoperative bleeding (33% vs. 8%, $p=0.04$), but this was insignificant by multivariate analysis. Two patients had a thromboembolic complication (13%) for which an estimated blood loss >500 ml was identified as a risk factor by univariate analysis (50% vs. 7%, $p=0.01$), but this was insignificant by multivariate analysis. The overall postoperative morbidity in this group was 47%. Patients who were not bridged with full-dose LMWH postoperatively had a higher complication rate (39% vs. 29%, $p=0.04$) as did those who were dismissed home on outpatient, full-dose LMWH (67% vs. 42%, $p=0.04$). However, neither of these variables was significant by multivariate analysis.

Discussion

In the review of the current literature, the rates of thromboembolic events in patients on chronic OAC in the perioperative period is reported to be 0–2% while bleeding complication rates range from 2% to 25%.[3–6,10,11] These data represent a very heterogeneous group of patients undergoing a wide spectrum of procedures with varied strategies for anticoagulation reversal and bridging. In our series, we report a 3% incidence of thromboembolic complications and a 10% incidence of bleeding complications in patients undergoing elective colon and rectal abdominal operations.

The sequelae of a thromboembolic event, especially arterial, are not inconsequential. Long-term disability from an arterial event is reported to be as high as 70–75% and 4–10% for a venous event, whereas subsequent disability from a major bleeding complication is 1–6%.[12–15] While we had no deaths in this subset of colon and rectal surgery patients, a previous study from our institution reported a mortality rate of 1.7% in all patients having OAC stopped periprocedurally.[10] These data highlight the significant risks associated with this patient population and the need for evidence-based guidelines.

From our data, we observed several different strategies to manage perioperative anticoagulation which appeared to be implemented based on the underlying indication for warfarin. This represents a significant bias in the data presented here which is a major limitation of our retrospective analysis. The only certainty is that more specific evidence-based guidelines relevant to the type of procedure are needed, which is why we have looked specifically at colon and rectal surgery patients.

Clearly, patients with known cerebrovascular disease are at the highest risk, based on our data, and should be aggressively managed to prevent a catastrophic thromboembolic event even at the risk of a bleeding complication. Furthermore, when patients did have a bleeding complication, it was most commonly managed non-operatively with observation, with or without transfusion. However, due to the retrospective nature of our data, we cannot say with any certainty that any bleeding complication was due directly from anticoagulation. In fact, the majority of patients who were transfused postoperatively received only packed red blood cells as opposed to receiving clotting factors suggesting that anticoagulation may not have played a large role in many of those cases—although, nearly half of those patients transfused intraoperatively for bleeding did receive clotting factors. Lastly, we did not identify any risk factors for bleeding that related to the perioperative management of anticoagulation.

Patients with mechanical heart valves were treated the most aggressively preoperatively, oftentimes being admitted and bridged with intravenous UH and then being maintained on intravenous UH postoperatively until a therapeutic INR was achieved after resumption of warfarin. While this contributed to an increased postoperative length of stay, it did not impact the postoperative bleeding or thromboembolic rates compared with the other groups, and so stronger consideration for outpatient bridging with LMWH should be given to this group of patients to reduce length of stay and the risks and costs associated with increased days in the hospital.

While the different bridging strategies did not seem to effect bleeding or thromboembolism risk among patients based on the indications for OAC, we did find differences on subgroup analysis in those patients on OAC for atrial fibrillation or a mechanical heart valve. Within the atrial fibrillation group, the use of full-dose LMWH postoperatively was associated with a higher bleeding complication rate. This could be interpreted as though these patients do not require aggressive bridging therapy; however, there were only two thromboembolic events in this group of patients, which severely underpowers our analysis. Furthermore, with less aggressive therapy, this group may have had more thromboembolic events.

In patients with mechanical heart valves, the use of laparoscopy and full-dose LMWH postoperatively were associated with greater morbidity. We do not feel that laparoscopy itself predisposes this subset of patients to more complications but that this reflects a selection bias in that these patients often have more co-morbid conditions and were referred for a laparoscopic approach in an attempt to minimize morbidity.

Total morbidity was not insignificant with an overall complication rate of 30%: bleeding complications accounted for one third of the total operative morbidity. Other reports have clearly linked the use of anticoagulants

to postoperative bleeding.[6–9] In our series, we did not identify any specific risk factors, including postoperative bridging therapy that predisposed patients to a bleeding complication. Furthermore, McBane et al. specifically looked at the risks associated with bridging therapy in 775 patients with venous thromboembolism and found no differences in thromboembolic or bleeding outcomes based on whether or not bridging therapy was used.[10]

Five patients (3%) suffered from a thromboembolic event which included a single PE and four CVAs. The only risk factor we identified by multivariate analysis was known cerebrovascular disease. Most reports of the incidence of thromboembolism in this patient group have failed to identify risk factors which can be attributed to the relatively low occurrence of this complication compared with bleeding.[3,5] However, McBane's review did find that malignancy was a predictor for thrombotic recurrence.[10] We looked at cancer as a risk factor but did not identify any correlation. Nonetheless, we would advocate aggressive perioperative management of patients with known cerebrovascular disease and/or a malignancy even if that means accepting a higher risk of postoperative bleeding.

In 2008, Thachil and colleagues published evidence-based recommendations determined by anticipated bleeding and thromboembolic risks.[16] Bleeding risk is classified as high, intermediate, or low based on the nature of the procedure. Procedures with a low bleeding risk can be performed without interruption of OAC as long as the INR is not supratherapeutic. When the bleeding risk is intermediate, management is dependent on the thromboembolic risk. For patients with a high bleeding risk, the authors recommend using intravenous UH because it is easily reversed, and they advise considering an inferior vena cava filter in patients with known deep venous thrombosis at high risk.

The American College of Chest Physicians also published evidence-based guidelines in 2008 that were similarly based on the patient's risk for thromboembolism as well as the procedural bleeding risks.[17] In these guidelines, preoperative management is based primarily on the patient's risk for thromboembolism. Postoperatively, resumption of anticoagulation is dependent on the perceived bleeding risk.

Patients with atrial fibrillation may not require as aggressive perioperative anticoagulation compared with those with mechanical heart valves, DVT, PE, or known peripheral and cerebrovascular disease. In fact, those patients with atrial fibrillation who were bridged with therapeutic LMWH had a higher rate of bleeding complications compared with those atrial fibrillation patients who were not bridged. The aggressive strategies used for patients with mechanical heart valves, specifically with UH, led to longer hospitalizations while bridging with LMWH in this subgroup of patients would be more advantageous in reducing hospital days and would still minimize the risks of bleeding and thromboembolism as seen in our series. Additionally, multiple reports have also demonstrated the safety and efficacy of LMWH in anticoagulating patients with and without mechanical heart valves.[18–22]

This study does have limitations. It is a retrospective review and therefore is inherently biased especially in regards to treatment strategies used based on the indications for OAC as our data analysis reflects. Furthermore, despite looking at a specific set of patients, colon and rectal surgery patients, there is still a large amount of heterogeneity. Finally, the complications rates were low that our statistical analyses may have been underpowered.

Conclusion

For patients who are on chronic OAC, the risks of bleeding versus a thromboembolic event are not negligible. This balance can make management of these patients difficult. Patients on OAC for known cerebrovascular disease have a higher risk for a postoperative thromboembolic event and should be managed with aggressive prophylaxis and, possibly, earlier resumption of therapeutic anticoagulation postoperatively. How the management of perioperative anticoagulation affects bleeding complications is still unclear. Despite published evidence-based guidelines for this subset of patients, this group remains very heterogeneous, and additional prospective data is needed to clarify the optimal management based on the type of procedure and its risk for bleeding versus the risk for thromboembolism.

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ORIGINAL ARTICLE

Outcomes of Right vs. Left Colectomy for Colon Cancer

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Abstract
Background Right colectomy (RC) is generally believed to be a simpler operation with better outcomes than left colectomy (LC). Our study was primarily intended to compare patient characteristics and perioperative outcomes between RC and LC in colon cancer patients, and secondarily to identify factors that increase the risk of developing postoperative abdominal abscess and/or anastomotic leak.
Methods Using the 2007 Nationwide Inpatient Sample database, we evaluated patients who underwent elective RC and LC for colon cancer.
Results A total of 50,799 patients underwent elective RC and LC for malignancy during 2007 (RC, 63.5%; LC, 36.5%). Overall, 9.6% were performed laparoscopically (RC, 9.7% vs. LC, 9.5%, $P=0.39$). The majority of patients were Caucasian; 54.2% of RC and 46.5% LC patients were female ($P<0.01$). RC patients were older (mean age, 70.8 vs. 65.8 years, $P<0.01$) and had more comorbidities. While LC had more overall intraoperative complications (RC, 0.30% vs. LC, 1.32%, $P<0.01$), RC had higher overall incidence of postoperative complications (28.43% vs. 26.75%, $P<0.01$). Mean length of hospital stay (RC, 7.37 days vs. LC, 7.38 days) and in-hospital mortality (RC, 1.37% vs. LC, 1.49%) were similar in both groups. Multivariate analysis identified Native American race [adjusted odd ratio (AOR), 2.02], chronic renal failure (AOR, 1.97), congestive heart failure (AOR, 1.72), chronic pulmonary disease (AOR, 1.40), metastatic disease (AOR, 1.34), male gender (AOR, 1.23), and LC (AOR, 1.12) all independently increased the risk of abscess and/or leak.
Conclusions RC patients were older and had more comorbidities and postoperative complications. Patient characteristics and comorbidities were more important in determining overall postoperative complications than anastomotic types.

Keywords Right colectomy · Left colectomy · Ileocolic anastomosis · Colocolic anastomosis · Colon cancer

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Introduction

Colectomy is a common surgical procedure for benign and malignant colorectal diseases. Patient's characteristics (age,[1], gender,[2,3] ASA score,[4,5]), comorbidities (i.e., congestive heart failure, renal failure,[6,7]), disease nature (benign vs. malignant),[8,9] and nutritional status[2,10] have all been shown to affect surgical outcomes after colorectal surgery. Surgical techniques (open vs. laparoscopy)[11,12] and details of the surgery (e.g., elective vs. emergent)[13] can also play important roles in determining the operative outcomes. In the surgical community, many surgeons believe that left colectomy (LC), which is often more technically challenging and requires a colocolic or colorectal anastomosis, has a

significantly higher incidence of anastomotic leakage, wound infection, overall complication rate, and longer length of hospital stay (LOS) than right colectomy (RC), which utilizes an ileocolic anastomosis.[14,15]

However, there are few studies comparing outcomes of RC and LC in colon cancer patients. As a result, our objective was to evaluate the differences in patient characteristics and perioperative outcomes between elective RC and LC for colon cancer. In addition, since abdominal abscess and anastomotic leakage are primary major complications following colorectal resection, which can adversely affect morbidity and mortality rates, we aimed to identify independent factors that contribute to higher risks of postoperative abdominal abscess and anastomotic leakage (abscess/leak).

Material and Methods

Database

Using the 2007 Nationwide Inpatient Sample (NIS) database, we analyzed outcomes of patients who underwent RC and LC with the primary diagnosis of colon malignancy. The NIS is comprised of a nationally representative sample of approximately 20% of U.S. community hospitals, resulting in a sampling frame that comprises approximately 90% of all hospital discharges in the USA. Data elements within the NIS are drawn from hospital discharge abstracts that allow determination of all procedures performed during a given hospital admission. It also contains discharge information on inpatient hospital stay, including patient characteristics, LOS, overall and specific postoperative morbidity, and observed and expected in-hospital mortality. Approval for use of the NIS patient-level data in this study was obtained from the Institutional Review Board of the University of California, Irvine Medical Center and the NIS.

Data Analysis

RC was defined by creation of an ileocolic anastomosis, whereas LC was defined by creation of a colocolonic or high colorectal anastomosis (either left hemicolectomy or sigmoidectomy). To identify hospitalizations resulting from RC and LC, all discharges with International Classification of Disease ninth revision (ICD-9) procedure codes for right hemicolectomy, left hemicolectomy, and sigmoidectomy in 2007 were selected (Table 1). In the next step, patients who had colon malignancy were identified by ICD-9 diagnosis codes. Because there was no distinct ICD-9 procedure code for laparoscopic colectomy in 2007, we identified laparoscopic procedures by using additional ICD-9 codes for diagnostic laparoscopy or laparoscopic lysis of adhesions in combination with open procedure codes. Also, we identified patients who underwent colectomy with diversion by using ICD-9 procedure codes for ileostomy or colostomy. Then, we divided our patients into two groups: RC (right hemicolectomy) and LC (left hemicolectomy and sigmoidectomy). For this study, patients with elective admission were selected for comparison of outcomes in RC and LC. Patient characteristics of interest included age, gender, race, and comorbidities. Other data of interest included perioperative complications, in-hospital mortality, LOS, and total hospital charges.

Table 1 ICD-9 procedure and diagnosis codes

Procedure and diagnosis	ICD9 code
I. Procedure	
Right hemicolectomy	45.73
Left hemicolectomy	45.75
Sigmoidectomy	45.76
Diagnostic laparoscopy	54.21
Laparoscopic lysis of adhesion	54.51
Ileostomy	46.20, 46.21, 46.22, 46.23, 46.01
Colostomy	46.10, 46.11, 46.13, 46.03
Ureter repair	568, 56.82, 56.89
Bladder repair	57.81
Splenectomy and splenic repair	41.5, 41.43, 41.95
Liver repair	50.6, 50.61, 50.69
II. Diagnosis	
Malignant neoplasm of colon	153.0, 153.1,….,153.9
Urinary tract infection	599.0, V1302
Pneumonia	482.9, 486
Acute renal failure	584, 584.9
Respiratory failure	518.81, 518.82, 518.4, 518.5
Deep vein thrombosis	453.4, 453.40, 453.41, 453.42
Pulmonary embolism	415.1, 415.9
Myocardial infarction/ angina	410.1,…,410.9, 413.0, 413.1, 413.9
Ileus	560.1
Bowel obstruction	560, 560.9, 560.81
Abdominal abscess	998.59
Anastomotic leakage	997.4
Wound infection	998.31, 998.32, 682.2
Postoperative fistula	998.6

Statistical Analysis

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC), incorporating recommended discharge and hospital weights. Discharge weight was used

to create national estimates based on the sampling of the data for all analyses. Descriptive statistics were performed using chi-square and *t* tests where appropriate. We used multivariate regression analysis to identify independent roles of patient demographics, comorbidities, the type of operation (RC vs. LC), and surgical techniques (laparoscopic vs. open) in postoperative abscess/leak in RC and LC. Statistical significance was set at *P* values <0.05 and odds ratios and 95% confidence intervals that excluded one.

Results

In 2007, 76,818 patients underwent RC and LC for colon cancer, among which 34.46% had emergent/urgent procedures. Of the 50,799 elective colectomies, 63.5% underwent RC, and 36.5% had LC. Similarly, of the 26,019 emergent/urgent RC and LC, 65.6% underwent RC, and 34.6% had LC. Only 9.6% of these elective cases were performed laparoscopically (RC, 9.7% vs. LC, 9.5%, $P=0.39$). Also, the majority of patients did not have any type of diversion (ileostomy or colostomy) in both groups (RC, 97.10% vs. LC, 93.88%; $P<0.01$).

The average age of RC patients was higher than LC (70.85 years vs. 65.82 years, $P<0.01$). Among all elective patients, 9.2% were 50 years old or younger (RC, 7.1% vs. LC, 12.9%, $P<0.01$). The majority of RC patients were female, while the majority of LC patients were male (RC, 54.2% vs. LC, 46.5%, $P<0.01$). Also, the majority of patients were Caucasian in both groups (RC, 80.1% vs. LC, 75.7%, $P<0.01$; Table 2). When considering comorbidities, RC patients had a significantly higher incidence of diabetes mellitus, hypertension, congestive heart failure, chronic pulmonary diseases, renal failure, and anemia, while LC patients had higher rates of obesity and peripheral vascular disorders. Liver diseases and alcohol abuse were not significantly different between groups. Interestingly, equivalent numbers of patients from both groups had metastatic cancer at the time of surgery (RC, 30.7% vs. LC, 30.9%, $P=0.77$).

Intraoperatively, not surprisingly, LC had a higher incidence of ureter, bladder, and splenic injuries during procedures. However, liver injuries were not significantly different between the groups (Table 3). The overall postoperative complication rate was higher in RC patients (28.43% vs. 26.75%, $P<0.01$). Although abdominal abscess was more prevalent in LC (RC, 3.19% vs. LC, 3.88%, $P<0.01$), there was no significant difference in anastomotic leakage between the two groups (RC, 1.24% vs. LC, 1.39%), but overall abscess/leak was significantly higher in LC patients (RC, 4.89% vs. LC, 4.25%). In looking at postoperative complications other than abdominal abscess and leak, RC had significantly higher rates of urinary tract infection, pneumonia, and ileus; however, there were no significant differences observed in acute renal failure, respiratory failure, myocardial infarction/angina, deep vein thrombosis, pulmonary emboli, fistula, wound infection, and bowel obstruction between the two groups. Also, there were no significant differences observed in mean LOS (RC, 7.37 days vs. LC, 7.38 days, $P=0.93$) and in-hospital mortality rates (RC, 1.37% vs. LC, 1.49%, $P=0.29$) between the two groups.

Table 2 Patient characteristics in right (RC) and left colectomy (LC)

Patients characteristics	RC *N*=32,277	LC *N*=18,522	*P* value
Demographics (%)			
Mean age (year)	70.8	65.8	<0.01
Female	54.2	46.5	<0.01
Race			
White	80.1	75.7	<0.01
Black	9.1	9.1	
Hispanic	5.3	6.6	
Asian–Pacific Islander	2.6	4.9	
Native American	0.9	0.7	
Other	2.0	3.0	
Comorbidities (%)			
Diabetes mellitus	18.7	17.2	<0.01
Hypertension	55.9	52.2	<0.01
Congestive Heart Failure	7.1	5.7	<0.01
Chronic pulmonary disease	15.1	13.9	<0.01
Liver disease	1.7	1.7	0.58
Obesity	6.6	7.4	0.01
Chronic renal failure	4.6	3.8	<0.01
Alcohol abuse	3.6	3.3	0.07
Peripheral vascular disease	1.1	1.3	0.01
Metastatic cancer	30.7	30.9	0.77
Anemia	25.5	15.2	<0.01

In multivariate regression analysis, factors predictive of higher postoperative abscess/leak were Native American (adjusted odd ratio [AOR], 2.02), chronic renal failure (AOR, 1.97), congestive heart failure (AOR, 1.72), chronic pulmonary disease (AOR, 1.40), presence of metastatic disease (AOR, 1.34), male gender (AOR, 1.23), and LC (AOR, 1.12). There was no effect of age, diabetes, hypertension, liver disease, anemia, alcohol abuse, peripheral vascular disease, obesity, and surgical technique (laparoscopic vs. open) on abscess/leak in this patient population (Table 4).

Discussion

In 2007, the average age of patients undergoing RC was 70.8, which was significantly older than LC patients (65.8).

Table 3 Perioperative outcomes in right (RC) and left colectomy (LC)

Outcomes	RC N=32,276	LC N=18,522	P value
Intraoperative complications (%)			
Ureter	0.05	0.22	<0.01
Bladder	0.06	0.16	0.01
Splenic	0.20	1.01	<0.01
Liver	0.02	0.02	0.62
Overall Complication Rate	0.30	1.32	<0.01
Postoperative Complications (%)			
Urinary tract infection	1.67	1.21	<0.01
Pneumonia	2.58	2.29	0.04
Acute renal failure	3.42	3.36	0.70
Respiratory failure	4.35	4.40	0.80
Myocardial infarction/ angina	0.90	0.78	0.13
Deep vein thrombosis	0.50	0.52	0.75
Pulmonary emboli	0.25	0.19	0.18
Ileus	17.36	15.38	<0.01
Abdominal abscess	3.19	3.88	<0.01
Anastomotic leakage	1.24	1.39	0.15
Abscess and/or leakage	4.25	4.89	<0.01
Fistula	0.09	0.10	0.88
Wound infection	1.85	1.84	0.92
Bowell obstruction	1.78	1.66	0.44
Overall complication rate	28.43	26.75	<0.01
Length of stay (days)			
Median	6	6	
Mean	7.37	7.38	0.93
In-hospital mortality (%)	1.37	1.49	0.29
Mean total hospital charges ($)	44,183	48,700	<0.01

Table 4 Multivariate regression analysis: independent risk factors for abscess and/or anastomotic leakage in elective right and left colectomy in colon cancer

Variables	Odds ratio (95% CI)	P value
Age group		
≤65	Reference	Reference
>65	0.89 (0.79–0.99)	0.04
Gender		
Female	Reference	Reference
Male	1.23 (1.10–1.36)	<0.01
Race		
White	Reference	Reference
Black	1.20 (1.00–1.42)	0.15
Hispanic	1.32 (1.07–1.62)	0.79
Asian/Pacific Islander	1.26 (0.96–1.66)	0.57
Native American	2.02 (1.30–3.14)	0.04
Other	1.55 (1.16–2.07)	0.30
Comorbidities		
No comorbidity	Reference	Reference
Diabetes mellitus	0.82 (0.710–0.947)	<0.01
Hypertension	0.83 (0.75–0.935)	<0.01
Congestive heart failure	1.72 (1.44–2.07)	<0.01
Chronic pulmonary disease	1.40 (1.22–1.60)	<0.01
Liver disease	0.62 (0.38–0.98)	0.04
Renal failure	1.97 (1.60–2.41)	<0.01
Alcohol abuse	1.05 (0.68–1.61)	0.83
Peripheral vascular disease	1.03 (0.79–1.35)	0.80
Obesity	1.14 (0.94–1.39)	0.18
Anemia	0.85 (0.74–0.96)	0.01
Metastatic cancer	1.34 (1.20–1.50)	<0.01
Surgical technique		
Laparoscopy	Reference	Reference
Open	1.10 (0.92–1.32)	0.27
Surgical type		
Right colectomy	Reference	Reference
Left colectomy	1.12 (1.01–1.25)	0.03

Although showing that the incidence of left colon and rectal cancers in the USA is declining while right colon cancer rates remains stable, Meza's study only showed a small difference between incidences of right and left colon cancers (right colon cancer, 55% vs. left colon cancer, 45%),[16] our study shows RC was almost twice as common as LC for malignancy in 2007 (63.5% vs. 36.5%). It is likely, if rectal cancer cases are included, the left side still accounts for a majority of cases.

Unfortunately, almost one third of both RC and LC patients had metastatic disease at the time of colon resections. Currently, even though the US Preventive Task Force recommends colorectal cancer screening in adults 50 to 75 years old,[17] only 55% of adults 50 years or older were screened in 2008.[18] Barriers to perform effective screenings such as long wait,[19] lack of regular access to primary physicians, and high out-of-pocket costs[18] could contribute to this high incidence of metastasis. Additionally, our study showed 9.2% of all patients and unfortunately rate of metastatic cancer at time of surgery was significantly higher in patients younger than 50 years old (39.4%) compared with patients older than 50 years old (29.8%). Obviously, this group would not typically be considered for screening in the absence of significant family history.

In 2007, more than 90% of colon cancer resections were open procedures. Despite the low number of laparoscopic cases, there was a favorable trend in the growth of laparoscopic colectomy in treating colorectal cancers. In 2000, only 1.4% of colorectal cancer cases were performed laparoscopically, and in 2004, it increased to 4.3%.[20] In our report, we find that 9.6% of colon cancer cases in 2007 underwent laparoscopic colectomy. While the concern of port-side tumor recurrence slowed the adoption of laparoscopy for colorectal cancer

resection,[20] current studies have shown that cancer recurrence is similar in laparoscopic and open colectomy.[21,22]

While many studies have reported different comparative results of intraoperative variables between RC and LC, most of them compared intraoperative blood loss and operative durations.[23,24] Few studies have looked at intraoperative injuries. In our study, consistent with the belief that LC is more technically challenging, we find that intraoperative complications like ureter, bladder, and splenic injuries were significantly higher in LC.

Our study shows overall postoperative complication rate was more prevalent in RC, although the difference was arguably not clinically significant. Many studies have shown no difference in postoperative morbidity between RC and LC in elective and emergent situations,[23,25] while another reported a higher incidence of postoperative complications in LC for benign and malignant colorectal diseases.[26] Our results could be affected by many factors like higher average age and higher incidence of comorbidities, which were more prevalent in RC patients.

In our study, ileus was the most common postoperative morbidity (16.65%), and its incidence appeared to be similar to Iyer et al. (17.4%),[27] but lower compared to Asgeirsson et al. (24%).[28] Even with new attempts to reduce postoperative ileus such as multimodal analgesia (e.g., NSAIDS), epidural anesthesia, and fast tract recovery programs, ileus was still a problem during colorectal surgery recovery. Our overall incidence of anastomotic leaks (1.29%) was favorably lower compared to other studies (1.9% to 6.9%).[4,25,29] Despite the belief that LC was more technically challenging and prone to higher anastomotic leak rate than RC,[14,15] we found no difference in the incidence of anastomotic leak between the groups.

Other reports have demonstrated that advanced age, comorbidities, and postoperative complications increased LOS.[30,31] However, despite the increased average age and higher incidence of both preoperative comorbidities and postoperative complications in RC population, we find that LOS was comparable between the two groups (RC, 7.37 days vs. LC, 7.38 days). Similarly, there was no significant difference in mortality rates.

We looked at abscess and leak rate separately as well as together as it is often difficult to distinguish the two clinically, and the treatments of these are dependent on clinical presentation more than a diagnosis. In multivariate regression analysis, although male gender (AOR, 1.23) and Native American (AOR, 2.02) (as a non-modifiable factor) independently increased the risk of developing postoperative abscess/leak, comorbidities were more influential in determining the abscess/leak risk. Among these, patients with chronic renal failure (AOR, 1.97), congestive heart failure (AOR, 1.72), chronic pulmonary disease (AOR, 1.40), and metastatic cancer (AOR, 1.34) were shown to have the highest risks for developing abscess/leak. As a result, medical optimization of preoperative condition prior to precede elective colectomy and diligent postoperative attention should be given to patients with these conditions in order to decrease abscess and leak rate and their related morbidities. With regard to effect of type of procedure on abscess and/or leak, while many studies[11,12,22] have demonstrated that laparoscopic colectomy results in fewer incidences of anastomotic leakage and abscess, these studies contained a considerable potential selection bias. With risk adjusted analysis, we found that open operation was not associated with higher incidence of abscess and/or leak.

Our study limitations are similar to other studies making use of a large administrative database. The NIS database is compiled from discharge abstract data and is limited to in-hospital stay without outpatient follow-up data and lacks information on readmissions, 30-day morbidity, and mortality which are significant indicators of surgical outcomes. For example, abscess or leaks that occur or are recognized after discharge would not be captured in this database. Therefore, our calculation of the abscess or leak rate probably underestimates the actual rate. A dedicated laparoscopic colectomy ICD-9 code was not in effect until 2009, which may have led to inaccuracies and underestimates in laparoscopic case collection. We also were unable to determine cases that were converted from laparoscopic to open. Lastly, there are other potential factors predictive of anastomotic leaks that are not available for analysis within the NIS database such as the experience of an individual surgeon, annual case volume, and specifics of the surgical technique.

In conclusion, patients with RC were older and had more comorbidities than LC patients. While the technique of LC resulted in higher intraoperative complication rate, RC patients had more overall postoperative complications. Endpoint outcomes (LOS, mortality) were similar between RC and LC populations. Hence, our results suggest that anastomotic complications were more influenced by patient characteristics and comorbidities than the differences in anastomotic type (colocolonic and colorectal anastomoses in LC vs. ileocolic anastomosis in RC). Thus, LC can be performed as safely as RC for colon cancer. In the future, prospective studies should be performed to evaluate short-term and long-term outcomes in colon cancer patients.

Conflicts of interest In this study, all authors have no conflicts of interest or financial ties to disclose.

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ORIGINAL ARTICLE

MELD-Based Indices as Predictors of Mortality in Chronic Liver Disease Patients Who Undergo Emergency Surgery with General Anesthesia

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Abstract
Background Underlying chronic liver disease is associated with high morbidity and mortality after emergency surgery, which complicates clinical decisions over performing such surgery. In addition, the Child–Turcotte–Pugh (CTP) score is limited in its ability to predict postoperative residual liver function. This study was designed to determine whether the scores of the Model for End-stage Liver Disease (MELD)-based indices are effective predictors of mortality following emergency surgery in patients with chronic liver disease.
Method Medical records of 53 chronic liver disease patients who underwent emergency surgery under general anesthesia from 2001 to 2008 were analyzed retrospectively.
Results Median preoperative CTP score was 6 (5–12); MELD, 11 (6–33); MELD-Na, 15 (7–34); integrated MELD (iMELD), 33 (14–64); and MELD to sodium ratio, 8 (4–24). During a median 11-month follow-up period, 19 (35.8%) patients died. Five of them (26.3%) had operative mortality (i.e., mortality within 30 days after surgery). On multivariate analysis, CTP class C was correlated with operative mortality, and estimated blood loss above 300 ml and the iMELD score above 35 were significantly correlated with overall mortality.
Conclusions iMELD reflects underlying liver function and predicts overall mortality more accurately than CTP and other MELD-based indices scores do in chronic liver disease patients after emergency surgery with general anesthesia.

Keywords Chronic liver disease · Emergency · Surgery · MELD-based indices · CTP score

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Introduction

Extrahepatic surgery in patients with chronic liver disease has a higher morbidity and mortality than in patients without chronic liver disease[1] primarily because of the higher risk of complications.[2] Hepatic dysfunction may lead to hemorrhage and infection;[3] general anesthesia itself induces a reduction in blood flow to the liver, increasing the risk of ischemic injury; and postoperative medications may induce hepatic toxicity.[4]

Mortality and the rate of hepatic decompensation are approximately four times higher after emergency surgery than after elective surgery,[5] and emergency surgery is the only independent predictor of the duration of hospital stay.[6] Thus, perioperative management of patients with chronic liver disease undergoing emergency surgery requires careful attention. Although no mortality or cases of hepatic

decompensation following emergency operation have been reported with preoperative Model for End-stage Liver Disease (MELD) score lower than 11 points or the Child score lower than seven points, many patients with chronic liver disease have higher scores than these.[5] Thus, the number of patients with chronic liver disease who can safely undergo emergency surgery may be severely limited in spite of liver residual function. In a situation requiring emergency operation, patients had experienced hypovolemic, malnutrition status, and even septic condition. In this situation, the Child–Turcotte–Pugh (CTP) and MELD scores are limited in their ability to predict residual liver function. The MELD plus sodium (MELD-Na) score showed a more accurate predictive value of survival than the MELD score in patients with decompensated liver cirrhosis awaiting liver transplantation.[7–9] The scores of MELD-based indices (MELD-Na, integrated MELD [iMELD], MELD to sodium ratio [MESO]) have been evaluated as predictive parameters of mortality in cirrhotic patients.[10] In this study, we examined the predictive value of the MELD-based indices scores for mortality in liver disease patients who undergo emergency surgery with general anesthesia.

Methods

Patients

We examined the medical records of 53 patients with chronic liver disease who underwent emergency extrahepatic surgery under general anesthesia between 2001 and 2008 at the Severance Hospital, Yonsei University Health System in Seoul, Korea.

Definition and Diagnosis of Chronic Liver Disease

Chronic liver diseases included alcoholic liver disease, chronic hepatitis virus infection, and cirrhosis, regardless of cause. Diagnosis was made based on the clinical (alcohol consumption history, symptoms and signs of hepaticoencephalopathy, and varix finding on esophagogastroduodenoscopy) and laboratory (liver function test, platelet count and international normalized ratio (INR), hepatitis B antigen and hepatitis C antibody) and radiologic features (atrophy and nodular surface of the liver, ascites, splenomegaly, etc.).

Definition of Operative Risk and CTP, MELD, and MELD-Based Indices

The risk level of operation was classified as low, moderate, or high.[11] By using preoperative clinical and laboratory data, the CTP and MELD scores of patients were calculated—the latter according to the formula used by Freeman et al.[12] To avoid a negative score, values lower than 1.0 were considered equivalent to 1, and the maximal creatinine was limited to 4.0 mg/dl. The MELD-Na and iMELD scores were calculated according to the formula used by Biggins et al.,[7] and MESO was calculated according to the formula used by Huo et al.[13]

Outcomes

Operative mortality was defined as death within 1 month after surgery or during hospital stay after surgery. Operative and overall mortalities were assessed. The patients were divided into those who died and those who survived during the total study period. These groups of survivors and non-survivors were then analyzed, and the following variables were assessed for correlation with mortality: clinical characteristics, surgical characteristics, and the scores of CTP, MELD, and MELD-based indices.

Statistical Analysis

Statistical analysis was performed using the SPSS v15.0 (SPSS Inc., Chicago, IL, USA). All continuous variables are presented as a median (range), and the categorical variables as a number (percentage). To compare survival and non-survival groups, the Mann–Whitney ranked sum test was used for continuous variables, and the Fisher's exact test for categorical variables. The receiver operating characteristic (ROC) curve was analyzed to determine cutoff values for operation time, estimated blood loss, transfusion amount, and the scores of CTP, MELD, and MELD-based indices that had the most appropriate sensitivity and specificity for differentiating between survival and non-survival groups. The cutoff values were validated by the area under the ROC curve (AUC). For the univariate analysis of predictors of mortality, the log-rank test was used, and the forward stepwise regression of Cox's proportional hazard model was used for the multivariate analysis. A p value <0.05 was considered significant.

Results

Clinical Characteristics

A total of 53 patients with chronic liver disease underwent emergency surgery with general anesthesia. Forty-two of them (79.2%) were male, and the median age of all patients was 55 years (13–85 years). The median follow-up period was 11 months (range, 1–91 months). Forty-two (79.4%) patients had liver cirrhosis. Fifteen of them had hepatocellular carcinoma (HCC). The etiology of liver disease was

hepatitis B virus infection in 25 (47.2%) which was most prevalent, followed by alcoholism in 14 (26.4%). Nine (17%) patients had a CTP class of C.

Indications for Emergency Surgery and Operative Data

The most common indications for emergency operation were acute appendicitis in 15 (28.3%) patients and panperitonitis due to ulcer perforation in 16 (30.2%) patients. Table 1 indicates the number of surgery performed by type. These included surgeries of low, medium, and high risk. The category of surgeries that were performed most often (n=22, 41.5%) had a high risk.

The median length of hospital stay was 12 days (3–73 days). The median operation time was 98 min (11–396 min). Median estimated blood loss was 50 ml (0–11,000 ml), and blood loss was minimal in both open and laparoscopic surgeries which did not involve resection of an organ. The greatest blood loss was 11,000 ml in a patient undergoing total gastrectomy for a bleeding gastric ulcer. The median length of stay in the intensive care unit was 2 days (0–33 days). The number of patients who underwent low-risk surgery was 15 (28.3%), medium-risk surgery 16 (30.2%), and high-risk surgery 22 (41.5%).

Mortality

During the study period, 19 of the 53 patients died. Five of them (9.4%) occurred within 1 month after surgery. Most mortality cases were due to liver failure. Three cases were due to HCC carcinomatosis and hematologic cause. Table 2 shows the clinical and surgical characteristics of survivors

Table 1 Characteristics of disease entities and operative procedures (n=53)

Disease entities	Number of patients, (%)	Operative procedure	Surgery performed, n
Appendicitis	15 (28.3)		
		Appendectomy	8
Acute appendicitis	14	Laparoscopic appendectomy	6
Appendicitis, perforated	1	Appendectomy	1
Hernia	5 (9.4)		
Inguinal	2	Lichenstein hernioplasty	2
Umbilical	3	Repair of umbilical hernia[a]	3
Cholecystitis	5 (9.4)		
Acute cholecytitis	4	Laparoscopic cholecystectomy	4
GB empyema	1	Cholecystectomy	1
Panperitonitis	16 (30.2)		
GU perforation	14	Primary repair and omentopexy[b]	9
		Resection of stomach[c]	3
		Diagnostic laparoscopy[d]	1
		Feeding jejunostomy[d]	1
Sigmoid ulcer perforation	1	T colon loop colostomy	1
SBP	1	Denver shunt removal	1
Bleeding	3 (5.7)		
Ulcer bleeding	2	Total gastrectomy	1
		Gastrojejunostomy, Splenectomy	1
Variceal bleeding	1	Bleeder ligation	1
Hemoperitoneum	4 (7.6)		
Small bowel perforation	1	Segmental resection of small bowel	1
Stab wound	1	Hematoma evacuation	1
Spleen origin[e]	2	Splenectomy	2
Other	5 (9.4)		
Hepatoma rupture	1	Irrigation and drainage	1
Pancreatic pseudocyst	1	Distal pancreatectomy	1
Perianal fistula	1	Curettage of perianal fistula tract	1
Intestinal obstruction	1	Segmental resection of small bowel	1
Periappendiceal abscess	1	Ileocecectomy	1

GB gallbladder, *GU* gastric ulcer, *SBP* spontaneous bacterial peritonitis, *T colon* transverse colon

[a]Two cases were segmental resection of small bowel

[b]One case was a laparoscopic repair

[c]One case was a laparoscopic resection

[d]The site of perforation could not be found because cancer sealed off the site of perforation

[e]Onecase was a spleen laceration and the other was splenic vein pseudoaneurysm rupture

Table 2 Comparison of clinical and operative characteristics among patients who survived or died

Variables	Survivors (n=34)	Non-survivors (n=19)	p value
Median age (years)	54 (13–80)	56 (41–85)	0.110
Sex, n (%)			
Female	9 (26.5)	2 (10.5)	0.170
Male	25 (73.5)	17 (89.5)	
Liver disease, n (%)			
Alcohol liver disease	3 (8.8)	0 (0.0)	0.04
Viral hepatitis[a]	7 (20.6)	1 (5.3)	
Cirrhosis[b]	24 (70.6)	18 (94.7)	
Laboratory finding			
Albumin, mg/dL	3.6 (2.0–4.9)	2.9 (1.8–4.7)	0.018
Bilirubin, mg/dL	1.0 (0.3–25.9)	1.6 (0.5–11.9)	0.120
INR	1.17 (0.9–2.17)	1.27 (0.92–3.49)	0.067
PLT, ×1,000 μL	123 (27–436)	119 (15–355)	0.772
Na	137 (130–144)	135 (126–144)	0.027
Median CTP score	6 (5–11)	8 (5–12)	0.017
CTP class, n (%)			
A	23 (67.6)	7 (36.8)	0.015
B	8 (23.5)	6 (31.6)	
C	3 (8.9)	6 (31.6)	
Median MELD score	9 (6–27)	16 (6–33)	0.012
Median MELD-Na score	12 (7–28)	21 (7–34)	0.003
Median iMELD score	31 (14–50)	40 (22–64)	0.002
Median MESO score	7 (4–20)	12 (4–24)	0.009
Operation risk, n (%)			
Low	12 (35.3)	3 (15.8)	0.059
Moderate	11 (32.4)	5 (26.3)	
High	11 (32.4)	11 (57.9)	
Admission duration (days)	10 (3–57)	14 (4–73)	0.028
Operation time (min)	91 (11–230)	129 (50–396)	0.05
Intensive care unit stay duration (days)	0 (0–6)	3.5 (0–33)	0.009
Bleeding amount (mL)	25 (0–3,500)	400 (0–11,000)	0.089
Transfusion amount (mL)	0 (0–1,000)	0 (0–5580)	0.106

Continuous variables were presented as median (range) and analyzed by Mann–Whitney ranked sum test, and categorical variables were presented as a number (percentage) and analyzed by Fisher's exact test

CI confidence interval, *CTP* Child–Turcotte–Pugh, *MELD* Model for End-stage Liver Disease, *Na* sodium; *iMELD* integrated MELD, *MESO* MELD to sodium ratio

[a]Six patients had hepatitis virus B infection, and two had hepatitis virus C infection

[b]Liver cirrhosis included 11 cases of alcoholic liver cirrhosis

and non-survivors. The following characteristics significantly differed between survivors and non-survivors: prevalence of alcoholic liver disease, viral hepatitis, and cirrhosis (p= 0.04); preoperative albumin level (p= 0.018), sodium level (p=0.027); length of hospital stay (p= 0.028); and length of intensive care unit stay (p= 0.009). The median bleeding and transfusion volumes did not significantly differ between survival and non-survival groups. The scores of CTP (p=0.015), MELD (p=0.012), MELD-Na (p=0.003), iMELD (p=0.002), and MESO (p=0.009) were significantly higher in non-survival group.

Predictors of Mortality

The preoperative CTP, MELD, and MELD-based indices scores were compared. As shown in Fig. 1, the MELD-Na and iMELD scores showed a wider distribution than the other scores, and this distribution differed significantly between survivors and non-survivors. Based on the analysis of the ROC curves, the optimal cutoff values for predicting overall mortality were seven points for CTP, 11 for MELD, 16 for MELD-Na, 35 for iMELD, and 8 for MESO (Fig. 2). The AUCs for the MELD-Na and iMELD scores were 0.739 and 0.750, respectively—higher than those for CTP, MELD, and MESO scores. Using these cutoff values, the sensitivity ranged from 63.2% to 78.9% (highest for the MELD-Na), and the specificity ranged from 67.6% to 70.6% (highest for the MELD-Na and iMELD). The positive predictive values (PPV) of the MELD-Na and iMELD were 60% and 58.3%, which were higher than PPVs of CTP, MELD, and MESO scores (52.2%, 54.2%, and 50%). The negative predictive values (NPV) for the

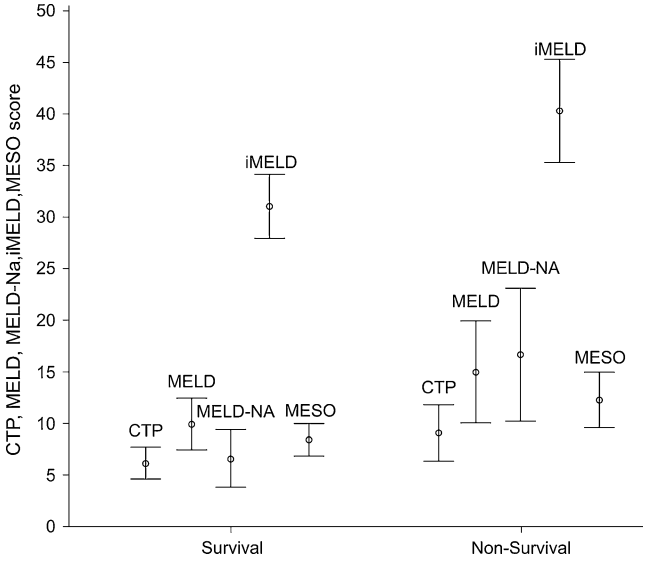
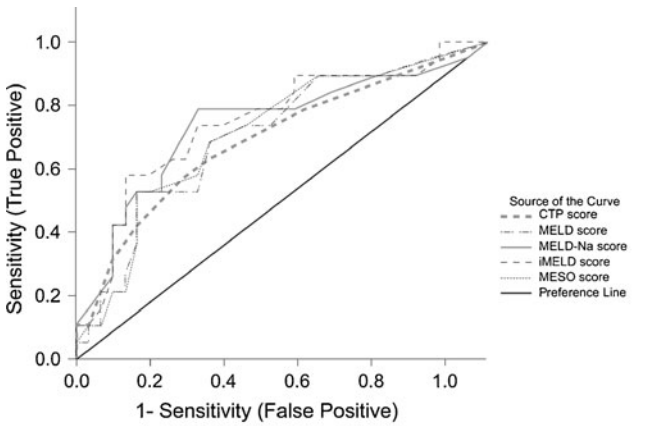


Fig. 1 The distribution of CTP, MELD, MELD-Na, iMELD, and MESO scores among patients with chronic liver disease who survived and died after emergency surgery. MELD-Na and iMELD show most distinguishable distribution between survival and non-survival

MELD-Na and iMELD were 85.7% and 82.8%, which were also higher than those of CTP, MELD, and MESO scores (76.7%, 79.3%, and 80%). According to the univariate analysis, CTP class, transfusion amount, estimated blood loss, CTP, MELD, MELD-Na, iMELD, and MESO scores were significantly correlated with operative mortality. The followings were significantly correlated with



Value	Cut-off	AUC	p Value	Sensitivity	Specificity	PPV	NPV
CTP	7	0.693	.021	63.2	67.6	52.2	76.7
MELD	12	0.707	.013	68.4	67.6	54.2	79.3
MELD-Na	16	0.739	.004	78.9	70.6	60	85.7
iMELD	35	0.750	.003	73.7	70.6	58.3	82.8
MESO	8	0.714	.01	73.7	58.8	50	80

Fig. 2 Calculation and assessment of cutoff values for the CTP, MELD, MELD-Na, iMELD, and MESO scores. The receiver operating characteristic (ROC) curve was used to define cutoff values for CTP, MELD, and MELD-Na scores. MELD-Na and iMELD have higher AUCs, sensitivities, specificities, positive predictive values, and negative predictive values than those of other scores

mortality during the entire follow-up period: age, operation time, CTP class, transfusion amount, estimated blood loss, albumin, INR, sodium, CTP, MELD, MELD-Na, iMELD, and MESO scores. However, in multivariate analysis, CTP class C (p=0.022, hazard ratio [HR]=12.889) was correlated with the operative mortality and estimated blood loss above 300 ml (p<0.001, HR=8.929) and the iMELD score above 35 (p=0.001, HR=7.109; Table 3).

Discussion

Approximately 10% of patients with chronic liver diseases are required to undergo surgical procedures other than liver transplantation for the last 2 years of their lives.[14] The morbidity and mortality of patients with chronic liver disease are influenced by the severity of the liver disease and the type of surgery.[11] Therefore, the presence or absence of chronic liver diseases is evaluated prior to elective surgery. Comprehensive history taking, physical examination, laboratory tests, and radiologic examination are performed. This screening may reveal a previously undetected chronic liver disease or a change in the severity of a previously diagnosed chronic liver disease. In such cases, preoperative management and cautious planning of surgery and anesthesia may reduce the risk of complications and death.

Because postoperative morbidity and mortality are higher in patients with chronic liver disease rather than those without it, numerous studies have focused on how to conduct an effective preoperative evaluation and determine which patients should be eligible for surgery. In the 1960s, the Child score was developed to predict the outcome of placement of a portosystemic shunt.[15] The mortality after abdominal surgery in Child class A patients has been reported to be 10%, Child class B, 30–

Table 3 Multivariate analysis of predictors of postoperative and overall mortality

Mortality	Variable	Hazard ratio	p	95% CI
Operative[a]	CTP class C vs A	12.889	0.022	1.441–115.316
Overall[b]	iMELD score ≥35	7.109	0.001	2.284–22.126
	Estimated blood loss ≥300 ml	8.929	<0.001	2.69–29.636

CI confidence interval, *CTP* Child–Turcotte–Pugh, *MELD* Model for End-stage Liver Disease, *Na* sodium; *iMELD* integrated MELD, *MESO* MELD to sodium ratio

[a] Adjusted for estimated blood loss, transfusion amount, CTP class, CTP score, MELD score, MELD-Na score, iMELD, and MESO

[b] Adjusted for age, operation time, CTP class, transfusion amount, estimated blood loss, albumin, international normalized ratio, sodium, CTP, MELD, MELD-Na, iMELD, and MESO scores

31%; and Child class C, 6–82%.[14,16] In 1973, the Child classification system was modified to the Child–Turcotte–Pugh (CTP) score which has been widely used to predict the risk of surgery in patients with liver cirrhosis.[17] The CTP score does not include renal or respiratory dysfunction, which are prevalent in patients with severe liver diseases, such as decompensated cirrhosis.[18] To assess the risk of placement of a transjugular intrahepatic portal shunt, the MELD score was introduced in 2000,[19] and it has been used to allocate patients awaiting liver transplantation.[20] In addition, several studies examined whether the MELD score was valuable as an outcome predictor of hepatectomy in patients with cirrhosis or HCC.[21,22] The usefulness of CTP vs. MELD scores in predicting postoperative morbidity and mortality of patients with chronic liver disease has been compared, and conflicting results have been produced. Some of these studies reported that the two scores were not significantly different in predicting outcomes,[5,23] while others indicated that the MELD score was more predictive.[6,24,25]

In patients with chronic liver disease, emergency surgery increased mortality and the rate of hepatic decompensation.[5] It is well known that emergency surgery is more significantly correlated with mortality than elective surgery.[5,23,26] However, in the patients who underwent only emergency surgery, studies to evaluate predictors of mortality are rare. The results of those studies including both elective and emergency surgery were conflicting, too. Patients requiring emergency surgery might have infection, inaccurate volume replacement and fasting status, and such conditions can change the score of CTP and MELD.[27] Moreover, in patients with advanced cirrhosis, complications such as variceal bleeding, ascites, and hepatorenal syndrome have been considered to be major causes of mortality.[28] Nevertheless, the preoperative MELD score does not predict the likelihood of these complications. Yoo et al.[29] showed that the preoperative MELD score did not correlate well with the severity of postoperative ascites and hepatic encephalopathy. In particular, ascites is a major complication of liver cirrhosis and has been associated with hyponatremia and severe portal hypertension.[30,31] Because of this association between ascites (a marker of severe liver disease) and hyponatremia, the MELD-Na score was developed. However, studies of the MELD-Na are not abundant. Some reports have indicated that the MELD-Na score is a more accurate predictor of survival than the MELD score in patients awaiting liver transplantation.[7–9]

We examined how well CTP, MELD, and MELD-based indices scores predicted mortality among patients with chronic liver disease who underwent only emergency surgery with general anesthesia. Operative mortality (9.4%) in our study was similar to that of large series.[5,11] However, in comparison with mortality of emergency operation, our operative mortality was lower than that of others. We thought that the cause was a difference of operation type. We determined that the best cutoff values for assessing the risk of operative mortality were 10 points for the CTP, 19 for the MELD, 20 for the MELD-Na, 40 for the iMELD, and 14 for the MESO score. The AUCs for the MELD-Na and the iMELD were the highest. The MELD-Na and iMELD showed best values of sensitivity, specificity, PPV, and NPV. These scores and other clinical and surgical characteristics were assessed as predictors of operative and overall mortality. An iMELD score above 35 and estimated blood loss above 300 ml were correlated with the overall mortality after surgery, but the operative mortality was correlated with only CTP class C. In univariate analysis, low albumin, sodium level, and intraoperative transfusion amount were positively associated with mortality, which is similar to other studies.[5,23,24] However, our study showed CTP class C as an only independent prognostic factor in the operative mortality as like the reports of some studies.[2,6] Telem et al.[26] and Costa et al.[10] suggested the amount of estimated blood loss and iMELD scores as predictors of mortality. In our study, intraoperative blood loss above 300 ml and iMELD-Na above 35 points were found as predictors for overall mortality in multivariate analysis. Among disease entities, appendicitis or panperitonitis that did not perform organ resection occupied a high portion in our study, and the total number of patients was only 53. Our results do not show superiority of MELD-based indices compared to CTP score in predicting operative mortality because of low severity of surgery and the small number of patients.

In conclusion, among the examined variables, iMELD could be considered the best predictor of mortality of chronic liver disease patients who undergo emergency non-hepatic surgery with general anesthesia. Since the severity of surgical procedure is classified differently in other studies, the classification system needs to be modified to compare our study with other studies. Mortality may also be adversely affected by more severe forms of surgery, hypotension during surgery,[5] and operation time longer than 2 h.[20] Though the predictive value of the iMELD should be assessed in cases with these other variables, we suggest that surgery should be undertaken with minimal intraoperative blood loss by using laparoscopy and avoiding organ resection, and surgery itself should be avoided until recovery of liver function, if possible, in patients with chronic liver disease and iMELD-Na scores above 35 points. Additional large-scale prospective studies of preoperative predictors of mortality and perioperative therapeutic strategies are required to improve survival rates in this setting.

Conflict of Interest The authors disclose no conflicts.

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ORIGINAL ARTICLE

Clinical Outcomes and Prognostic Factors of Cancer Patients with Pyogenic Liver Abscess

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Abstract
Purpose Pyogenic liver abscess (PLA) of cancer patients often has a poor prognosis, but corresponding prognostic factors are less investigated. This study aimed to identify predictors of mortality in cancer patients with PLA.
Patients and Methods Medical records of 85 consecutive cancer patients (46 with hepatobiliary pancreatic cancer, 14 with gastrointestinal cancer, and 25 with non-digestive system cancer) having PLA who were admitted to two university hospitals were retrospectively reviewed. The predictors of mortality were determined using Cox regression model.
Results The overall case fatality rate was 33%. In multivariate analysis, the greater Acute Physiology and Chronic Health Evaluation II score (P=0.028), multiloculated abscess (P=0.025), and polymicrobial infection (P=0.003) were associated with mortality. In subgroup analysis of the 25 patients with multiloculated abscess undergoing percutaneous catheter drainage as primary treatment, the case fatality rates of patients with a solitary smaller abscess (size<5 cm), those with a solitary larger abscess (size>5 cm), and those with larger multiple abscesses were 0%, 36%, and 85%, respectively (P= 0.002; using χ^2 for trend).
Conclusions The advanced disease stage, multiloculated abscess, and polymicrobial infection posed a greater mortality risk in cancer patients with PLA. Moreover, an early surgical approach should be considered for cancer patients having large, multiloculated complex PLAs.

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Keywords Pyogenic liver abscess · Risk factor · Mortality · Neoplasm

Introduction

Pyogenic liver abscess (PLA) is an uncommon but potentially lethal disease affecting human beings worldwide with a crude incidence rate ranging from two to 45 cases per 100,000 hospital admissions-year.[1–5] Underlying malignancy, besides diabetes mellitus and biliary tract disorders, is a common coexisting disease among PLA patients and accounts for 5% to 42% of these patients in various countries.[1,2,6–14] In the literature, concomitant malignancy unlike other underlying disorders has been found to be a risk factor for PLA mortality.[1,8,10] Despite the improvement in diagnostic imaging techniques and therapeutic modalities, the case fatality rate of PLA patients with underlying malignancy has varied from 11% to 80% in the last two decades[8,10,12,14–17]; nevertheless, these rates remain unacceptably high. Awareness of the clinical presentation and prognostic factors of high-risk patient groups is very important. Some studies have attempted to explore the clinical course and prognostic factors of PLA patients with underlying malignancy[12,16,18]; however, an appropriate assessment of the risk factors for mortality regarding abscess characteristics and/or microbiological information was lacking in the previous reports. To identify prognostic factors for PLA patients with underlying malignancy, we conducted a retrospective study to collect detailed clinical information of these patients, including clinical manifestations, imaging and laboratory findings, microbiologic studies, treatment, and outcomes.

Materials and Methods

Study Subjects and Settings

From January 2000 through December 2009, medical records of all patients >18 years of age who had been discharged with the diagnosis of PLA from the Chung Shan Medical University Hospital (CSMUH) and China Medical University Hospital (CMUH) were reviewed retrospectively. CSMUH and CMUH are, respectively, 1,324- and 2,036-bed teaching hospitals in central Taiwan. PLA was defined based on the following conditions: (a) evidence of one or more discrete abscess cavities of the liver from imaging studies (endoscopic retrograde cholangiopancreatography, abdominal ultrasonography (US), and/or computerized tomography (CT) scans with contrast enhancement) and (b) positive blood or abscess culture results. In total, 751 patients with PLA were admitted to CSMUH (n=233) and CMUH (n=419) during this period. Of these patients, 85 (11%) PLA patients (29 from CSMUH and 56 from CMUH) who had coexisting malignant disease were included in our study. All types of cancer were confirmed histopathologically. This study was approved by the Institutional Review Board of each hospital.

Data Collection and Variable Definition

Demographic data, clinical presentations, and course, laboratory, microbiological, and imaging findings, treatment, and outcomes were reviewed and analyzed. PLA patients with underlying malignancy included in this study were divided into three groups based on their primary neoplastic sites. Hepatobiliary pancreatic cancer group comprised patients whose cancers originated from the hepatic parenchyma, biliary system, and pancreas. Gastrointestinal cancer group was composed of patients whose cancers originated from the esophagus, stomach, and small and large intestines. Non-digestive system cancer group included patients whose cancers originated from neither hepatobiliary pancreatic nor gastrointestinal sites. The severity of illness on admission was evaluated with the Acute Physiology and Chronic Health Evaluation (APACHE) II scoring system in the first 24-h period after arrival.[19] The APACHE II scoring assessment was modified according to recommendation of Knaus et al.[20] and Meakins et al.[21] so that the unavailable measures of arterial pH and partial pressures of oxygen were assigned a score of zero in the scoring system because arterial blood sampling is not indicated for every patient at the time of admission. The patient's status prior to admission was assessed using the Eastern Cooperative Oncology Group performance scale.[22] Aspiration or biopsy of the cavity lesion for cytological or pathological examination was performed to rule out liver tumor when a predominately solid or tumor-like liver lesion was depicted in the images (US or CT). The imaging results were assessed and reviewed by a well-trained and licensed radiologist. Abscesses were considered cryptogenic in origin when no causative lesions were demonstrated. Multiple abscesses was defined as the presence of normal intervening liver parenchyma separating multiple abscesses and/or evidence that the abscesses were in different segments of the liver. Multiloculated abscess was defined as an abscess with enhancing internal septations on contrast-enhanced CT. Abscess specimens obtained from imaging-guided percutaneous needle aspiration (PNA) or imaging-guided percutaneous catheter drainage (PCD) were processed by Gram stain, bacterial cultures (standard aerobic and anaerobic diagnostic methods), and tests for antimicrobial susceptibility.[23] Initial empirical broad-spectrum antibiotics were administered intravenously after blood and/or liver abscess specimens had been

obtained. Antibiotics were subsequently tailored, if necessary, based on the culture and sensitivity results. The multidrug resistant (MDR) isolate was defined as the pathogen resistant to three or more of the antibiotic classes. Response to treatment was evaluated in each patient by a series of follow-up abdominal US or CT scans of the liver in the hospital and/or at the time of subsequent office visits after discharge. Hospital mortality was defined as death during the same hospital admission for PLA.

Statistical Analysis

Comparisons between groups for continuous variables were made using either the Student's *t* test or the Mann–Whitney *U* test, as appropriate. Categorical variables were compared between groups, with either the chi-square test or Fisher's exact test (if the expected value of at least one cell was <5). The relationships between (1) demographics, clinical features, laboratory results, and therapeutic variables and (2) mortality were analyzed. Variables significant by univariate analysis were subjected to the Cox regression with a forward method to identify significant independent risk factors for mortality. Hazard ratios and 95% confidence intervals were estimated in the Cox regression model. The statistical analyses above were performed with SAS software, version 8.2 (SAS Institute Inc., Cary, NC, USA). A two-tailed p value <0.05 was considered statistically significant.

Results

Demographic Data, Concomitant Diseases, Clinical Features, and Origin of Liver Abscess

Those 85 PLA patients with underlying malignancy (46 with hepatobiliary pancreatic cancer, 14 with gastrointestinal cancer, and 25 with non-digestive system cancer) had a mean age of 65.5±17.4 years. The group with hepatobiliary pancreatic cancer comprised 18 patients with cholangiocarcinoma, eight with hepatocellular carcinoma, eight with pancreatic cancer, six with gallbladder cancer, three with hepatocellular carcinoma and pancreatic cancer, and three with cholangiocarcinoma and pancreatic cancer. The group with gastrointestinal cancer was composed of four patients with gastric cancer, eight with colorectal adenocarcinoma, and two with esophageal cancer. The 25 patients with non-digestive system cancer included five patients with renal cell carcinoma, four with cervical carcinoma, three with bladder cancer, three with gum cancer, three with leukemia, two with soft tissue sarcoma, two with lung cancer, two with nasopharyngeal carcinoma, and one with brain cancer. Significant differences were noted between the survival and non-survival groups with respect to gender, APACHE II score on admission, the type of cancer, the presence of fever/chills, jaundice, disturbance of consciousness, and ascites on admission, and the proportion of biliary or cryptogenic origin of liver abscess. The detailed demographic data, clinical features, concomitant disorders, and origin of 85 cancer patients with PLA are shown in Table 1.

Microbiological, Laboratory, and Imaging Findings

In patients from whom blood cultures were obtained, the recovery frequency of bacterial blood culture was 67% (54 out of 81 patients) with 63 isolates. In patients from whom abscess cultures were obtained, the recovery frequency of bacterial abscess culture was 95% (81 out of 85 patients) with 152 isolates. *Escherichia coli* (49%) was the most commonly isolated aerobe among these patients, followed by *Klebsiella pneumoniae* (48%). *Bacteroides* spp. (67%) were most frequently seen among 21 anaerobic isolates. Forty-six percent of polymicrobial infections were mixed aerobic–anaerobic. Patients in non-survival group were more likely to have *E. coli* infection; polymicrobial or MDR isolates; elevated aspartate aminotransferase or serum albumin levels; the presence of multiple, bilobar, or multiloculated abscesses; and the occurrence of pleural effusion, and they were less likely to be infected with *K. pneumoniae* compared to patients in the survival group. Thirteen (57%) of the 23 patients with multiple abscesses had multiloculated abscesses. Microbiological, laboratory, and imaging findings in the 85 patients are exhibited in Table 2.

Therapeutic Modality and Clinical Outcome

Treatment and outcomes are shown in Table 3. Each patient was initially treated with one of three therapeutic methods: (a) antibiotic therapy only, (b) antibiotics plus imaging-guided PNA, or (c) antibiotics plus imaging-guided PCD. All patients initially received parenteral empirical antibiotics, including cephalosporins, penicillins, aminoglycosides, and metronidazole. The choice of initial treatment was based on the preference of the clinician in charge or the condition of the patient. A total of 45 patients (53%) initially received either first- or second-generation cephalosporins with or without gentamicin; there was no difference in initial antibiotic treatment between the survival and non-survival groups (p=0.399). Only seven patients did not receive PCD in conjunction with antibiotics as the primary treatment. Three patients with non-digestive system cancer, who each had a solitary liver abscess with size >3 cm in diameter and cryptogenic etiology, underwent a primary intermittent PNA that was performed by a clinician with great skill in this procedure, and all three

Table 1 Demographic data, clinical features, and concomitant diseases among 85 cancer patients with pyogenic liver abscess

Variable	All patients (n=85)	Survivor (n=57)	Non-survivor (n=28)	p
Gender, male (%)	44 (52)	34 (60)	10 (36)	0.038
Age, mean±SD (years)	65.5±17.4	63.6±18.9	69.5±13.4	0.142
Duration of symptoms before admission, mean±SD (days)	6.2±5.0	6.8±5.2	4.8±4.2	0.107
Duration of diagnosis made after admission, mean±SD (days)	1.3±3.0	1.4±3.4	1.2±2.0	0.844
APACHE II score on admission, mean±SD (points)	16.2±5.1	15.4±4.7	17.9±5.6	0.041
ECOG performance status, mean±SD (points)	1.5±0.8	1.5±0.9	1.5±0.7	0.884
Type of cancer, No. (%)				0.007
Hepatobiliary pancreatic cancer	46 (54)	26 (46)	10(72)	
Gastrointestinal cancer	14 (17)	8 (14)	6 (21)	
Non-digestive system cancer	25 (29)	23 (40)	2 (7)	
Coexisting diseases,[a] no. (%)				
Diabetes mellitus	34 (40)	21 (37)	13 (46)	0.396
Biliary disorders[b]	35 (41)	26 (46)	9 (32)	0.236
Alcoholism	8 (9)	4 (7)	4 (14)	0.430
Liver cirrhosis	10 (12)	7 (12)	3 (11)	1.000
Uremia	5 (6)	2 (4)	3 (11)	0.326
Symptoms on admission,[a] no. (%)				
Fever/chills	78 (92)	55 (97)	23 (82)	0.036
Abdominal pain	44 (52)	31 (54)	13 (46)	0.490
Malaise	43 (51)	28 (49)	15 (54)	0.700
Respiratory symptoms[c]	39 (46)	29 (51)	10 (36)	0.187
Anorexia	34 (40)	25 (44)	9 (32)	0.300
Nausea/emesis	30 (35)	20 (35)	10 (36)	0.955
Signs on admission,[a] no. (%)				
Body temperature >38.3°C	60 (71)	39 (68)	21 (75)	0.532
RUQ tenderness	41 (48)	28 (49)	13 (46)	0.815
Jaundice	34 (40)	12 (21)	22 (79)	<0.001
Blood pressure <90/60 mmHg	18 (21)	11 (19)	7 (25)	0.545
Murphy's sign[d]	8 (9)	6 (11)	2 (7)	1.000
Hepatomegaly	3 (4)	1 (2)	2 (7)	0.251
Disturbance of consciousness	3 (4)	0	3 (11)	0.033
Ascites	10 (12)	0	10 (36)	<0.001
Origin of abscess, no. (%)				
Biliary origin[e]	56 (66)	34 (60)	22 (79)	0.084
Cryptogenic origin	20 (24)	18 (32)	2 (7)	0.013
Others[f]	9 (11)	5 (9)	4 (14)	0.469

APACHE Acute Physiology and Chronic Health Evaluation, *ECOG* Eastern Cooperative Oncology Group, *RUQ* right upper quadrant, *SD* standard deviation

[a] Patients fitting into multiple categories were counted in each category

[b] Biliary disorders including biliary stone diseases (cholelithiasis, choledocholithiasis, or hepatolithiasis) and prior hepatobiliary surgery

[c] Respiratory symptoms including cough, dyspnea, or chest distress

[d] Murphy's sign: deep inspiration or cough during subcostal palpation of RUQ producing increased pain and inspiratory arrest

[e] Biliary origin of liver abscess including suppurative cholangitis and acute cholecystitis

[f] Other origins of liver abscess including a recent history of transcatheter arterial embolization for hepatocellular carcinoma (n=2), a recent surgery (n=2), pancreatitis (n=3), and empyema of gallbladder (n=2)

patients subsequently survived. The remaining four patients who had a history of underlying hepatobiliary pancreatic cancer initially received only antibiotics because of multiple small liver abscesses (size <2 cm in diameter), and two eventually died. Twenty-eight patients with biliary obstruction required biliary drainage via endoscopic retrograde

Table 2 Bacterial, laboratory, and imaging findings among 85 cancer patients with pyogenic liver abscess

Variable	All patients (n=85)	Survivors (n=57)	Non-survivors (n=28)	p
Microbiological characteristics, no. (%)				
Escherichia coli infection[a]	42 (49)	18 (32)	24 (86)	<0.001
Klebsiella pneumoniae infection[b]	41 (48)	37 (65)	4 (14)	<0.001
Anaerobic infection[c]	19 (22)	12 (21)	7 (25)	0.681
Polymicrobial infection[d]	41 (48)	17 (30)	24 (86)	<0.001
MDR isolates	37 (44)	16 (28)	21 (75)	<0.001
Bacteremia	54 (67)[e]	36 (66)[f]	18 (69)[g]	0.736
Laboratory findings, no. (%)				
White blood cell count (>10^4 or <3,000 cells/mm^3)	72 (85)	46 (81)	26 (93)	0.205
Hemoglobin (<14 g/dL in male, <12 g/dL in female)	78 (92)	50 (88)	28 (100)	0.090
Aspartate aminotransferase (>40 U/L)	55 (65)	38 (67)	17 (61)	0.589
Serum albumin (<3.5 g/dL)	62 (73)	34 (60)	28 (100)	<0.001
Serum total bilirubin (>1.3 mg/dL)	59 (69)	35 (61)	24 (86)	0.022
Promthrombin time (>13.1 s)	53 (62)	35 (61)	18 (64)	0.797
Serum creatinine (>1.3 mg/dL)	36 (42)	27 (47)	9 (32)	0.182
Imaging findings, no. (%)				
Multiple abscesses	23 (27)	4 (7)	19 (68)	<0.001
Gas-forming abscess	16 (19)	13 (23)	3 (11)	0.180
Bilobar abscess	13 (15)	5 (9)	8 (29)	0.025
Abscess >5 cm in diameter	63 (74)	41 (72)	22 (79)	0.511
Multiloculated abscess	27 (32)	12 (21)	15 (54)	0.002
Abscess rupture	4 (5)	3 (5)	1 (4)	1.000
Pleural effusion	41 (48)	21 (37)	20 (71)	0.003

MDR multi-drug resistant, *SD* standard deviation

[a] *E. coli* infection: *E. coli* was cultured in blood and/or abscess cultures

[b] *K. pneumoniae* infection: *K. pneumoniae* was cultured in blood and/or abscess cultures

[c] Anaerobic infection: anaerobic isolates were cultured in blood and/or abscess cultures

[d] Polymicrobial infection: mixed bacterial flora were cultured in blood and/or abscess cultures

[e] Blood cultures being obtained in 81 patients

[f] Blood cultures being obtained in 55 patients

[g] Blood cultures being obtained in 26 patients

cholangiopancreatography or percutaneous transhepatic cholangiography. Secondary surgical intervention was required in nine patients (four with initial antibiotics alone and five with initial PCD) with hepatobiliary pancreatic cancer. Of the nine patients having a secondary aggressive procedure, five had good clinical response to subsequent intervention and four died of uncontrolled sepsis. All 27 patients with multiloculated abscesses received PCD as primary treatment. Among these patients with multiloculated abscesses, the case fatality rates of patients with a smaller solitary abscess (size within 3–5 cm in diameter), those with a larger solitary abscess (size >5 cm in diameter), and those with larger abscesses (size >5 cm in diameter) combined with multiple abscesses were 0% (0 out of 3), 36% (4 out of 11), and 85% (11 out of 13), respectively (P=0.002; using χ^2 for trend). Of the six recurrences, two were successfully treated with repeated PCD and four died. No metastatic infection developed in all patients. During hospitalization, 28 patients died, yielding an overall hospital mortality rate of 33%. The averaged duration of follow-up after discharge was 4.8±3.7 months.

Analysis of Prognostic Factors Related to Mortality

Significant clinical variables obtained from univariate analyses as shown in Tables 1 and 2 were subjected to multivariate analysis, with a result of three variables attaining statistical significance in the Cox regression model: APACHE II score on admission (P=0.028), multiloculated abscess (P=0.025), and polymicrobial infection (P=0.003) (Table 4).

Table 3 Treatment and outcomes among 85 cancer patients with pyogenic liver abscess

Variable	All patients (n=85)	Survivors (n=57)	Non-survivors (n=28)	p
Initial treatment, no. (%)				0.575
Antibiotics alone	4 (5)	2 (4)	2 (7)	
PNA/PCD plus antibiotics	81 (95)	55 (96)	26 (93)	
Duration of intravenous antibiotics, mean ± SD (days)	24.9±15.1	22.9±10.8	28.9±21.0	0.086
Duration of total (intravenous + oral) antibiotics, mean ± SD (days)	37.2±21.4	39.8±20.9	32.0±22.0	0.116
Time to defervesce after admission, mean ± SD (days)	9.5±10.8	8.0±7.1	12.7±15.6	0.057
Secondary procedure needed, no. (%)	9 (11)	5 (9)	4 (14)	0.469
Recurrence, no. (%)	6 (7)	2 (4)	4 (14)	0.088
Hospital stay, mean ± SD (days)	29.1±17.9	27.4±15.3	32.6±22.1	0.209

PCD percutaneous catheter drainage, *PNA* percutaneous needle aspiration, *SD* standard deviation

Discussion

Our study disclosed that greater severity of illness, multiloculated abscess, and polymicrobial infection were related to mortality in cancer patients with PLA. From our result, the bacterial and abscess characteristics—polymicrobial infection and multiloculated abscess—appeared to play an important role in the prognosis of cancer patients with PLA. As far as we are aware, this finding has not been previously reported. The mean APACHE II score on admission herein was >16, a number higher than the corresponding scores in previous studies involving general PLA patients with results ranging between 8 and 10.[8,14,15,24] This indicates that cancer patients with PLA may be prone to poor underlying physical conditions and consequently carry a higher risk of fatality. The presence of underlying hepatopancreatobiliary cancer was not a significant risk factor of mortality, a finding in contrast to the observation of Yeh et al.[12] This discrepancy between studies may be attributed to variant study populations.

The frequency of polymicrobial infections is increasing in cancer patients in comparison with that in non-cancer patients.[25,26] Approximately half of cancer patients with PLA in our series had polymicrobial infections, which is higher than the corresponding recovery rate in cancer patients with other sites of infection, ranging from 8% to 32%.[27,28] Current investigations suggest that polymicrobial infections involving sepsis, multiple organ failure, or death may be the consequence of an inability to kill invading pathogens effectively due to immunosuppression.[29–31] Additionally, nearly one half of polymicrobial infections appeared to be mixed aerobic–anaerobic infections. The synergistic effect of this mixed aerobic–anaerobic infection can result in the progression of tissue damage, protect the bacteria from host defenses, inhibit phagocytic killing, protect against the toxic effects of oxygen, induce abscesses, and enhance the virulence of mixed infection.[32,33] Because it takes about 1 week to obtain anaerobic culture results, anaerobic coverage should be considered as the initial empirical antibiotics (including carbapenems, broad-spectrum penicillins combined with a β-lactamase inhibitor, third- or fourth-generation cephalosporins plus metronidazole, and ciprofloxacin plus metronidazole) being administered for cancer patients with PLA.[34]

We found that multiloculated abscesses viewed on images were a significant risk factor for mortality in cancer patients with PLA, a finding similar to the reports of Liew and other investigators.[13,35] Multiloculated abscess of the liver has been increasingly found with the evolution of diagnostic imaging techniques, yet its mechanism has not been fully elucidated. The possible explanations for this configuration include (a) a coalescent process of clustering

Table 4 Prognostic factors in relation to mortality by multivariate analysis for 85 cancer patients with pyogenic liver abscess

Variable	HR[b] (95% CI)	p
APACHE II score on admission (points)	1.1 (1.1–1.2)	0.028
Multiloculated abscess (presence vs. absence)	2.6 (1.1–5.9)	0.025
Polymicrobial infection[a] (presence vs. absence)	5.5 (1.8–17)	0.003

APACHE Acute Physiology and Chronic Health Evaluation, *CI* confidence interval, *HR* hazard ratio

[a] Polymicrobial infection: a mixture of different bacteria growing in blood or abscess cultures

[b] Using Cox regression with a forward method

abscesses in the formation of a larger solitary abscess in which the septation components can be broken and liquefied and these clustering abscesses can communicate with each other[36,37] and (b) the aggregation of multiple small locules under an immature form of abscess with poor liquefaction cannot be fused and communicate with each other.[38,39] The abscess characteristics may influence the effectiveness of percutaneous drainage. Barakate and other authors reported that the effectiveness of PCD for multiloculated abscesses might be reduced due to compartmentalization of abscesses with thick, viscid pus and surgical intervention as the initial step for eradication of multiloculated liver abscesses had a favorable result with less treatment failure, less need for secondary procedures, or a shorter hospitalization compared with those receiving percutaneous drainage.[13,35,40–42] An early surgical approach may be considered as a reasonable therapeutic modality for cancer patients with large multiloculated complex liver abscesses; however, the effectiveness of this modality needs more prospective experiments to prove its efficacy.

A potential limitation of this study relates to the inherent weakness of its retrospective design. Our data were limited to what had been recorded in the medical records; clinical presentation according to medical records may inevitably have insufficient information that could impact the validity and attenuate the findings. Furthermore, we could not assess the APACHE II arterial blood parameters in all patients. In practice, arterial blood sampling is not routinely measured in every patient on admission unless the patient's disease is severe or critical. According to Knaus et al.,[20,21] when data have not been collected, they can be assumed to have a weight of zero; this assumption has been tested and verified. However, the present study included the largest sample size of its kind focusing on PLA with concomitant malignancy.[12,16]

Conclusion

We demonstrated that the presence of greater APACHE II scores, multiloculated liver abscess, and polymicrobial infection were independent predictors of mortality in cancer patients with PLA. Clinicians should consider applying an early surgical approach to cancer patients with PLA exhibiting a poor response to primary treatment, particularly to those having large multiloculated complex abscesses.

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ORIGINAL ARTICLE

The Role of Preoperative [18F]Fluorodeoxyglucose Positron Emission Tomography in Predicting Early Recurrence After Curative Resection of Hepatocellular Carcinomas

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Abstract
Purpose ^{18}F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) scan reflects tumor differentiation and predicts clinical outcome in patients with hepatocellular carcinoma (HCC). We investigated the correlation of PET scans with tumor differentiation and early tumor recurrence (time-to-recurrence <1 year).
Methods We reviewed the medical records of 93 patients with HCC who underwent curative resection at our hospital from August 2004 through December 2008. PET scans were performed preoperatively, and the maximum standardized uptake value of the tumor (SUV_{tumor}) and the tumor-to-non-tumor SUV ratio (TNR) were calculated from FDG uptake.
Results Twenty-six (27.9%) had recurrences and 12 of them (46.2%) had early recurrences. SUV_{tumor} and TNR correlated strongly with tumor differentiation ($p<0.001$). Early recurrence-free and the overall survival rates in the low TNR group (TNR <2.0) were higher than in the high TNR group (TNR ≥2.0) ($p=0.015$, $p=0.013$). According to univariate analysis, predictors of early tumor recurrence were large tumor size (≥5 cm), high TNR (≥2), high SUV_{tumor} (≥4), and high Edmoson–Steiner grade. However, on multivariate analysis, none of the examined factors were statistically significant independent predictor.
Conclusion PET scans reflect tumor differentiation in HCCs. Because high TNR (TNR ≥2) and SUV_{tumor} (SUV ≥4) were these cutoff point significant predictors in univariate analysis, future studies with more statistical power are needed to assess the significance.

Keywords Hepatocellular carcinoma · Early recurrence · ^{18}F-FDG PET

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Introduction

Hepatocellular carcinoma (HCC) is a fatal malignant tumor with the sixth highest incidence worldwide among malignant tumors and the third highest mortality.[1,2] In Korea, the incidence of HCC has been reduced greatly because of the hepatitis B virus vaccine.[3] Liver resection is a radical treatment method for managing early liver cancer. However, tumor recurrence after curative surgery has limited treatment outcomes. Tumor size, capsular invasion, positive tumor resection margins, satellite nodules, microvascular invasion, serum alpha-fetoprotein, and serum alanine transaminase have been reported as risk factors associated with early recurrences.[4–7] The recurrence rate within 1 year after radical resection is 16.7–40.2%,[4,8–10] and the interval from radical surgery to recurrence is an important predictor

of survival after recurrence.[11] Recurrences of cancer within 1 year after surgery are associated with a higher morality than recurrences after 1 year treated in the same manner.[8] In addition, patients who develop multicentric recurrences within 1 year after surgery die within 20 months after recurrence.[12] Therefore, studies have been conducted to elucidate predictors of early recurrence which was defined as the recurrence of HCC within 1 year after curative surgery.[4,8–10,12–14]

Recent research has focused on imaging modalities that may complement clinocopathological predictors of early recurrence. In particular, ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) has been used as a predictor of outcomes in various cancers, such as those of the head and neck, pancreas, colon, cervix, as well as non-small cell lung cancer and malignant lymphoma.[15–18] We previously reported that HCCs with high uptake of ^{18}F-FDG are more aggressive, based on the profile of gene expression, than HCCs with low uptake of ^{18}F-FDG.[19] Tumors with the enhancement of ^{18}F-FDG uptake on PET scans had poor differentiation and reduced expression of *p*-glycoprotein. Thus, we suggested that ^{18}F-FDG PET is a useful tool for predicting outcomes of HCCs.[20] ^{18}F-FDG PET has also been helpful in evaluating treatments and predicting clinical outcomes in liver malignancies.[21] In the current study, we sought to determine whether or not preoperative ^{18}F-FDG PET of HCCs could predict early recurrence—i.e., within 1 year after curative surgery.

Materials and Methods

Patients Selection

This retrospective study was conducted with data from patients who underwent curative liver resection for primary HCC from August 2004 to December 2008. All surgeries were performed by a single surgeon to control for potential differences in surgical technique among surgeons. The institutional review board approved the study and the need for informed consent was waived because of the retrospective design. Preoperative ^{18}F-FDG PET scans were performed in all patients. Patients were excluded from the study if they were treated with chemotherapy before surgery that can affect tumor characteristics (e.g., transcatheter arterial chemoembolization, transcatheter arterial chemoinfusion, etc.). Liver mass was confirmed as HCC in all patients by other imaging tests such as computed tomography (CT) or magnetic resonance imaging (MRI) in addition to ^{18}F-FDG PET. A total of 93 patients satisfied these criteria and were included. All patients were followed up for at least 12 months after

Table 1 Patients demographic characteristics according to their recurrence patterns

Characteristics	Early recurrence (n=12)		Recurrence after 1 year (n=14)		Recurrence free (n=67)	
	No. (%)	Mean±SD (range)	No. (%)	Mean±SD (range)	No. (%)	Mean±SD (range)
Mean age, years		54.3±8.6 (41–65)		48.9±10.6 (30–69)		52.7±9.3 (31–72)
Viral hepatitis status						
HBV	11 (92)		11 (79)		63 (96)	
HCV	1 (8)		2 (14)		2 (2)	
Non-B, non-C	0		1 (7)		2 (2)	
AFP level, IU/ml						
Median (range)		214.3 (1.9–18,982.6)		112.2 (25.0–34,080.0)		55.3 (1.5–31,358.0)
ICG R15, %						
Median (range)		8.6 (5.7–22.2)		9.5 (3.3–44.6)		9.1 (3.2–25.5)
Predictive values of PET						
SUV_{tumor} (median, range)		4.3 (2.0–11.6)		3.3 (2.5–10.5)		3.2 (1.9–14.9)
TNR (median, range)		1.9 (1.0–4.0)		1.3 (0.9–3.2)		1.3 (0.8–4.2)
Operation type						
Segmentectomy	0 (0)		2 (14)		8 (12)	
Bisegmentectomy	5 (42)		6 (43)		7 (10)	
Trisegmentectomy	2 (16)		0 (0)		19 (29)	
Hemihepatectomy	5 (42)		6 (43)		33 (49)	

SD standard deviation, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *AFP* alpha-fetoprotein, *ICG R15* indocyanine green retention rate at 15 min, *PET* positron emission tomography, *SUV* maximum standardized uptake value, *TNR* tumor-to-non-tumor SUV ratio

Table 2 Pathologic characteristics and outcomes of the patients

Characteristics	Early recurrence (n=12)		Recurrence after 1 year (n=14)		Recurrence free (n=67)	
	No. (%)	Mean±SD (range)	No. (%)	Mean±SD (range)	No. (%)	Mean±SD (range)
Size (cm)						
Median (range)		5.5 (2.5–10.5)		3.5 (2.3–8.0)		3.2 (1.0–10.5)
Number						
Single	11 (92)		12 (86)		62 (93)	
Multiple	1 (8)		2 (14)		5 (7)	
Surgical margin (cm)						
Median (range)		2.0 (0.2–4.0)		2.4 (2.2–7.5)		2.4 (0.0–10.0)
Microvascular invasion						
No	5(42)		7 (50)		30 (55)	
Yes	7(58)		7 (50)		37 (45)	
Intrahepatic metastasis						
No	11 (92)		13 (93)		66 (99)	
Yes	1 (8)		1 (7)		1 (1)	
Histologic grade						
EM 1	0 (0)		0		4 (6)	
EM 2	6 (50)		8 (57)		30 (45)	
EM 3	6 (50)		6 (43)		33 (49)	
TNM stage						
Stage I	0 (0)		2 (14)		12 (18)	
Stage II	8 (67)		7 (51)		44 (65)	
Stage IIIA	4 (33)		5 (35)		9 (13)	
Stage IIIB	0 (0)		0 (0)		2 (4)	
Mean overall survival, months		27.6±16.3 (5.3–50.9)		36.6±13 (14.2–61.6)		31.8±13.5 (8–62.5)
Mean disease-free survival, months		6.3±3.18 (2.3–11.3)		18.4±8.6 (12.1–46)		26.7±13.4 (5.5–56.9)

SD standard deviation, *EM* Edmonson–Steiner classification, *TNM* tumor–node–metastasis

surgery. During the follow-up, patients were screened for AFP at 1 month after operation and then every 2–3 months and underwent CT scan every 4 months for 1 year after operation and every 6 months after that. When the recurrent diseases were suspected, MRI was taken to confirm the tumor recurrence.

^{18}F-FDG PET Method

All patients were imaged by a whole body PET camera (GE Advance, Milwaukee, WI, USA) prior to surgery. Prior to the test, the patient fasted for a minimum of 6 h, and blood glucose level was controlled to lower than 140 mg/dl.

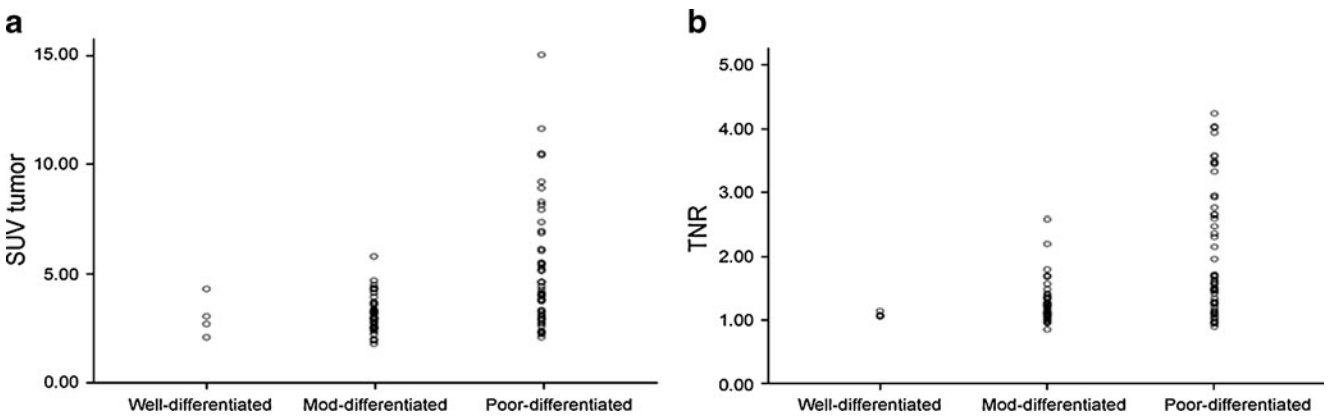

Fig. 1 SUV_{tumor} and TNR correlated significantly with EM grade (all p values<0.001)

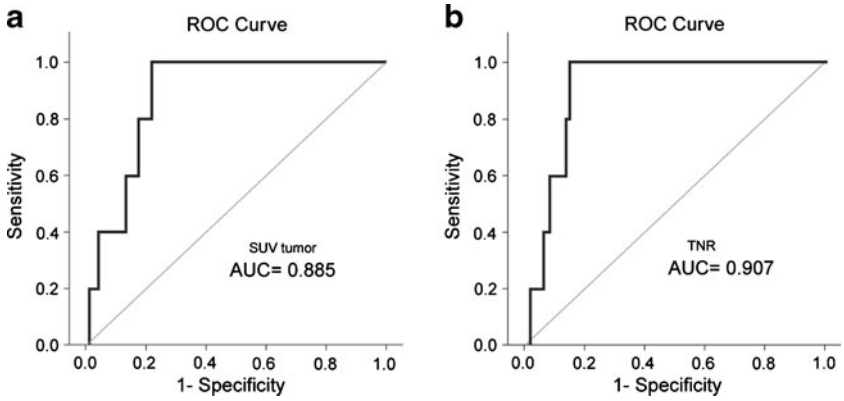

Fig. 2 ROC curves for prediction of early recurrence based on SUV_{tumor} and TNR

Approximately 370 MBq ^{18}F-FDG was injected intravenously, and after 50–60 min, the area from the neck to the knee was imaged using the 2D mode. For semiquantitative evaluation, the maximum standardized uptake value of the tumor (SUV_{tumor}) was calculated by measuring the absorption of ^{18}F-FDG by tumors in the region of interest (ROI), and the tumor-to-non-tumor ratio (TNR) was measured simultaneously by comparing the SUV of tumors with the SUV of adjacent tissues.

$$SUV_{tumor} = [\text{maximal radioactivity concentration in ROI (in microcurie per gram)/injected dose (in microcurie per gram)/patient's weight (in kilograms)}]$$

$$TNR = [\text{SUV of tumor tissue/SUV of the adjacent normal tissue}]$$

Statistical Analysis

All quantitative data are presented as mean±standard deviation, unless otherwise noted. The following factors were included in the statistical analysis: tumor size, the number of tumors, the presence of micrometastasis, the presence of intrahepatic metastasis, the condition of the resection margin, tumor–node–metastasis (TNM) disease stage, tumor differentiation grade according to the Edmonson–Steiner classification, and SUV_{tumor} and TNR obtained by ^{18}F-FDG PET. The correlation of tumor differentiation grade with PET results was assessed with a one-way analysis of variance and Tukey's *B* test. The predictive value of PET results for early tumor recurrence was determined by analysis of the area under the receiver operating characteristic (ROC) curve. A univariate analysis and survival curves were obtained by Kaplan–Meier test. Multivariate regression analysis was performed using Cox proportional hazards model to identify the independent prognostic factors for survival and recurrences. Software used to perform these analyses was the SPSS ver. 15 (SPSS Inc. Chicago, IL, USA). Statistical significance was defined by a p value<0.05 or a 95% confidence interval that did not include 1.

Results

Patient Characteristics

The patients were classified as early recurrence group, recurrence after 1-year group, and recurrence-free group according to their recurrence pattern. Among 93 patients,

Table 3 Significant predictors of overall survival

Prognostic factor	*p* (univariate)	*p* (multivariate)	Hazard ratio from multivariate analysis
SUV_{tumor}			
SUV <4 or SUV ≥4	0.005	0.395	0.544
TNR			
TNR <2 or TNR≥ 2	0.013	0.356	0.448
Disease-free interval			
DFI <12 months or DFI ≥12 months	0.002	0.038	3.733
TNM stage			
I, II, III, IV	0.025	0.311	0.356

SUV_{tumor} maximum standardized uptake value of tumor, *TNR* tumor-to-non-tumor SUV ratio, *DFI* disease-free interval, *TNM* tumor–node–metastasis

Table 4 Significant predictors of early recurrence-free survival

Prognostic factor	*p* (univariate)	*p* (multivariate)	Hazard ratio frommultivariate analysis
SUV_{tumor}			
SUV <4 or SUV ≥4	0.026	0.699	0.712
TNR			
TNR <2 or TNR ≥2	0.015	0.831	0.834
EM grade			
High or Low	0.022	0.194	0.329
Tumor size			
Size ≥5 cm or <5 cm	0.006	0.146	0.380

SUV_{tumor} maximum standardized uptake value of tumor, *TNR* tumor-to-non-tumor SUV ratio, *EM grade* Edmonson–Steiner classification

26 had recurrences during the follow-up period (i.e., 27.9% recurrence rate), and 12 of these had early recurrences (i.e., within 1 year; 12.9% early recurrence rate). Table 1 shows the patients demographic information and the operation type underwent. Mean age of all patients was 52.4± 9.5 years. Markers for hepatitis B virus were present in 91.3% of patients, and markers for hepatitis C virus in 5.3%. The mean SUV_{tumor} was 4.24, and the mean TNR was 1.69. Anatomical liver resections for primary tumors were performed in all patients, and the rate of hemi-hepatectomy was 48.3%.

Table 2 summarizes the pathologic characteristics according to their recurrence patterns. The Edmonson–Steiner class histological grade I was in 12.9% of patients and III in 26.9%. Microvascular invasion was found in 51 patients (54.8%). When TNM disease stage was classified according to the American Joint Committee on Cancer Committee, Seventh Edition, 14 patients (15%) had stage I disease, 59 (63.4%) had stage II, 18 (19.4%) had stage IIIA, and 2 (2.2%) had stage IIIB. The mean follow-up period was 31.9±13.9 months, and the mean disease-free interval was 22.9±9.5 months.

Correlation of PET with Tumor Differentiation

When histological grades were divided to three levels according to the Edmonson–Steiner classification, SUV_{tumor} and TNR obtained from the ^{18}F-FDG PET scan showed a statistically significant correlation with the three histological differentiation grades ($p<0.001$, Fig. 1).

The ROC Curve for Prediction of Early Recurrence

The ROC curves for SUV_{tumor} and TNR in relation to early recurrence were analyzed. With respective cutoff points of 4 and 2, the area under the curves were 0.885 and 0.907, and the predictive power was significant (Fig. 2).

Statistical Analysis for Overall Survival and Early Tumor Recurrence

In the univariate analysis, the factors that correlated significantly with overall survival were SUV_{tumor} ≥4, TNR ≥2, the differentiation of tumor, and different TNM stages (Table 3). Significant risk factors for early recurrence were SUV_{tumor} ≥4, TNR ≥2, Edmonson–Steiner grade III, and tumor size larger than 5 cm in the univariate method (Table 4). The early recurrence rate associated with SUV_{tumor} ≥4 was 22.2%, and with SUV_{tumor} <4, 7% (p= 0.026). The early recurrence rate associated with TNR ≥2 was 23.5%, and TNR <2, 6% (p=0.017).

In the multivariate analysis, one of the tested risk factors that disease-free interval (1 year) proved to be an independent factor for overall survival (Table 3), otherwise, none of the examined risk factors correlated significantly with early recurrence (Table 4). Figure 3 shows the early recurrence-free survival and overall survival curves according to SUV_{tumor} and TNR.

Comparison of Overall Survival and Disease-Free Survival Between The Groups Divided with SUV_{tumor} and TNR

All the patients were divided into four groups according to SUV_{tumor} and TNR. In the univariate analysis, there was significant difference for overall survival (p=0.030, Fig. 4), but not for disease-free survival (p=0.278, Fig. 4). Furthermore, in an analysis between SUV_{tumor} and TNR in both high group and low group, the difference of overall survival and disease-free survival became more distinct in two group matching comparison (Fig. 4).

Discussion

^{18}F-FDG PET is a useful non-invasive diagnostic imaging tool that can detect primary and metastatic malignant lesions. As a result, it can be used to accurately determine the stage of disease and the therapeutic response.[22–25] For the diagnosis of primary HCC, sensitivity of ^{18}F-FDG PET is relatively low,[26–30] nonetheless, it is helpful in evaluating treatment outcomes and determining prognosis.[20] ^{18}F-FDG PET is particularly sensitive in the diagnosis of metastatic tumors of the liver because glucose-6-phosphatase, which converts FDG-6-phosphate to FDG, is abundant in the normal liver but hardly present in metastatic hepatic tumors.[26,31] Glucose-6-phosphatase activity varies depending on the type of hepatic malignancy. FDG metabolism is nearly normal in highly differentiated HCCs but notably

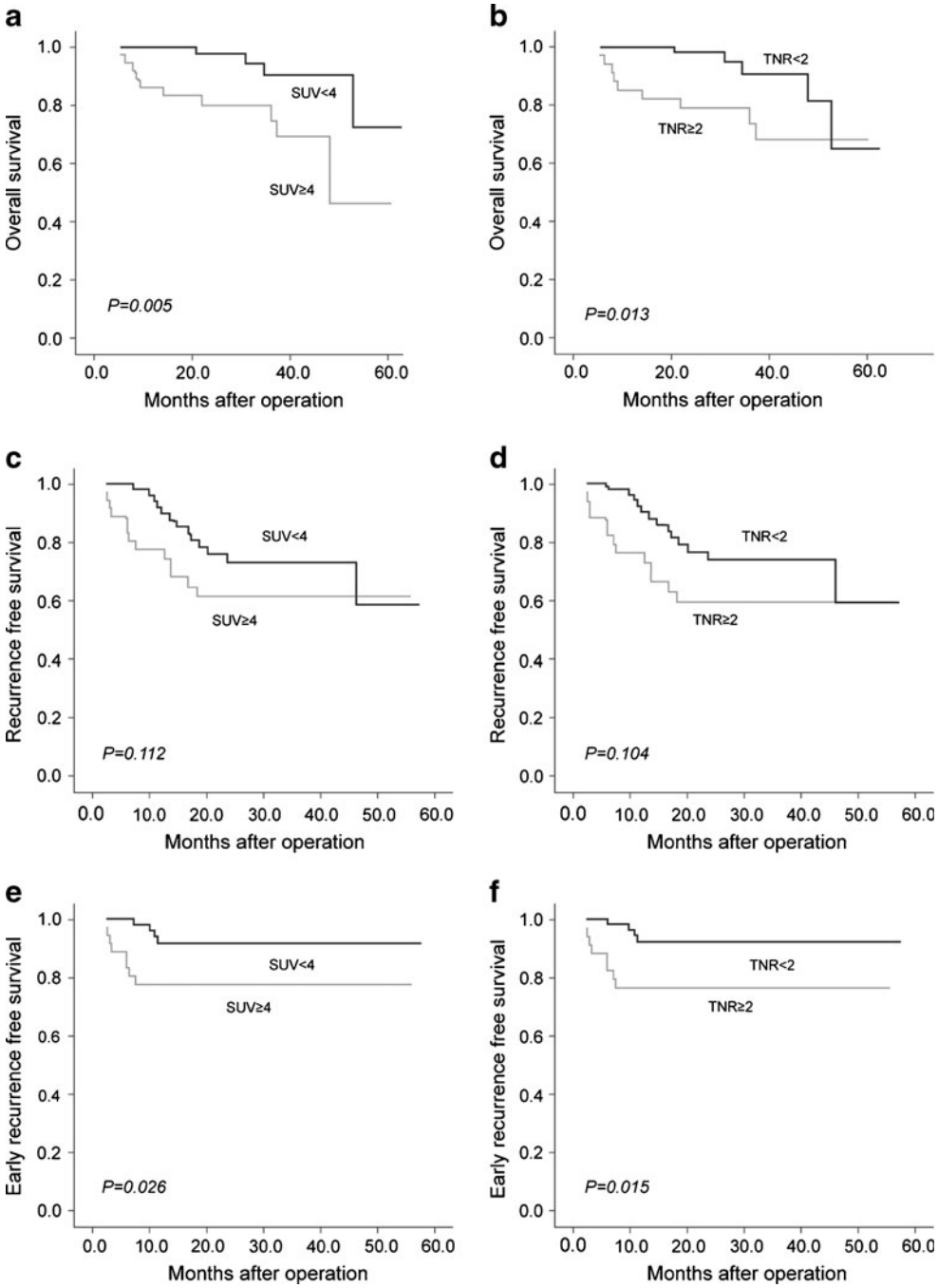

Fig. 3 Survival curves according to SUV_{tumor} and TNR using the Kaplan–Meier method. SUV_{tumor} and TNR significantly correlate with overall survival and early recurrence-free survival in univariate analysis

deteriorated in undifferentiated HCCs.[26,31] Therefore, highly differentiated HCCs accumulate ^{18}F-FDG like the normal liver, inducing a relatively weak signal strength of ^{18}F-FDG. As a result, the intensity of ^{18}F-FDG in preoperative ^{18}F-FDG PET scans may be a predictor of the differentiation grade of HCC.

In our study, the tumor differentiation was graded from 0 to 3, according to the Edmonson–Steiner classification, and compared with SUV_{tumor} and TNR distribution in each group (with and without early recurrence). The poorer (higher) the differentiation grade, the higher was the value of SUV_{tumor} and TNR (Fig. 1). In other words, the preoperative, noninvasive ^{18}F-FDG PET predicted the differentiation grade based on the postoperative histological examination.

When the ROC curves for SUV_{tumor} and TNR were analyzed, the respective cutoff values of 4 and 2 were significantly predictive of early recurrences. In the analysis of the ROC curves, the area under the curves was 0.885 for SUV_{tumor} with a cutoff of 4 0.907 for a TNR cutoff of 2 (Fig. 2). In univariate survival analysis, the incidence of early recurrence was higher in the group with $SUV_{tumor} \geq 4$

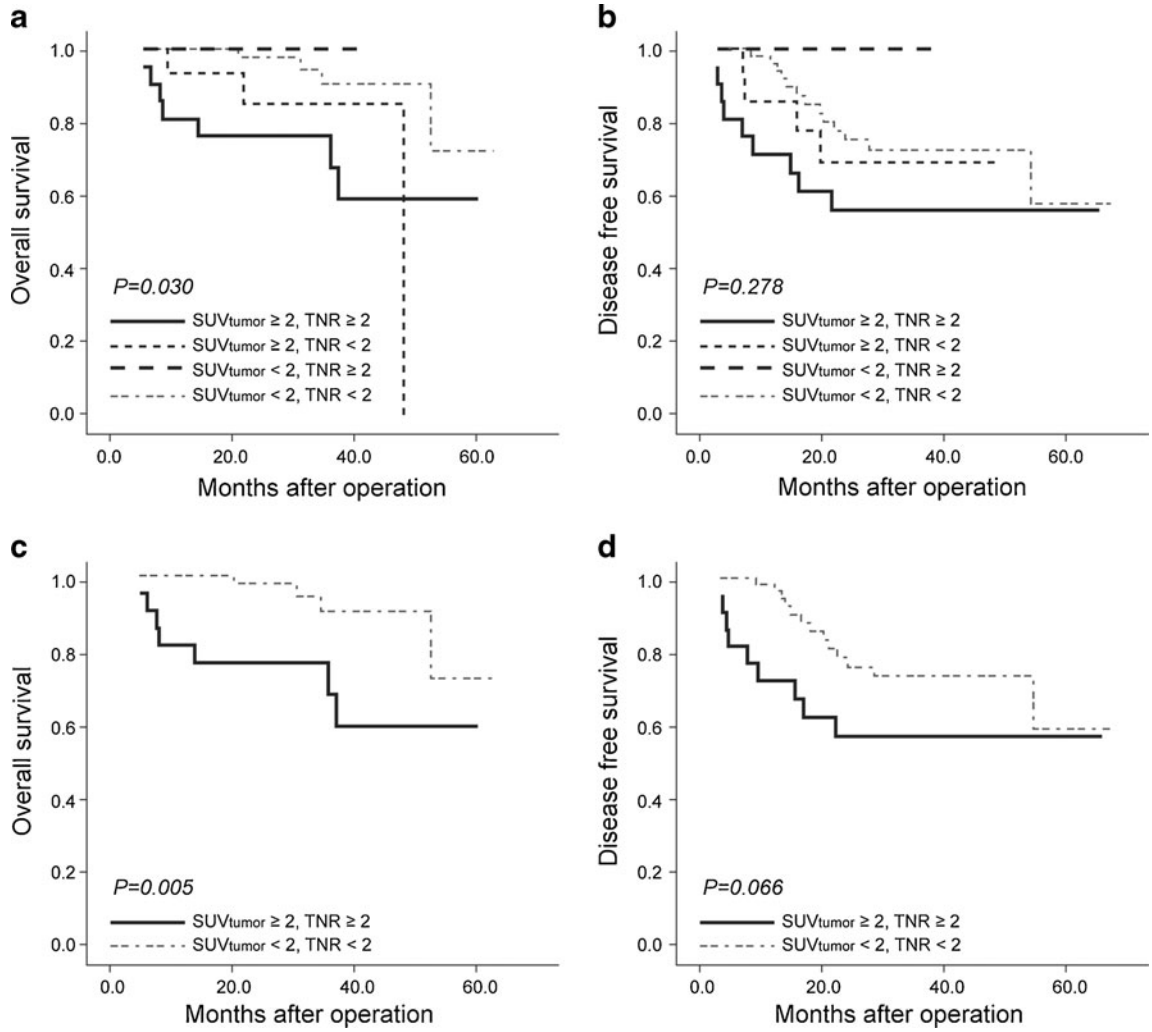

Fig. 4 Survival analysis between subdivided groups according to the cutoff value of SUV_{tumor} and TNR. **a** Overall survival between all groups. **b** Disease-free survival between all groups. **c** Comparison of high SUV_{tumor} and high TNR group with low SUV_{tumor} and low TNR group in overall survival analysis. **b** Comparison of high SUV_{tumor} and high TNR group with low SUV_{tumor} and low TNR group in disease-free survival analysis

and in the group with TNR ≥2 (Table 4, Fig. 3). In addition, the univariate analysis indicated that a poor differentiation grade was associated with early recurrence (Table 4). The mean value of SUV_{tumor} and TNR of the early recurrence group and the negative group without early recurrence showed significant differences. Based on our results, the differentiation grade, SUV_{tumor}, TNR, and tumor size were significantly associated with the early recurrence within 1 year after surgery in univariate but insignificant in multivariate. In a multivariate study for overall survival, disease-free interval was proven to be a poor prognostic factor. This finding was concordant to the conventional thought. In the tailored division study according to the predictive values of PET scan, the survival difference found in the comparison between subdivided groups suggests the clinical availability of PET scan with the identification of high-risk populations (Fig. 4). These results suggest that ^{18}F-FDG PET scan will not have a dominant role in a predictive scheme for HCC recurrence for recurrence and survival of patients with hepatocellular carinoma, but it may be useful as one of a panel of predictive factors. These results are preliminary and require further investigations.

Other studies have shown a statistically significant correlation between risk factors such as microvascular invasion and early recurrence,[4,8,9] but our results did not confirm this. One explanation for this may be that patients with the same risk factors in the different studies differed in whether or not they received aggressive adjuvant chemotherapy. Among the 93 patients in our study, 51 had microvascular invasion. Among them, 20 received systemic chemotherapy by intrahepatic arterial injection of adriamycin three times after surgery; however, the patients with microvascular invasion in previous studies may not have undergone the same chemotherapy regimen. In addition,

among the 51 patients with microvascular invasion, 24 had SUV_{tumor} ≥4 or TNR ≥2. Among them, 11 patients received systemic chemotherapy with intrahepatic arterial injection of adriamycin, which may be why, on multivariate analysis, SUV_{tumor} and TNR were not significantly predictive of early recurrence. Studies on postoperative systemic chemotherapy administered by intrahepatic arterial injection in patients with adverse prognostic indicators are ongoing.[32,33] Although these studies have yet to demonstrate the effectiveness of these therapies, they may have acted as confounding variables in our study. Indeed, Lee et al. studied patients with HCC who underwent ^{18}F-FDG PET scans prior to liver transplantation and found that a high TNR was associated with recurrence within 1 year after surgery.[34] Therefore, additional larger studies in the population we examined (i.e., patients with HCC who undergo curative resection) are warranted to further assess the clinical utility of SUV_{tumor} and TNR in predicting early recurrences.

Our results showed that early recurrence is a significant predictor of overall survival, in accordance with earlier studies. In contrast, we did find on univariate analysis that SUV_{tumor} and TNR correlated significantly with overall survival (Table 3, Fig. 2). Furthermore, recent studies have evaluated the efficacy of ^{11}C-acetate tracers and/or ^{18}F-FDG in diagnosing primary HCC.[35,36] ^{11}C-acetate acts as a substrate for β-oxidation for the synthesis of lipid acid and cholesterol in the Krebs cycle. Synthesis of lipid acid is a major mechanism by which ^{11}C-acetate is absorbed by hepatic tumors. In this way, ^{11}C-acetate is delivered into the Krebs cycle, and thus ^{18}F-FDG-negative hepatic tumors may potentially be detected with ^{11}C-acetate studies.[36] In highly differentiated HCCs that may not absorb ^{18}F-FDG well, the phenomenon of enhanced absorption of ^{11}C-acetate has in fact been shown.[37] Therefore, if imaging studies could combine both ^{18}F-FDG and ^{11}C-acetate, they may reveal the biological characteristics of HCC more precisely and aid in predicting outcomes and informing therapeutic decisions.

Conclusion

We found that, in patients with HCC who undergo curative resection, preoperative, noninvasive ^{18}F-FDG PET and its associated SUV_{tumor} and TNR are useful indicators of tumor differentiation and may be predictive of early tumor recurrence and overall survival.

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ORIGINAL ARTICLE

Perioperative Outcomes for Open Distal Pancreatectomy: Current Benchmarks for Comparison

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Abstract
Background Open distal pancreatectomy (ODP) outcomes have largely relied on single-institution data from high-volume, tertiary centers. To provide contemporary, national benchmarks of ODP outcomes, we examined the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database.
Methods Using the ACS-NSQIP database (2005–2007), we identified 868 cases of ODP. Operative time, intraoperative transfusion, and length-of-stay (LOS) data were compiled. Univariate and multivariate analyses were performed adjusting for age, body mass index, diagnosis, creatinine, albumin, hematocrit, and American Society of Anesthesiologists (ASA) classification for likelihood of any postoperative complication and severe complication (composite endpoint: organ space surgical site infection, reoperation, or death).
Results Thirty-day overall complication, severe complication, and mortality rates were 27.2%, 11.6%, and 1%, respectively. Mean operative time was 206 min (±86), 18.1% patients required intraoperative red blood cell transfusion (median 2 units), and median LOS was 6 days. Predictors of any complication or severe complication were renal insufficiency, hypoalbuminemia, and worsening ASA classification. Malignant diagnosis was not associated with poorer outcomes.
Discussion ODP remains the gold standard for lesions of the pancreatic body or tail. The current analysis reflects nationwide data that may serve as current benchmarks for both open and laparoscopic techniques.

Keywords Open distal pancreatectomy · Perioperative outcomes · Morbidity · Mortality

Introduction

Primary management of a diverse array of lesions arising from the pancreatic body and tail is that of surgical resection, and open distal pancreatectomy (ODP) is the gold standard procedure for such lesions. However, such resections are relatively uncommon and thus current estimates of perioperative morbidity and mortality are largely from single-institution series.[1–9] Reported rates of morbidity and mortality vary widely within these series—likely reflecting the biases of these institutions which tend to be academic, high-volume, tertiary referral centers.

Increasing enthusiasm exists for minimally invasive laparoscopic approaches [i.e., laparoscopic distal pancreatectomy (LDP)] for surgical resection of these pancreatic lesions. As is typical with any advance in technology, the safety and efficacy of LDP is under careful scrutiny. Recent studies have suggested shorter operative times,[7] less operative blood loss,[7,8,10] decreased hospital length of stay,[4,5,8,10] and faster return to normal activities.[5] Morbidity/mortality rates and pancreatic fistula rates have been reported as comparable to ODP.[5,6,8] The ODP outcomes to which they are compared, however, are often from within the same single-institution, high-volume centers in which the LDPs are performed. As such, these data are susceptible to referral and ascertainment bias and thus

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may lack generalizability as outcomes for comparison. Furthermore, as some of these reports include time periods spanning more than a decade and/or include patients treated over 15 years ago, the results may not reflect current perioperative care.

Secondary to this lack of current national outcomes for ODP, we sought to examine 30-day morbidity and mortality outcome data using a large, contemporary, and high-quality nationwide surgical outcomes database and identify predictors of poor outcomes.

Materials and methods

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) is a national initiative set forth by the American College of Surgeons to improve the quality of surgical care. It is comprised of validated, risk-adjusted perioperative 30-day outcomes data abstracted by specialty trained nurse reviewers and audited centrally. Begun in October, 2004, ACS-NSQIP currently collects data from 255 hospitals representing a spectrum of private hospitals and tertiary care academic medical centers. ACS-NSQIP abstracts data on 9 patient demographic variables, 9 surgical profile variables, 53 preoperative patient variables, 21 intraoperative variables, and 41 postoperative occurrence, laboratory, and discharge variables (https://acsnsqip.org/main/program_data_collection.asp). Data are collected, validated, and submitted by a trained surgical clinical reviewer at each participating site. There are standardized data definitions, annual audits of each site's data, as well as inter-rater reliability audits conducted on a routine basis to ensure data quality. Participating ACS-NSQIP hospitals and their researchers have full access to the Participant Use Files (PUFs) containing data from all participating sites. As the University of California (UC), Davis Medical Center is a participating ACS-NSQIP site, the researchers had full access to the PUF files and a data-use agreement was signed. Since ACS-NSQIP patient information is de-identified, this study qualified as exempt from UC Davis Institutional Review Board approval.

The ACS-NSQIP database (2005–2007) was used to identify 1,313 patients undergoing 'partial resection of the pancreas' using CPT codes 48140. Cases with moribund American Society of Anesthesiologists (ASA) classification 5 patients, emergent cases, and cases with any laparoscopic component or extra-pancreatic procedure were excluded. Entry criteria were met by 868 patients.

The sex, age, and race/ethnicity of each patient were obtained as were the surgical operative time (from commencement of skin incision to completion of skin closure), surgical length of stay (from date of surgery to hospital surgical service discharge date) for each case. All preoperative, intraoperative, and postoperative ACS-NSQIP variables were abstracted. Postoperative diagnosis was categorized into benign, malignant, or indeterminate using ACS-NSQIP recorded ICD-9 codes. Importantly, ACS-NSQIP does not provide information on histologic type, histologic grade, size of tumor, or margin status. Occurrences of pancreatic fistula are coded as organ space surgical infection, and severity and grade of fistula are not recorded and thus could not be analyzed. Organ space surgical infections are not necessarily limited to pancreatic fistula and may include a heterogeneous group of complications including pancreatic leak, intra-abdominal abscess, or other infected intra-abdominal fluid collections. Data on socioeconomic status, participation in clinical trials, are also not abstracted and therefore could not be analyzed.

Univariate analyses were performed using all 53 preoperative ACS-NSQIP variables for likelihood of postoperative complication and severe complication (composite endpoint: organ space infection, reoperation, or death). Multivariate analysis were performed using logistic regression likelihood models, adjusting for patient age, body mass index (BMI), serum creatinine, serum albumin, serum hematocrit, diagnosis type, and ASA classification. Covariates were evaluated for nonlinearity and interactions among variables and models were adjusted for multiple comparisons and subgroups.

Analyses were conducted using commercially available software; PASW version 18.0.2 (SPSS, Chicago, IL).

Results

Baseline patient clinical characteristics

Clinical and demographical characteristics of the study cohort are presented in Table 1. Median age was 59 years (range 18–85), 52.6% were female, and the majority of patients (78.2%) were white. While 46.7% of patients were ASA 1 or 2, 51.4% of patients were ASA 3. Median BMI was 27 (range 14–59). Whereas 83.4% of patients had a preoperative serum creatinine value less than 1.2 mg/dl, only 1.2% of patients had a value greater than 2.0 mg/dl. While 68.9% of patients had a serum albumin greater than 3.5 g/dl, 1.0% had values less than 2.5 g/dl. The majority of patients were not anemic, as 78.7% of patients had a hematocrit percentage between 35% and 50%. The most common patient comorbidities were hypertension requiring medication (45.4%), smoking (22.9%), diabetes mellitus requiring medication (10.0%), and preoperative dyspnea (9.0%).Final pathology demonstrated that slightly over one third of patients (n=331; 38.1%) had a malignant diagnosis, nearly half of patients (n=415; 47.8%) had a benign diagnosis, and the remaining 122 patients (14.1%) had an indeterminate diagnosis.

Table 1 Baseline patient clinical characteristics (n=868)

Variable	Mean (SD), %
Age (years; median; range 18–85)	59
Female	52.6
Ethnicity	
Asian/Pacific Islander	2.6
Hispanic	4.4
Black	7.5
White	78.2
ASA classification	
½	46.7
3	51.4
4	2.0
Body mass index (median; range 14–59)	27
Creatinine (mg/dl)	1.0 (±0.7)
Albumin (g/dl)	4.0 (±0.5)
White blood cell count (/dl)	7.3 (±2.7)
Hematocrit (%)	39.6 (±4.9)
Comorbidities[a]	
Hypertension (n=394)	45.4
Smoker (n=199)	22.9
Diabetes mellitus (n=151)	17.4
Dyspnea (n=87)	10.0
Weight loss (n=78)	9.0
Chronic obstructive pulmonary disease (n=49)	5.6
Diagnosis type	
Malignant (n=331)	38.1
Benign (n=415)	47.8
Indeterminate (n=122)	14.1

[a] Prior cerebrovascular accident, recent myocardial infarction, angina, congestive heart failure, active pneumonia, ascites, bleeding disorder, renal dysfunction, recent chemoradiotherapy found in <5% of patients

Perioperative outcomes

Mean operative time was 206 (±86) min; median operative time was 189 min (range 36–882; Fig. 1). A number of 157 patients (18.1%) required intraoperative packed red blood cell transfusion. Of those that received transfusion, the median number of units administered was 2 (range 1–13). Overall, the incidence of 30-day morbidity or severe complication were 27.2% (n=236) and 11.6% (n=101), respectively (Table 2). The most common complications were organ space surgical infection (8.1%), systemic sepsis (6.7%), superficial surgical site wound infection (4.8%), pneumonia (4.7%), and urinary tract infection (4.4%).3.3% (n=29) of patients required reoperation within 30 days of their distal pancreatectomy. Nine patients died within 30 days of the procedure for an overall mortality rate of 1.0%. Of these nine patients, five suffered pulmonary

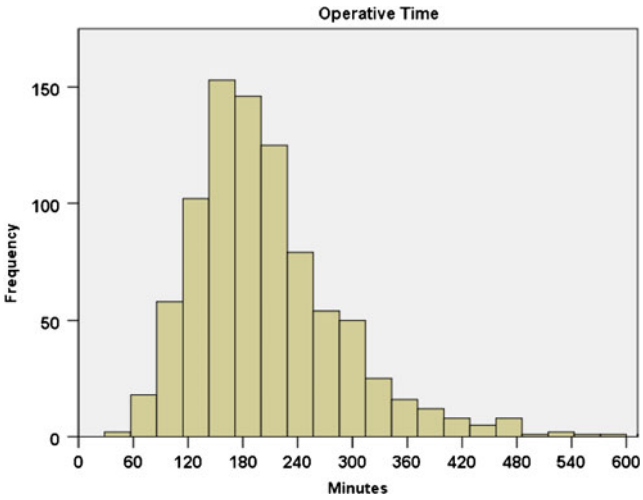

Fig. 1 Histogram of operative times for open distal pancreatectomy (n=868)

complications (pneumonia, sepsis, and need for re-intubation), three suffered infectious complications (organ space surgical infection), and two suffered renal failure necessitating hemodialysis. Mean LOS was 8.1 days (±7.1); median LOS was 6 days (range 0–119; Fig. 2).

Multivariate analysis

Multivariate analyses for any complication and severe complications are presented in Table 3. Hypoalbuminemia was an independent predictor of any complication (OR 1.94, 95% CI 1.12–3.38) and severe complication (OR

Table 2 Postoperative 30-day outcomes (n=868)

Outcome	Percentile (%)
Any complication (n=236)	27.2
Severe complication[a] (n=101)	11.6
Mortality (n=9)	1.0
Type of complication[b]	
Organ space infection (n=70)	8.1
Systemic sepsis (n=57)	6.7
Superficial surgical site infection (n=42)	4.8
Pneumonia (n=41)	4.7
Urinary tract infection (n=38)	4.4
Prolonged mechanical ventilation (n=29)	3.3
Reoperation (n=29)	3.3
Surgical length of stay: median 6 days (range 0–119); mean 8.1 (±7.1) days	

[a] Composite outcome: organ space surgical infection, reoperation, or death

[b] Cardiovascular, neurological, bleeding, thrombotic complications found in <3% of cases

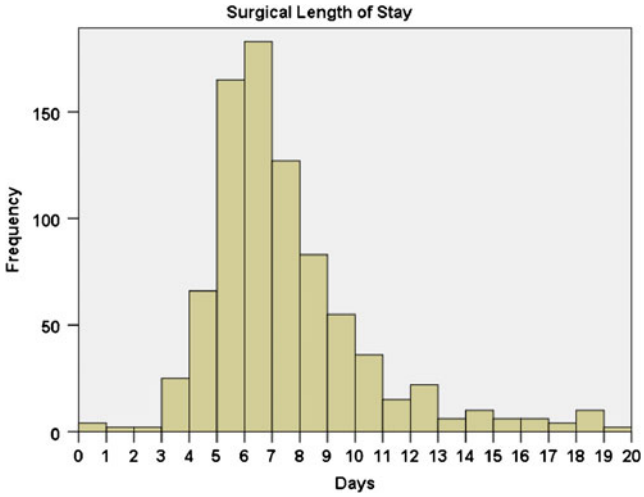

Fig. 2 Histogram of surgical lengths of stay after open distal pancreatectomy (n=868)

Table 3 Multivariate analyses of predictors of any and severe complications[a] (n=868); odds ratio (95% confidence interval)

Variable	Any complication	Severe complication
Age (median 59 years)	1.00 (0.99–1.02)	1.00 (0.99–1.02)
BMI (median 27)	1.02 (1.00–1.05)	1.02 (0.98–1.05)
Diagnosis type		
Benign	1.00 (referent)	1.00 (referent)
Malignant	1.06 (0.75–1.49)	1.04 (0.65–1.68)
Unknown	0.81 (0.50–1.32)	0.82 (0.42–1.62)
Creatinine		
<1.2	1.00 (referent)	1.00 (referent)
1.2–2.0	1.43 (0.88–2.33)	*1.89 (1.02–3.49)
>2.0	0.89 (0.22–3.63)	0.82 (0.10–6.71)
Unknown	0.93 (0.38–2.23)	1.35 (0.45–4.07)
Albumin		
>3.5	1.00 (referent)	1.00 (referent)
2.5–3.5	*1.94 (1.12–3.38)	1.57 (0.74–3.34)
<2.5	3.23 (0.75–13.84)	*6.63 (1.39–31.57)
Unknown	1.04 (0.68–1.57)	1.06 (0.60–1.89)
Hematocrit		
36–49	1.00 (referent)	1.00 (referent)
>49	2.23 (0.29–17.22)	2.18 (0.21–23.05)
<36	0.89 (0.57–1.41)	0.76 (0.39–1.45)
Unknown	1.83 (0.77–4.36)	1.71 (0.58–5.04)
ASA classification		
½	1.00 (referent)	1.00 (referent)
3	*1.67 (1.19–2.33)	1.52 (0.95–2.44)
4	2.54 (0.91–7.08)	1.74 (0.45–6.75)

* Denotes significance, $p \leq 0.05$

[a] Composite outcome: organ space surgical infection, need for reoperation, or death

6.63, 95% CI 1.39–31.57). ASA classification was an independent predictor of any complication (OR 1.67, CI 1.19–2.33), but not severe complication. Preoperative renal insufficiency was an independent predictor of severe complication (OR 1.89, 95% CI 1.02–3.49). Age, BMI, preoperative hematocrit, and histopathologic diagnosis type were not significantly associated with 30-day perioperative morbidity or mortality.

Discussion

ACS-NSQIP data are abstracted from a spectrum of private hospitals and academic tertiary care medical centers (https://acsnsqip.org/main/about_sites.asp). To our knowledge, ours is the first nationwide evaluation and most contemporary analysis of perioperative outcomes for patients undergoing ODP. It has been shown that data from ACS-NSQIP is of high quality and highly reliable.[11] We demonstrate national 30-day morbidity and mortality rates of 27.2% and 1.0%, respectively. Median operative time was 189 min (range 36–882), 18.1% of patients required intraoperative red blood cell transfusion, and median LOS was 6 days. The outcomes are similar to that of published series for mortality (range 0–4%) and morbidity (range 18.8–57%; Table 4). There is one recent publication that has examined national mortality outcomes of pancreatic surgeries. McPhee et al. examined the in-hospital mortality for over 39,000 patients using the Nationwide Inpatient Sample undergoing pancreatic resection the Nationwide Inpatient Sample from 1998 to 2003. Of the 21% of patients who underwent distal pancreatectomy, they reported an overall mortality rate of 3.5%. High-volume (>18 pancreatic resections of all types/year) centers were found to have a mortality of 0.43% versus low-volume centers (<5 pancreatic resections/year)—a statistically significant finding ($p<0.0001$). Perioperative morbidity, and intraoperative outcomes were not reported.[12]

The ACS-NSQIP mortality of 1.0% presented in the current study falls within the mortality ranges of low- and high-volume centers as reported by McPhee et al. This likely is due to multiple factors. Inclusion criteria for McPhee et al. was based upon ICD-9 procedure code 52.52, which captures laparoscopic and ODP albeit in that era it is likely most of the distal pancreatectomies were performed in an open fashion. A more plausible explanation for mortality differences are that the cases analyzed by McPhee et al. captured a nonhomogenous population of distal pancreatectomies including other concomitant procedures. ACS-NSQIP is primarily composed of urban and academic medical centers which are presumably higher-volume pancreatic surgery centers. Our reported mortality of 1% is more comparable to the high-volume centers than the

Table 4 Summary of perioperative outcomes from previously reported series

Study	Setting (years)	*n*	Mortality (%)	Morbidity (%)	Operative time (mean/SD)	LOS (mean/SD)
Lillemoe et al.[1]	Single institution 1984–1997	235	0.9	31	284 (132)	15 (15)
Nathan et al.[2]	Single institution 1984–2006	704	<1	33	n/a	7
Fahy et al.[9]	Single institution, 1994–99	51	4	47	n/a	n/a
Stutchfield et al.[3]	Single institution 1994–2006	65	3	39	n/a	n/a
Eom et al.[4]	Single institution 1995–2006	167	0	24.2	194 (64)	13.5
Velanovich et al.[5]	Single institution 1996–2003	41	n/a	27	n/a	8
Nakamura et al.[6]	Single institution 2000–2007	16	n/a	18.8	282	25.8
Finan et al.[7]	Single institution 2002–2007	98	n/a	n/a	200	8.6
Kooby et al.[10]	Eight institutions 2002–2006	200	1	57	226 (101)	9.2 (6)
Baker et al.[8]	Single institution 2003–2008	85	2.0	35.1	253 (32)	8.6 (7)

low-volume centers represented in the Nationwide Inpatient Sample database.

There are, however, other operative parameters which are unable to be captured within ACS-NSQIP. Closure of the pancreatic remnant remains a controversial topic; there remains no consensus on association of closure method or ligation of the main duct and Grade A fistulas with no clinical sequelae or Grade B/C fistulas requiring clinical intervention.[2,13–16] Thus, the pancreatic remnant closure method and utilization of ligation of the main pancreatic duct have had no proven association with postoperative morbidity and mortality and thus lack of this information is unlikely to skew our results. There exists no defined ACS-NSQIP code for pancreatic fistula. ACS-NSQIP nurse reviewers are instructed to code pancreatic fistulas as organ space surgical infections. Organ space surgical infections, however, are not limited to pancreatic fistulae and include other infected intra-abdominal fluid collections. Our ACS-NSQIP abstracted organ space surgical infection incidence of 8.1% is comparable to the summation of incidence of pancreatic fistulae (5%) and intra-abdominal abscesses (4%) in the seminal review of Lillemoe et al.[1] of 235 patients undergoing distal pancreas resection over a 13-year period. Although there has been interest in expanding ACS-NSQIP and developing a hepatobiliary-specific outcomes collection database as part of an ACS-NSQIP oncology initiative, none exists currently. Thus, we are unable to comment on the true incidence of pancreatic fistula in our study population, and we are unable to comment on the grade or severity of fistulae.

As the CPT code 48140 is a bundled code for distal pancreatectomy which includes utilization of concomitant splenectomy if needed, we were unable to reliably identify those cases in which splenectomies were performed. In the Lillemoe et al. series, 84% of patients received concomitant splenectomy. They found that those undergoing concomitant splenectomy, however, had a similar complication rate (30%) as those that did not undergo splenectomy (29%) and that there was no statistical difference in operative time (splenectomy 4.6 vs. 5.1 h; $p=0.69$) or intraoperative blood loss ($p=0.14$). These findings are similar to previous research into splenic preservation during distal pancreatectomy[17–19] showing similar perioperative outcomes for distal pancreatectomy with and without splenectomy. Thus, lack of information on the utilization of splenectomy is unlikely to skew data on perioperative morbidity and mortality.

The ACS-NSQIP database includes a variety of patient-derived variables that can be used for risk stratification beyond intraoperative or disease-related variables. Hypoalbuminemia, worsening ASA classification, and renal insufficiency were all predictors of increased likelihood of perioperative complications. These findings are an important aspect of preoperative surgical decision making and facilitate preoperative risk assessment. Similar to the report by Lillemoe et al., we did not find an association between the nature of the pancreatic disease (i.e., malignant or benign) and differing perioperative morbidity and mortality; malignant lesions did not predict an increase in overall morbidity (OR 1.06; 95% CI 0.75–1.49) or severe complications (OR 1.04; 95% CI 0.65–1.68).

Conclusion

ODP remains the gold standard to which LDP is compared. Our analysis utilizing a rigorously updated, prospective, nationwide surgical outcomes database of 868 patients undergoing ODP is the largest and most contemporaneous series of which we are aware. These results reflect nationwide data that may serve as current benchmarks to which patients undergoing LDP should be compared.

Conflicts of Interest None.

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ORIGINAL ARTICLE

A Systematic Review and Meta-analysis of Survival and Surgical Outcomes Following Neoadjuvant Chemoradiotherapy for Pancreatic Cancer

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Abstract
Introduction This systematic review and meta-analysis aims to characterize the surgically important benefits and complications associated with the use of neoadjuvant chemoradiotherapy for the treatment of both resectable and initially unresectable pancreatic cancer. Studies were identified through a systematic literature search and analyzed by two independent reviewers. Survival, peri-operative complications, death rate, pancreatic fistula rate, and the incidence of involved surgical margins were analyzed and subject to meta-analysis.
Methods Nineteen studies, involving 2,148 patients were identified. Only cohort studies were included.
Results The meta-analysis found that patients with unresectable pancreatic cancer who underwent neoadjuvant chemoradiotherapy achieved similar survival outcomes to patients with resectable disease, even though only 40% were ultimately resected. Neoadjuvant chemoradiotherapy was not associated with a statistically significant increase in the rate of pancreatic fistula formation or total complications.
Conclusion Patients receiving neoadjuvant chemoradiotherapy were less likely to have a positive resection margin, although there was an increase in the risk of peri-operative death.

Keywords Neoadjuvant treatment · Pancreatic neoplasms · Chemoradiotherapy · Systematic review · Meta-analysis

Introduction

The prognosis for patients with carcinoma of the pancreas continues to be poor despite advances in diagnostic techniques and oncological treatments.[1] For most patients, potentially curative surgery is not possible because of systemic metastasis, advanced nodal disease, or a localized tumor that is not amenable to resection due to invasion of vital local structures. In addition, the long-term survival is poor even in patients with early-stage disease who have undergone apparently curative surgery.[1] The rationale for neoadjuvant chemoradiotherapy (NCRT) may be to down-stage in order to permit resection, to improve the rate of resection with clear margins, or to reduce the incidence of

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late relapse. For patients with locally advanced disease, chemoradiotherapy had been the treatment most often recommended on the basis of two randomized controlled trials (RCT).[2,3] This was questioned after the publication of data showing a survival disadvantage in association with an intensive NCRT regimen when compared with gemcitabine-based chemotherapy alone.[4] For potentially resectable pancreatic cancer, although currently underway,[5] there are no RCT published at this time comparing NCRT to primary resection. A large number of studies, the majority case series, have been published over the last 25 years. A small number of non-randomized cohort studies have also been published. The topic of NCRT has also recently been subject to systematic review.[6,7] We include in the meta-analysis only comparative, non-randomized studies (NRS) with a particular emphasis on outcomes of surgical significance including peri-operative complications, positive resection margin, pancreatic fistula formation and survival.

Methods

Data Sources

A search was made of the MEDLINE database from 1950 to the 52nd week of 2010 and of the EMBASE database from January 1980 to the 52nd week of 2010. The OVID search engine (Version OvidSP_UI03.02.04.102; Ovid Technologies, New York, USA) was used. The MESH heading "pancreatic neoplasms" yielded 46,212 hits in MEDLINE and "pancreas tumor" 61,538 in EMBASE. The MESH heading "neoadjuvant therapy" yielded 6,756 hits in Medline and 2,462 in EMBASE. The results of the pancreatic neoplasms search were combined with the neoadjuvant therapy search results to produce 232 hits in MEDLINE. The results of the pancreas tumor search were combined with the neoadjuvant therapy search results to produce 137 hits in EMBASE. Searching of the bibliographies of the retrieved manuscripts yielded an additional 77 potentially relevant studies to produce a final study population of 309 studies. Only one non-English language cohort study was identified.[8] This was translated, but the data in the manuscript was not presented in a manner suitable for analysis. Animal studies and other non-English language manuscripts were excluded. After exclusion of the otherwise non-relevant studies, 110 papers were retrieved and the full article examined.

Study Selection

No RCTs were identified. We included studies regardless of publication status, date of publication, and number of participants. Comparative studies of different chemotherapy or radiotherapy regimens, articles with no control group, reporting only toxicity data, where no radiotherapy was administered or otherwise not relevant, were excluded. This process yielded a final study group of 19 manuscripts. A summary of the search strategy is provided in Fig. 1.

Data Extraction

Each of these 19 articles were independently reviewed by two of the authors (PT and JL) who separately extracted data on the following categories: dates over which the study was conducted, the details of the pancreatic cancer (including location in the pancreas, stage, resectability, histological type and size), chemotherapy treatment both neoadjuvant and adjuvant (including chemotherapy agent and dosing regimen), radiotherapy treatment both neoadjuvant and adjuvant (including dose and fractionation), nature of surgery, surgical complications (including morbidity and

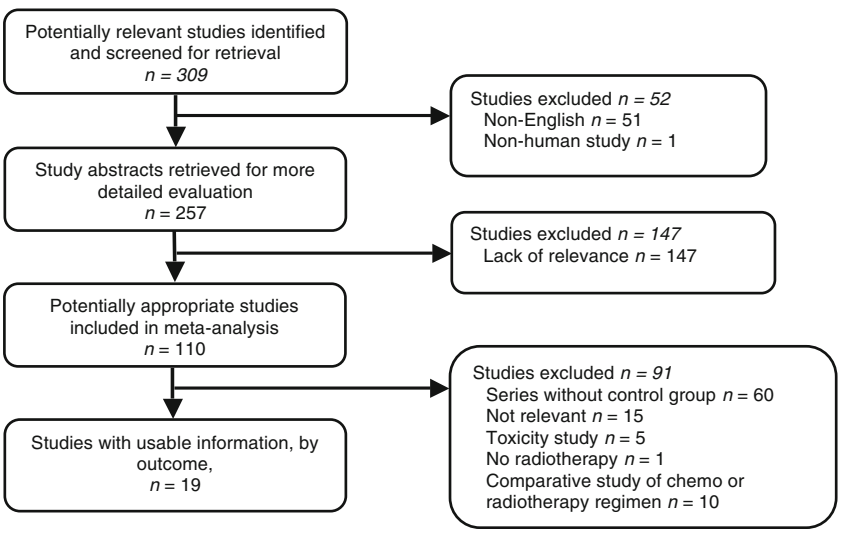

Fig. 1 Flow chart showing the search strategy used to identify studies

Table 1 Important characteristics of included studies

Author, year, [reference]	Design	Date of study	RT dose, fractionation	Chemotherapy	Status of patients receiving NCRT	Definition of status
Al-Sukhni 2003[12]	1	1996–1999	Photons 39.6 Gy (1.8 Gy per fraction) and neutrons 8 NGy (0.8 NGy per fraction)	PACE	Locally advanced, unresectable	Not stated
Allendorf 2008[13]	3	2000–2006	50.4 Gy 1.8 Gy per fraction	Gemcitabine, capecitabine, and doctaxal	Locally advanced, unresectable	Invasion of the SMV or PV or arterial abutment (SMA, HA, or CA) of ≥180°. Also thrombosis of the PV system.
Bruckner 1993[14]	1	NS	54 Gy. 20 fractions of 2 Gy followed by 7 fractions of 2 Gy	Continuous infusional 5FU, streptozocin, cisplatin and leucovorin	Unresectable	Encasing blood vessels or involving regional lymph nodes
Chao 2000[15]	3	1987–1999	50.4 Gy 1.8 Gy per fraction	Various regimens	Unresectable	Unresectable at initial exploration
Golcher 2008[16]	1	1995–2003	55.8 Gy to the involved field and 50.4 Gy to the regional lymph nodes	5-FU and mitomycin before 2001 and gemcitabine and cisplatin after 2001	Unresectable	Contact with main peripancreatic vessels greater than 180° or obvious signs of peritoneal carcinomatosis or distant metastases.
Greer 2008[17]	3	1993–2005	50.4 Gy 1.8 Gy per fraction	Various including 5FU, cisplatin, gemcitabine, and docetaxel	14 Unresesctable, 14 borderline, and 14 resectable	>180° involvement of the SMA, CA, SMV, or PV
Ishikawa 1994[18]	3	1985–1989	50 Gy 2 Gy per fraction	NS	Resectable	Peritoneal disease, hepatic metastasis, or invasion of surrounding tissues
Jessup 1993[19]	1	1990–1991	At least 45-Gy total dose	5FU	Unresectable	Exploratory laparotomy, back pain, or encasement of mesenteric vessels
Kim 2002[20]	3	1993–1999	NS	Various	NS	NS
Lind 2008[21]	3	2002–2004	50.4 Gy 1.8 Gy per fraction	Oxaliplatin and capecitabine	Borderline resectable	Involvement of a patent portal or mesenteric vein <50% of the circumference for a distance <2 cm and/or regional arterial encasement of <50% for a distance <2 cm.
Massucco 2006[22]	1	1999–2003	45 Gy 1.8 Gy per fraction	Various gemcitabine-based regimens	10 Unresectable 28 borderline resectable	Unresectable—the presence of vein thrombosis and/or arterial encasement. Borderline resectable—the presence of vein stenosis and/or arterial abutment
Pendurthi 1998[23]	3	1986–1996	50.4 Gy 1.8 Gy per fraction	5FU	Resectable	NS
Pingpank 2001[24]	3	1987–2000	50.4 Gy 1.8 Gy per fraction	Gemcitabine paclitaxel or 5FU-based regimens	Borderline resection or previous laparotomy	NS
Piperdi 2010[25]	3	2002–2007	50.4 Gy 1.8 Gy per fraction	5FU, gemcitabine or capecitabine-based regimens	8 Bordeline resectable and 11 unresectable	Unresectable—tumor encasement of SMA or CA >180°. Borderline resectable—an SMV-PV confluence that can be reconstructed even if short-segment venous occlusion is present, tumor abutment of SMA <180° or short-segment involvement of HA amenable to resection and reconstruction
Satoi 2009[26]	1	2000–2005	40 Gy 2 Gy per fraction	5FU with cisplatin or gemcitabine	Locally advanced (n=16) and potentially resectable (n=19)	NCCN guidelines
Snady 2000[27]	1	1989–1997	54 Gy 2 Gy per fraction	5-FU, streptozocin, and cisplatin	Unresectable	Malignant lymph nodes outside resection field, invasion of major vessels making resection unlikely without resection, and reconstruction of major vessels

Table 1 (continued)

Author, year, [reference]	Design	Date of study	RT dose, fractionation	Chemotherapy	Status of patients receiving NCRT	Definition of status
Spitz 1997[28]	3	1990–1995	Standard 50.4 Gy 1.8 Gy per fraction; rapid fractionation 30 Gy 3 Gy per fraction	5FU	Resectable	Absence of extrapancreatic disease, no evidence of tumor encasement of SMA or CA, and a patent SMV-PV confluence.
Vento 2007[29]	3	1999–2002	50.4 Gy 1.8 Gy per fraction	Gemcitabine	Resectable	NS
White 2006[31]	3	1994–200	Various. Mainly 45 Gy with 5.4 Gy boost to tumor bed.	Various. Predominantly infusional 5FU	Locally advanced (n=18) and potentially resectable (n=64)	Locally advanced—circumferential venous involvement and/or any arterial involvement. Potentially resectable—non-circumferential venous involvement.

RT Radiotherapy, *CRT* chemoradiotherapy, *CT* chemotherapy, *1* prospective cohort study, *3* retrospective cohort study, *PACE* cisplatin, cytarabine, caffeine, and continuous infusion (*CI*) 5-fluorouracil (*5-FU*), NS not stated, *NCCN* national comprehensive cancer network, *Gy* Gray

mortality), and survival (including median survival, disease-free, and overall survival). The extracted data were then crosschecked between the two authors to rule out discrepancy. In the event of disagreement, a third reviewer (KM) extracted the data.

Outcome Measures

The principle outcome was overall survival. Secondary outcomes included resection rates, surgical complication and mortality rates, and rates of involved surgical margin.

Statistical Methods

Meta-analyses were performed using Revman 5.0, (version 5.0.25 for Mac OS X, Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark).[9] For dichotomous outcomes, the odds ratio (OR) was calculated with a 95% confidence interval (CI) using the Mantel–Haenszel (MH) method. A random effects model was used. Heterogeneity of study results was assessed by the chi test and the I^2 statistic of inconsistency. Statistically significant heterogeneity was defined as P less than 0.1 or an I^2 statistic greater than 50%.[10] A funnel plot was used to explore bias for analyses with greater than ten studies.[11,12] Asymmetry in the funnel plot of study size against treatment effect was used to assess the risk of bias. ORs and 95% CI for time-to-event outcomes were estimated as described by Parmar et al. and pooled according to Peto's method.[13,14]

Results

Description of Studies

Nineteen[5,15–32] studies met the inclusion criteria and were incorporated in the review, accounting for 2,148 patients. The studies selected were all either prospective or retrospective cohort studies, constituting Scottish Intercollegiate Guidelines Network level 2 evidence.[33] NCRT was administered to 901 patients of whom 469 were subject to surgical resection. These were compared to 982 patients who did not receive NCRT of whom 811 underwent surgical resection. Four studies[21,26,31,32] enrolled primarily patients with resectable pancreas cancer, and the remaining 15 enrolled those with unresectable or borderline resectable lesions. In one study,[29] it was stated that no adjuvant treatment was given to the non-NCRT group. In eight studies, the use of adjuvant treatment received no comment and in the remaining ten studies adjuvant treatment was administered to a variable proportion of the non-NCRT patients. There were a variety of radiotherapy and chemotherapy regimens used in the studies included in the analysis. The most common radiotherapy regimen was 50.4 Gy in 28 fractions of 1.8 Gy per fraction. The most common chemotherapy regimens were based on gemcitabine and 5-fluorouracil. The characteristics of the included studies are summarized in Tables 1 and 2.

Overall Survival

All studies reporting appropriate data were included[15–17,19–22,26,29–32,34] in the analysis. A subgroup analysis was performed where NCRT was used in the setting of patients with primarily resectable[21,26,31,32] or unresectable, or borderline resectable disease.[15–17,19,20,22,29,30,34] For analysis of short-term peri-operative outcomes, all studies were included (see below); however, for survival meta-analysis, the studies were categorized into intention-to-treat (ITT) and non-ITT studies. If the survival of all recipients of NCRT (both those who did and did not undergo surgical resection) was compared to the control group undergoing primary resection, the study was designated an ITT analysis. This was the case in nine studies.[15–17,21–23,25,26,30] In nine studies, only the

Table 2 Important characteristics of included studies

Author, year, [reference]	Total no. of patients included	No. of patients receiving NCRT	No. of patients explored after NCRT	No. of patients resected after NCRT	No. of patients not receiving NCRT	No. of patients not receiving NCRT who were explored	No. of patients not receiving NCRT who were resected	Intention-to-treat analysis of survival[a]	Adjuvant treatment
Al-Sukhun 2003[12]	41	20	9	3	21	21	21	Yes	In non-NCRT group 21/21 received adjuvant CRT
Allendorf 2008[13]	245	78	59	59	167	167	139	Yes	NS
Bruckner 1993[14]	28	20	1	0	28	28	28	Yes	NS
Chao 2000[15]	86	40	28	22	33	33	33	No	NS
Golcher 2008[16]	302	103	50	21	58	151	58	No	NS
Greer 2008[17]	102	42	42	42	60	60	60	No	41/60 non-NCRT patients received adjuvant treatment
Ishikawa 1994[18]	54	23	17	17	31	31	19	Yes	NS
Jessup 1993[19]	40	16	10	2	24	24	15	Yes	8/24 non-NCRT patients received adjuvant treament: 6 CRT, 1 RT, 1 CT
Kim 2002[20]	163	87	3	1	76	0	0	Yes	NS
Lind 2008[21]	46	17	11	8	29	29	29	No	NS
Massucco 2006[22]	72	28	8	8	44	44	44	Yes	15/44 non-NCRT patients received adjuvant treatment
Pendurthi 1998[23]	48	25	25	25	23	23	23	Yes	18/23 non-NCRT patients received CRT
Pingpank 2001[24]	100	53	53	53	47	47	47	No	7/47 non-NCRT patients received CT
Piperdi 2010[36]	102	19	NS	11	83	NS	46	NS	26/83 non-NCRT patients received adjuvant therapy
Satoi 2009[26]	175	35	27	27	41	41	41	No	No adjuvant treatment
Snady 2000[27]	159	68	30	20	91	91	91	Yes	63/91 in non-NCRT received adjuvant treatment: 39 CRT, 24 CT alone
Spitz 1997[28]	142	91	67	52	51	51	19	No	In non-NCRT group 19/51 received adjuvant CRT
Vento 2007[29]	47	22	16	16	25	25	25	No	NS
White 2006[31]	196	114	82	82	50	50	50	No	In NCRT group: 25/82 received adjuvant CT. In non-NCRT group 62/50 received adjuvant CRT

RT radiotherapy, *CRT* chemoradiotherapy, *NCRT* neoadjuvant chemoradiotherpay, *CT* chemotherapy, *NS* not stated

[a] Intention-to-treat analysis of survival signifies inclusion in analysis of survival of patients who received or were intended to receive neoadjuvant CRT but were not resected

outcomes of those who underwent resection after NCRT were compared to the control group undergoing primary resection. In one study, it was not possible to determine how the survival analysis was performed.[28] Only studies designated ITT were included for survival meta-analysis. For the resectable group (Fig. 2a.), a total of 101 patients were included in the analysis of 1-year survival for which the Peto OR was 0.49 [0.22, 1.13]. For 2-year survival, only one ITT resectable study was available[21] and so meta-analysis could not be performed. In the setting of pancreatic cancer designated primarily unresectable (Fig. 2b, c.), a total of 531 and 603 patients were included in the analysis of 1-year and 2-year survival, respectively, for which the Peto ORs were respectively 0.56 [0.39, 0.80] and 1.03 [0.70, 1.51]. For the unresectable group, statistically significant heterogeneity was observed for both 1-year (I^2=59%) and 2-year (I^2=83%) survival. For the

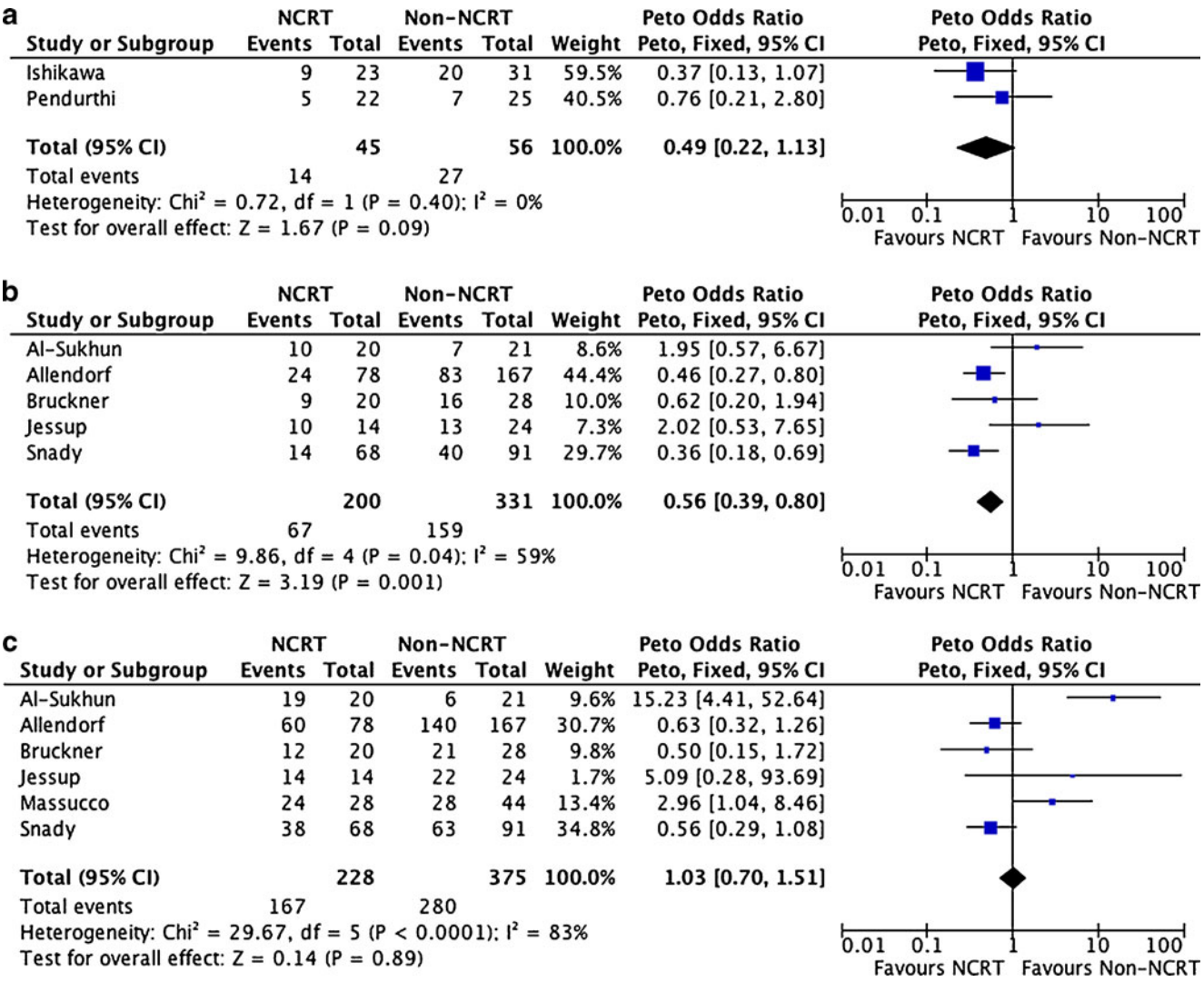

Fig. 2 Comparison of survival of patients receiving NCRT vs. those not receiving NCRT. **a** One-year survival for patients with resectable disease. One-year (**b**) and two-year (**c**) survival for patients with unresectable disease. *NCRT* Neoadjuvant chemoradiotherapy, *95% CI* 95% confidence interval

resectable group, the heterogeneity was not statistically significant. This survival meta-analysis suggests that patients with unresectable pancreatic cancer who received NCRT achieved similar, if not superior, survival outcomes to patients with resectable disease, even though only 40% (93/230) of the NCRT group ultimately underwent resection.

Secondary Outcomes

The secondary outcomes analyzed were total complication rate, peri-operative death rate, resection margin status, and pancreatic fistula rate. A total of 733 patients were included in the analysis of total complications. The M–H OR was 1.35 [0.97, 1.88], failing to demonstrate a statistically significant change in the risk of total peri-operative complications (Fig. 3a). A total of 588 patients were included in the analysis of the pancreatic fistula rate (Fig. 3b). There appeared to be no difference in the incidence of this complication (OR 1.41 [0.32, 6.26]). The analysis of death rate included 882 patients (Fig. 3c). This analysis demonstrated an increased risk of this complication in patients undergoing NCRT (OR 2.39 [1.18, 4.85]). The peri-operative death rate was 5.7% for the NCRT group and 3.2% for the group not receiving NCRT. When the resectable and unresectable groups were considered separately (Fig. 4a, b, respectively), the increased risk of peri-operative death appeared to be associated with resection performed in patients initially designated unresectable prior to NCRT (OR 2.58 [1.20, 5.54]). The meta-analysis of

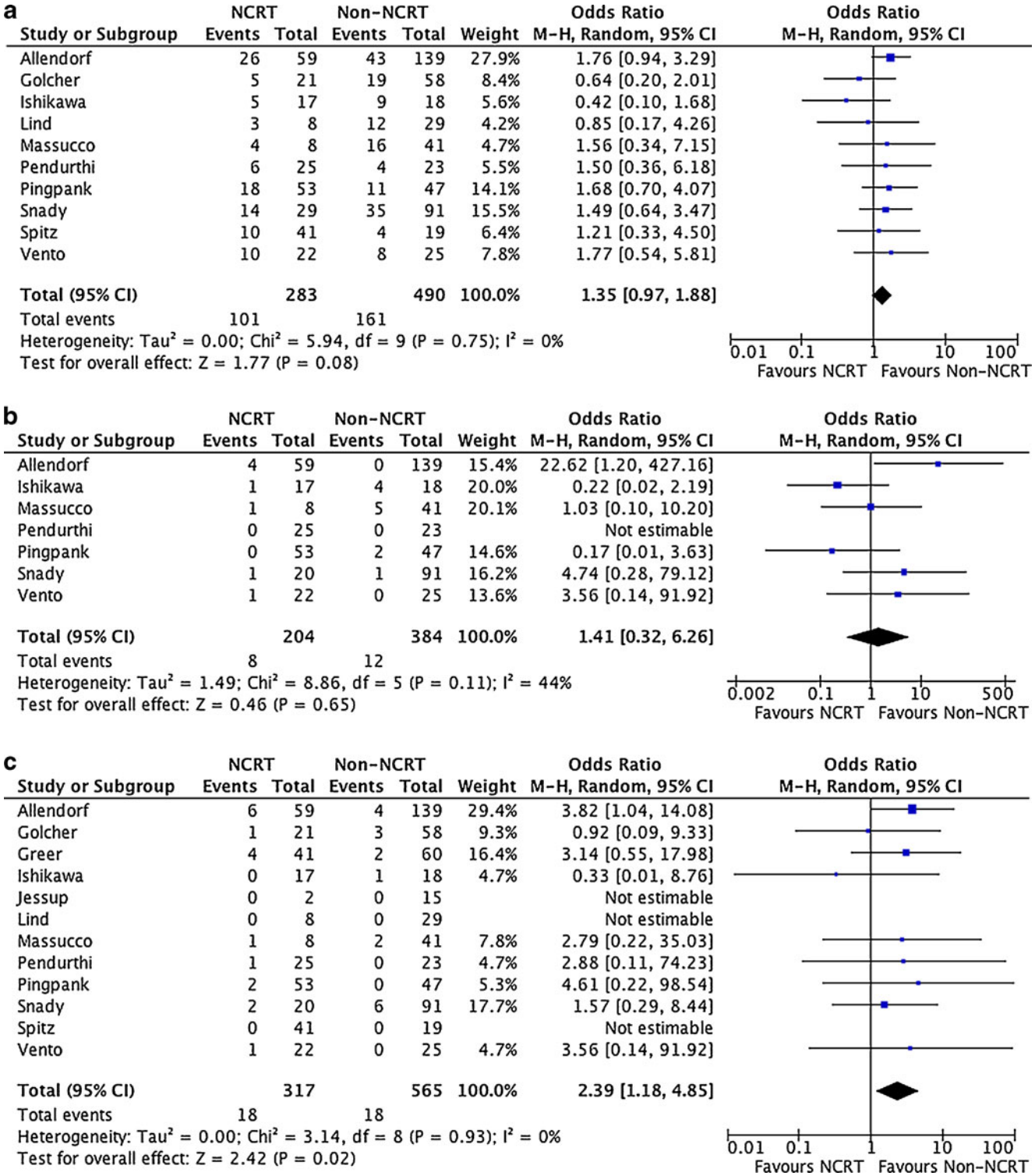

Fig. 3 Comparison of total complications (**a**), rates of pancreatic fistula formation (**b**), and peri-operative death (**c**) in patients receiving NCRT vs. those not receiving NCRT. *NCRT* Neoadjuvant chemoradiotherapy, *M–H* Mantel–Haenszel, *95% CI* 95% confidence interval

resection margin included 763 patients (Fig. 5). Only two studies with NCRT administered for resectable disease were included.[31,32] Overall, patients receiving NCRT were less likely to have a positive resection margin (OR 0.44 [0.29, 0.65]), and this effect was apparent even when only patients designated primarily unresectable were included in the analysis (OR 0.44 [0.28, 0.70]). There was no statistically significant heterogeneity for the outcomes of peri-operative

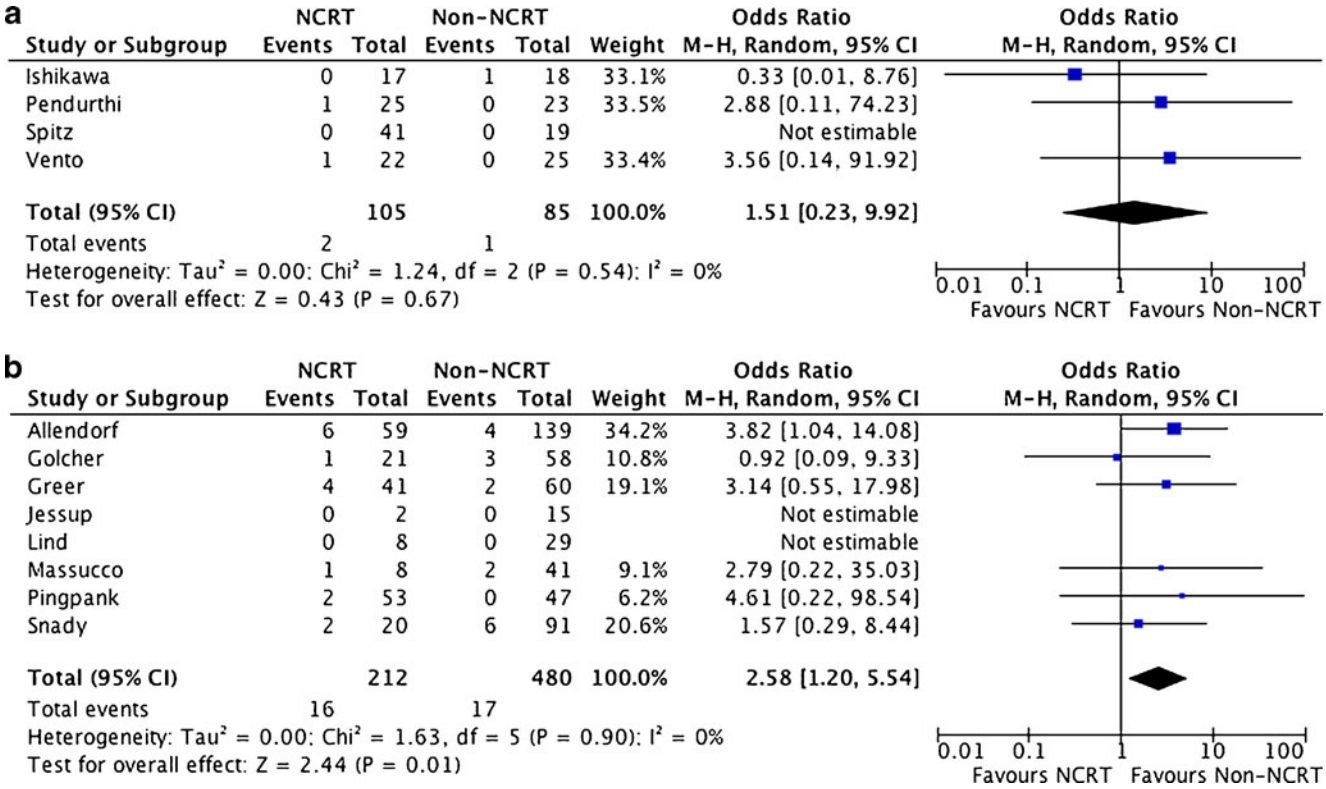

Fig. 4 Comparison of rates of peri-operative death in those who did vs. those who did not receive NCRT. **a** Patients with resectable disease and **b** patients with disease initially designated unresectable. *NCRT* Neoadjuvant chemoradiotherapy, *M–H* Mantel–Haenszel, *95% CI* 95% confidence interval

death rate (I^2=0%), total complications (I^2=0%), or pancreatic fistula rate (I^2=44%).

Reporting Bias

Funnel plot analysis was performed only where ten or more studies were included.[9] For peri-operative death, margin status, and total complications, there was no funnel plot asymmetry (Fig. 6).

Discussion

Neoadjuvant therapy has a number of putative advantages including downstaging, reduced incidence of positive resection margins, delivery of treatment to intact well-vacularized tissues,[35] and higher rates of treatment completion.[28] Neoadjuvant treatment, most importantly, may also facilitate selection for surgery of patients with favorable tumor biology. Those who do not develop progressive disease prior to surgery

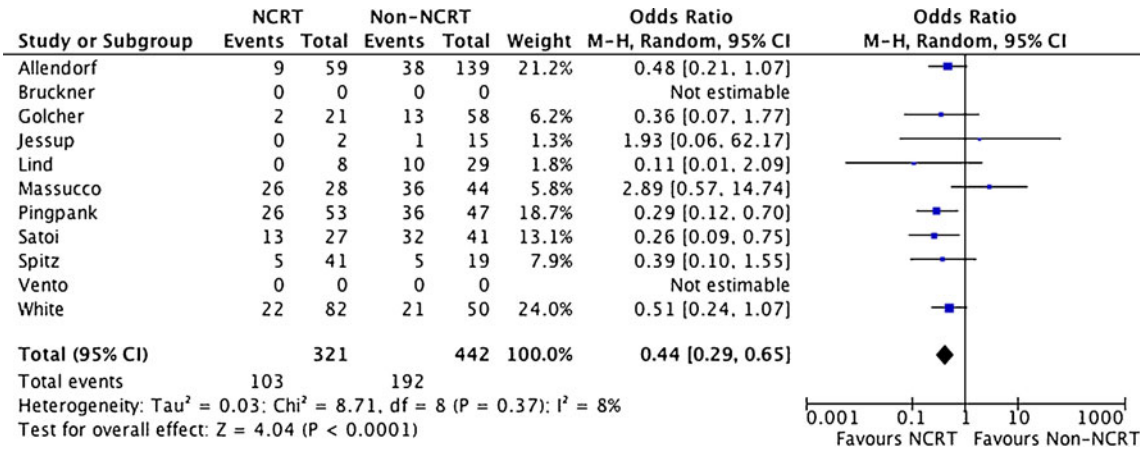

Fig. 5 Comparison of rates of positive resection margin in those who did vs. those who did not receive NCRT. *NCRT* Neoadjuvant chemoradiotherapy, *M–H* Mantel–Haenszel, *95% CI* 95% confidence interval

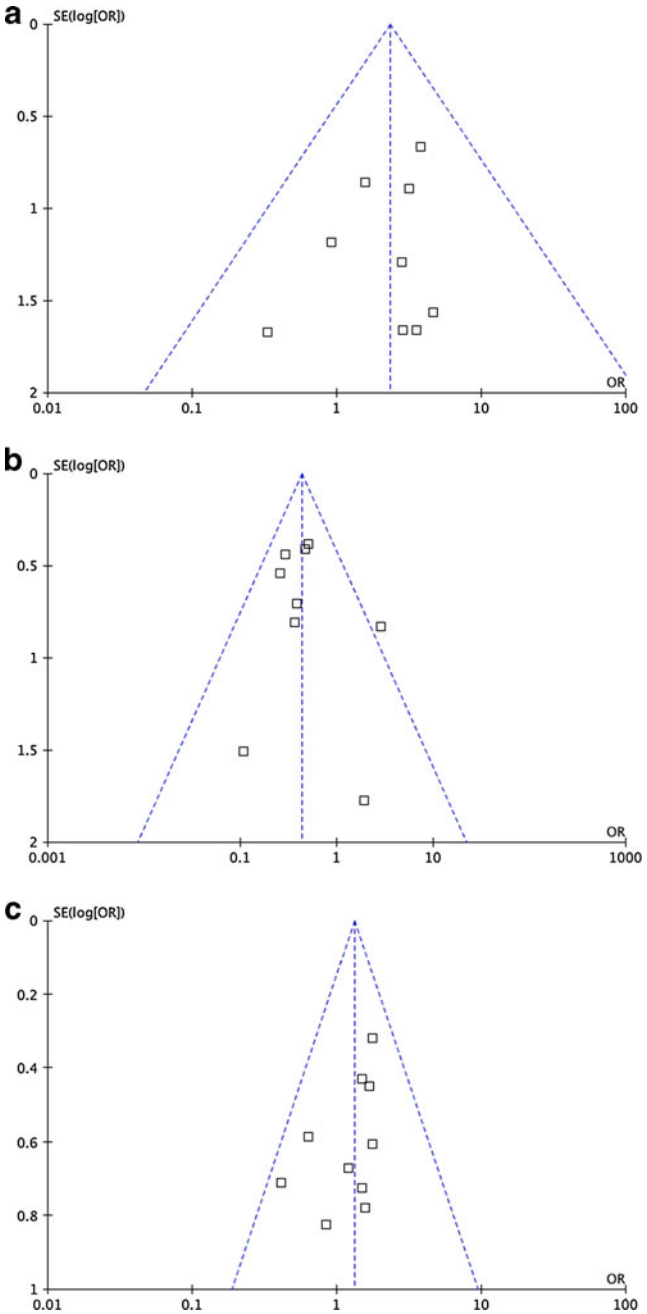

Fig. 6 Funnel plots of comparison of those who did vs. those who did not receive NCRT for outcomes **a** peri-operative death, **b** margin status, and **c** total complications. *NCRT* Neoadjuvant chemoradiotherapy, *SE* standard error, *OR* odds ratio

or who show a significant downstaging effect may have a better prognosis, and moreover, those with poor tumor biology are selected out via disease progression, thereby avoiding the morbidity of fruitless surgery.

This meta-analysis included only NRS, as RCT are not yet available.[5] Although there are problems with designing RCT in the setting of resectable or potentially resectable disease,[36] it is unlikely to be possible to perform RCT in the context of pancreatic cancer that is designated unresectable. In the majority of the NRS included in this analysis, the outcomes of patients receiving NCRT for unresectable cancers were compared to those of patients with cancers that undergo resection with or without adjuvant treatment. There is considerable heterogeneity evident in the meta-analysis, particularly with respect to survival outcomes. Whilst some of this heterogeneity may be attributable to differences in interventions (such as NCRT and surgery) and outcome assessments, it is likely in large part to be due to the systematic differences between the patients in the intervention groups, and this bias should be acknowledged. For each of the outcomes analyzed, not all of the 19 studies included in this review present data that can be used in each meta-analysis. This is a consequence of the heterogeneity of data reporting in these studies and has a potential to impact on the analysis outcomes through reducing the power of each analysis and through reporting bias.

The most significant limitation of the meta-analysis for unresectable disease is that the definitions of unresectability and borderline resectability are not consistent between the studies, or are not clearly described in the manuscript (Table 1). Although the definitions have recently undergone standardization,[37] the majority of the studies analyzed precede the adaption of such definitions or they have not been utilized by the authors. Nevertheless, there is likely to be relative homogeneity of concepts of resectability between the treatment and control arms within each study. Because only comparative studies have been included in the analysis, it is probable that there is balanced inconsistency between treatment and control groups in the meta-analysis. Because of this flaw, the data for unresectable pancreatic cancer must be interpreted with caution.

Neoadjuvant CRT is associated with a reduced risk of a positive resection margin. This outcome is somewhat counterintuitive, especially as the effect is observed primarily in the initially unresectable group, where the tumors were deemed to be unresectable prior to NCRT. Whilst the reduced incidence of positive resection margin may be due to a downstaging effect of NRCT, this outcome may also be confounded by other factors. Whilst there is insufficient data in the analyzed studies to substantiate the contention, the surgeon approaching a lesion initially deemed unresectable may be more likely to perform an extended resection (including a vascular resection), and thereby avoid positive microscopic margins.

Fibrosis is induced by pre-operative radiotherapy treatment,[38] and NCRT has been previously associated with a reduced occurrence of pancreatic fistula formation by hardening the pancreas.[39] However, in this meta-analysis, there was no evidence of a reduction in this frequency of this complication. The risk of peri-operative death was substantially higher in the group of patients receiving NCRT. This

may be due to the fact that patients receiving NCRT are more likely to have larger and more extensively infiltrating tumors requiring more radical surgery. In addition, immunosuppression induced by chemotherapy and tissue effects of radiotherapy may render surgery more difficult and healing of tissues less predictable. Nevertheless, there does not appear to be a detrimental overall effect on survival.

Recently published systematic reviews[6,7] have been able to provide evidence that up to a third of tumors initially designated unresectable are able to be resected after NCRT. Using more restrictive study selection criteria, our analysis shows a similar overall resectability rate of 40%. The patients who undergo resection after NCRT are likely to differ systemically in terms of tumor biology from those who remain unresectable. Because of the bias intrinsic in the design of these studies, we do not know whether the apparent benefits of NCRT represent a treatment or a selection effect. By focusing exclusively on comparative studies and those with an intention-to-treat design, this meta-analysis attempts to address this issue. Because of the exclusion of non-comparative studies, numerous high-quality prospective, single-arm phase II studies of neoadjuvant therapy that have been published over the past 20 years are not included in this analysis. Whilst many of these studies represent the best data available relating to the outcomes of administration of NCRT, they omit information relating to those patients who are either resected without NCRT or do not undergo resection.

The quality of data currently available is poor and we are unable to draw firm conclusions with respect to the main study outcome of overall survival. Survival outcomes in pancreatic cancer are poor irrespective of treatment modality. However, NCRT may offer the prospect of successful surgical treatment for a proportion of patients with a reduced frequency of positive resection margins although this may be associated with an increase in peri-operative complications and increased risk of peri-operative death.

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ORIGINAL ARTICLE

Pattern of Venous Collateral Development After Splenic Vein Occlusion in an Extended Whipple Procedure

Comparison with Collateral Vein Pattern in Cases of Sinistral Portal Hypertension

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Abstract
Introduction The risks of developing sinistral portal hypertension as a result of occlusion of the splenic vein close to its termination during a Whipple procedure are unclear. Our purpose was to compare the pattern of venous collateral development after splenic vein ligation in an extended Whipple procedure with the pattern of collateral development in cases of sinistral portal hypertension.
Methods Five patients underwent an extended Whipple procedure in which the splenic vein was divided and not reconstructed. Six to eight months later detailed mapping of venous return from the spleen was determined by contrast-enhanced multidetector computed tomography or in one case by 3D contrast-enhanced MRI. Spleen size and length of residual patent splenic vein were also measured. The literature on sinistral portal hypertension was evaluated to ascertain whether the venous collateral pattern in cases of left-sided portal hypertension was similar to the pattern that developed when the splenic vein was ligated at its termination in the Whipple procedure.
Results A length of splenic vein remained patent in all five patients, measuring 4.5 to 11.5 cm from the spleen. Splenomegaly did not develop. Blood returned from the spleen by multiple collaterals including collaterals in the omentum and mesocolon. These types of collaterals do not develop in sinistral portal hypertension, nor is residual patent splenic vein seen.
Conclusions Ligation of the splenic vein close to its termination in five patients resulted in a pattern of venous return different from patients that have developed left-sided portal hypertension.

Keywords Whipple procedure · Mesenteric vein resection · Superior mesenteric vein · Portal vein · Splenic vein · Sinestral portal hypertension · Left sided portal hypertension

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Cancers of the head of the pancreas frequently invade the superior mesenteric and portal veins. Multiple reports document feasibility of resecting these tumors, [1–18] and the topic has been the subject of three recent systematic reviews.[19–21] Most resections involve the right lateral portion of the veins or a cylinder of superior mesenteric vein below its confluence with the splenic vein, but occasionally, the termination of the splenic vein must be resected because of involvement of the confluence of the superior mesenteric and splenic veins. The splenic vein may then be reconstructed or ligated. Reconstruction adds to the complexity of the procedure, but occlusion of the vein risks the development of sinistral portal hypertension.[2,4] Surgical opinion seems to be divided in regard to the risk of developing sinistral portal hypertension under these circumstances. Some authors claim that splenic vein ligation is safe,[6,22] while others describe complications associated with sinistral portal hypertension.[2,4] Until now, the pattern

of venous collateral development after ligation of the termination of the splenic vein in a Whipple procedure has not been examined. The purpose of this study was to describe the pattern and to compare it to the pattern in cases of sinistral portal hypertension.

Methods

Five patients who underwent an extended Whipple procedure in which the pancreas and the splenic vein were divided at the point where the splenic artery comes onto the pancreas were the subjects of the study. The circumstances under which the resections were performed are described in the individual case reports.

The evaluation of the pattern of collateral development was performed 6–8 months after the operative procedure by contrast-enhanced multidetector computed tomography using thin sections (1–2 mm) or, in one case, by 3D contrast-enhanced MRI (using 4-mm images). These examinations were part of the routine follow-up of the patients. The images were sent to a dedicated 3D workstation (Vitrea; Vital Images; Minnetonka, MN) generating standard 2D reconstructions (multiplanar reconstructions and variable thickness maximum intensity projections [4–15 mm]) and 3D postprocessing (shaded-surface volume rendered images). Splenic size was evaluated in all planes, and the presence or absence of gastric and esophageal mucosal varices was determined. Splenomegaly was considered to be present when the spleen was 13 cm or greater in longest diameter.[23]

To perform vein mapping, veins emanating from the spleen were located. These were then traced through the abdomen on serial images until the veins ended in named major veins. The source transaxial images were used in all cases to generate a venous map, and all vein maps were confirmed on the 2D and 3D reconstructions. Photographs were then taken of standard cuts, MIP images, or 3D images to record the venous return pattern. The extent to which the splenic vein remained patent was also assessed by measuring the length of the residual opacified splenic vein from the splenic hilum to the point of obstruction.

Analysis of the Literature on Left-Sided Portal Hypertension as It Relates to the Present Study

The terms left-sided portal hypertension, sinistral portal hypertension, and splenic vein were entered in to the OVID database to seek relevant papers. In addition, there have been three collective reviews of this subject consisting of a total of 450 patients,[24–26] and the reference list in these papers was used for the same purpose. First, we sought to determine whether any collateral pathways were present in patients with sinistral portal hypertension other than the well-described pathway through the short gastric veins, stomach, and coronary vein. Next, we looked for information on the length of residual splenic vein, i.e., the distance between the spleen and the site of obstruction, in patients with left-sided portal hypertension. Finally, we determined whether any of the cases described in the review literature occurred after a Whipple procedure. With this information, the pattern of venous collateral development in cases of sinistral portal hypertension was compared to that which we observed in the five extended Whipple procedures.

Results

Clinical Course and Vein Mapping in Five Patients

Patient 1. Pancreatic Cancer with Vascular Invasion

Clinical Course A 56-year-old female presented with a pancreatic head tumor that involved the superior mesenteric vein and portal vein and abutted the anterior surface of the splenic vein. After neoadjuvant therapy, the tumor was minimally smaller. The patient underwent an extended Whipple procedure with resection of portions of the superior mesenteric, portal, and splenic veins. The splenic vein was divided approximately 2 cm to the left of its confluence with the superior mesenteric vein. The inferior mesenteric vein was also ligated and divided as part of this procedure. Reconstruction was by insertion of a venous interposition graft between the superior mesenteric and portal veins. The tumor was 3 cm in greatest diameter, margins were negative, 3/24 lymph nodes were involved, and the stage was T3N1M0. There was tumor invasion of the wall of the resected vein on microscopy. The postoperative course was complicated by deep vein thrombosis of the left leg treated with anticoagulation and a urinary tract infection treated with antibiotics. LOS was 12 days.

Spleen Size and Vein Mapping The effect of splenic vein occlusion was evaluated at 6 months after surgery by computed tomography. The vein graft was patent. The maximum longitudinal and transverse diameters of the spleen (9.7 and 6.0 cm) were normal. The splenic vein was patent for 5.8 cm from the hilum of the spleen. A new venous collateral system had developed, which drained blood from the splenic vein to the superior mesenteric vein through a circuitous route via what appears to be omental veins and veins along the transverse mesocolon. This collateral system is shown in Figs. 1 and 2. Note that the collateral pathway first passed anteriorly then inferiorly for a long distance, crossed the abdomen from left to right, and passed posteriorly and finally anteriorly again to enter the

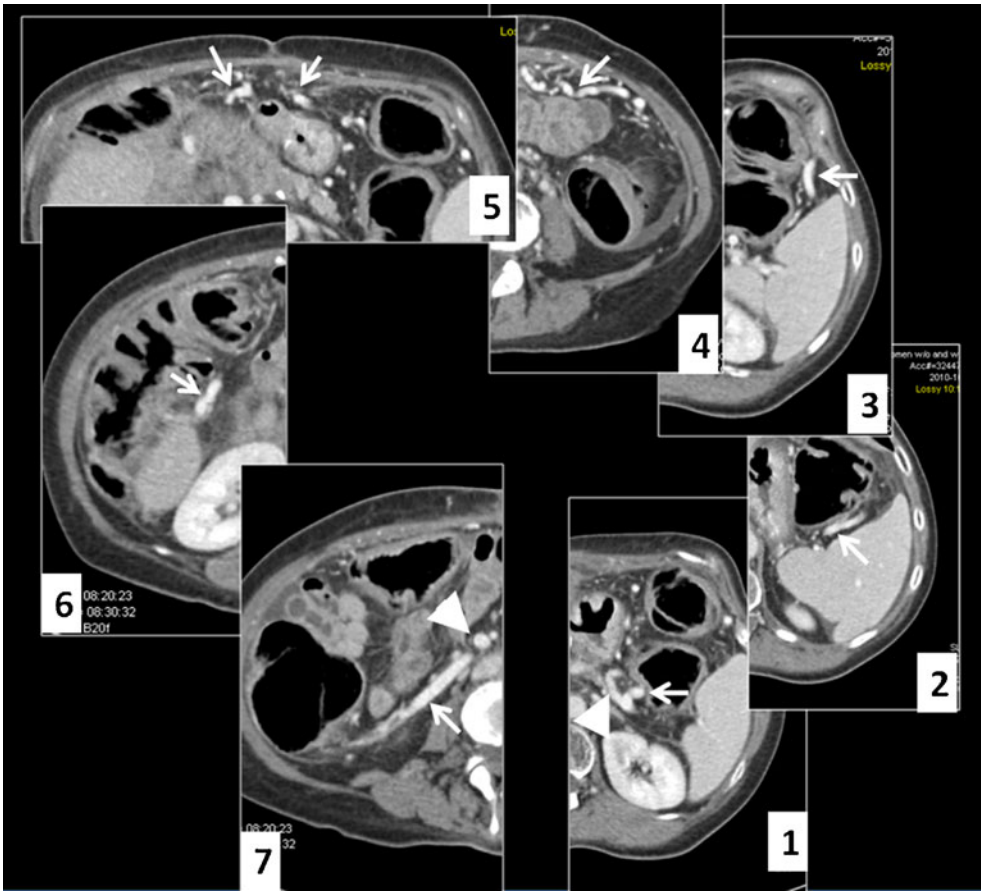

Fig. 1 Patient 1. Transverse postcontrast computed tomography. Veins originating in the splenic hilum [*1*] can be traced anteriorly, inferiorly, and across the abdomen through the omentum and transverse mesocolon [*2–6*] to end in the superior mesenteric vein [*7*]. Spleen size is normal

superior mesenteric vein on its right posterior aspect. The terminal vein in this collateral system measured 7 mm in diameter at the point at which it joined the superior mesenteric vein. A few enlarged venous collaterals could be seen in and around the stomach as well as some tiny esophageal veins. The coronary vein was not patent.

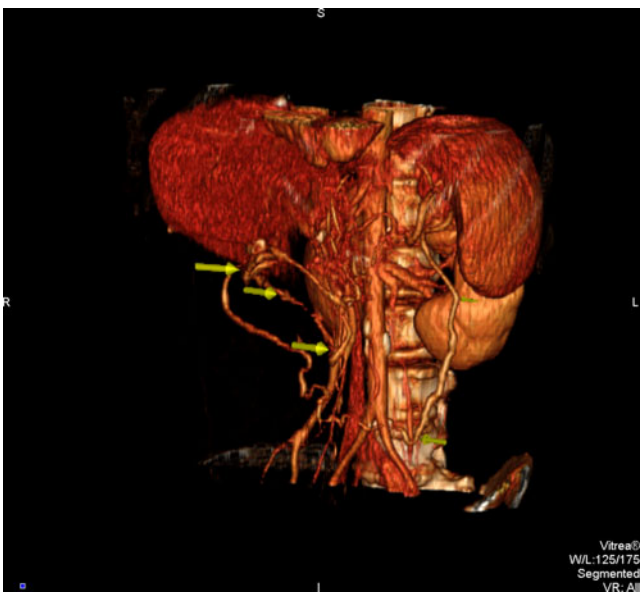

Fig. 2 Patient 1. Volume rendered 3D reconstruction showing the large collateral loop through the omentum (*yellow arrows*)

Patient 2. Pancreatic Cancer with Vascular Invasion

Clinical Course A 57-year-old female presented with a large cancer of the head, neck, and proximal body of the gland with complete obstruction of the superior mesenteric, splenic, and portal veins. Collateral veins were present, including enlarged gastric veins. After 9 months of chemoradiation, the disease was stable, except that soft tissue stranding was noted along the hepatic and superior mesenteric arteries. The patient underwent an extended Whipple procedure with resection of portions of the superior mesenteric, portal, and splenic veins. The splenic vein was divided approximately 2 cm to the left of its confluence with the superior mesenteric vein. The inferior mesenteric and middle colic veins were also ligated and divided. The portal vein was anastomosed to the superior mesenteric vein without interposition graft, with the length of resected vein being 3 cm. The tumor was 3 cm in greatest diameter, margins were negative, 0/30 lymph nodes were involved, and the stage was T3N0M0. Portions of the resected portal and superior mesenteric veins were obliterated. The postoperative course was unremarkable. LOS was 7 days.

Spleen Size and Vein Mapping The effect of splenic vein occlusion was evaluated 8 months after surgery by MR angiography. The vein anastomosis was patent. Spleen size was within normal limits. The maximum longitudinal diameter was 11 cm, and the maximum transverse diameter was 5.6 cm. The splenic vein was patent for 4.5 cm from the hilum of the spleen. Two venous collateral systems had developed to drain blood from the spleen. A superior route passed from splenic veins around and through the stomach to enter the portal vein (white arrowhead) via a patent coronary vein (Fig. 3a), while an inferior pathway passed from splenic veins through the root of the mesentery to the superior mesenteric vein (Fig. 3a, b). The terminal portions of these veins measured about 6 mm in diameter. There were no enlarged veins either in or around the esophagus.

Patient 3. Pancreatic Cancer with Vascular Invasion

Clinical Course A 48-year-old male presented with a mass 3.8 cm in diameter in the pancreatic head involving the superior mesenteric, portal, and splenic veins. Biopsy was positive for adenocarcinoma. Chemotherapy was given for 4 months, with reduction of the size of the tumor to 2.2 cm, but the veins were still all involved. The patient underwent an extended Whipple procedure with resection of portions of the superior mesenteric, portal, and splenic veins. The splenic vein was divided approximately 2 cm to the left of its confluence with the superior mesenteric vein. The inferior mesenteric and middle colic veins were also ligated and divided as part of this procedure. Reconstruction was by insertion of a venous interposition graft between the superior mesenteric and portal veins. The tumor was 2.2 cm in greatest diameter, margins were negative, 9/36 lymph nodes were involved, and the stage was T3N1M0. There was tumor invasion of the wall of the resected vein on microscopy. The postoperative course was unremarkable. LOS was 7 days.

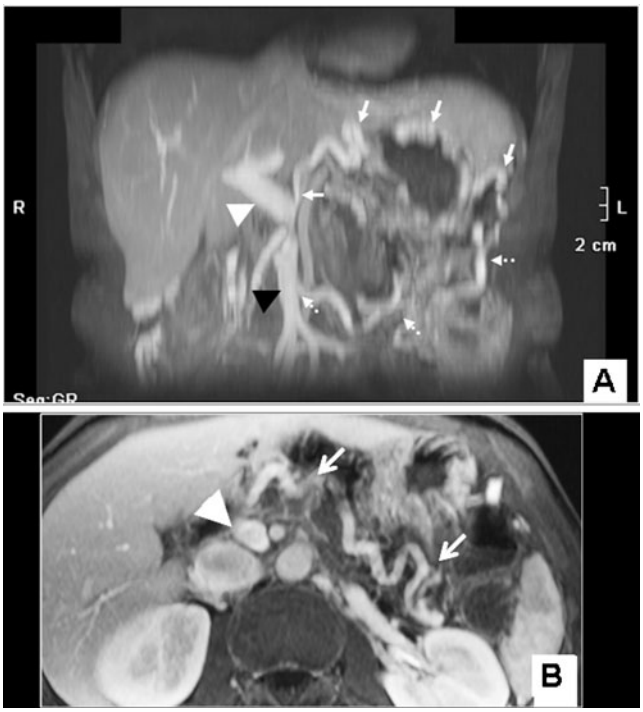

Fig. 3 Patient 2. Postcontrast, fat suppressed, T1 weighted magnetic resonance images. Two venous collateral systems are shown. **a** Coronal image. The superior route (*solid arrows*) passed from the splenic vein around and through the stomach to enter the portal vein (*white arrowhead*) via the coronary vein. The inferior route (*dotted arrows*) passed from the splenic veins through the root of the mesentery to the superior mesenteric vein (*black arrowhead*). **b** Transverse image. The inferior route (*arrows*) is seen better in the transverse view. The *white arrowhead* is the superior mesenteric vein

Spleen Size and Vein Mapping The effect of splenic vein occlusion was evaluated 6 months after surgery by computed tomography. The vein graft was patent. Spleen size was within normal limits and measured 12.0 cm in maximum longitudinal diameter and 7.7 cm in maximum transverse diameter. The splenic vein was patent for 9.2 cm from the hilum of the spleen. A collateral venous system had developed. Large veins ran from the spleen and entered a network of smaller veins around and in the stomach (Fig. 4). The veins within the stomach wall were small compared to the perigastric veins. These led to other large veins on the other side of the stomach, which joined an enlarged coronary vein that terminated in the portal vein. There were no visible veins in or around the esophagus.

Patient 4. YJ Ampullary Cancer with Severe Pancreatitis

Clinical Course 65-year-old female presented with cholangitis to an outside hospital and was intubated and managed in an ICU. The patient was transferred to our hospital after additional episodes of cholangitis and pancreatitis. Axial imaging and EUS showed thickening around the bile duct and pancreatitis, but no focal mass. The Ca19-9 was 96 IU (upper

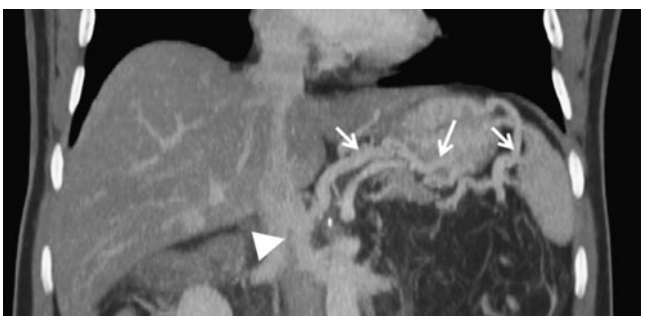

Fig. 4 Patient 3. Coronal MIP postcontrast computed tomography. Large veins from splenic hilum connect to a network of smaller veins around and in the stomach. These led to other large veins on the other side of the stomach, which united to form the coronary vein, which terminated in the portal vein (*arrowhead*)

limit of normal 37 IU). Biopsy was suspicious for malignancy. The patient was operated 2 months after initial presentation without a definite diagnosis of cancer. There was a palpable mass in the head of the pancreas, but the entire pancreas was firm. Dissection of the superior mesenteric vein was difficult due to firm adherence of the pancreatic neck, and bleeding was encountered when doing so. A biopsy of the pancreatic head showed adenocarcinoma. There was uncertainty regarding the extent of the tumor and its relationship to the veins. Dissection behind the body of the pancreas to the left of the axis of the superior mesenteric and portal veins was possible as there was less inflammation in this area. The pancreas and splenic vein were then divided about 2 cm to the left of the usual plane of division. Thereafter, an extended Whipple procedure with resection of portions of the superior mesenteric, portal, and splenic veins was completed. The inferior mesenteric vein was also ligated and divided as part of this procedure. Reconstruction was by primary anastomosis between the superior mesenteric and portal veins. Pathologic examination found a 1.5-cm tumor that arose from the ampulla of Vater and peritumoral pancreatitis. Margins were negative, 3/28 lymph nodes were involved, and the stage was T3N1M0. There was no tumor invasion of the wall of the resected veins on microscopy. The postoperative course was unremarkable. LOS was 7 days.

Spleen Size and Vein Mapping The effect of splenic vein occlusion was evaluated 6 months after surgery by computed tomography. The vein anastomosis was patent. Spleen size was within normal limits, measuring 9.3 cm by 4.7 cm in maximum longitudinal and transverse diameters, respectively. The splenic vein was patent for 10.5 cm from the hilum of the spleen. A collateral vein pathway had developed (Fig. 5). Veins could be traced from the splenic hilum to the splenic flexure of the colon. There, the veins joined a fine network of veins around and in the colonic wall. On the medial side of the splenic flexure, the fine network emanated into several distinct veins that then formed a single large vein, which coursed across the abdomen to join the superior mesenteric vein. There were no visible veins in or around the esophagus or in the stomach, but the gastric veins could be traced into a normal-sized coronary vein that terminated at the portal vein.

Patient 5. JF Vascular Accident

Clinical Course A 76-year-old female presented with a malignant mass in the duodenum and pancreas. Vessels were uninvolved. At surgery, the pancreas was edematous, and there was hemorrhage in the retroperitoneum secondary to preoperative endoscopic biopsy. The superior mesenteric vein was very thin walled, but a tunnel was successfully created behind the neck of the pancreas. While dissecting

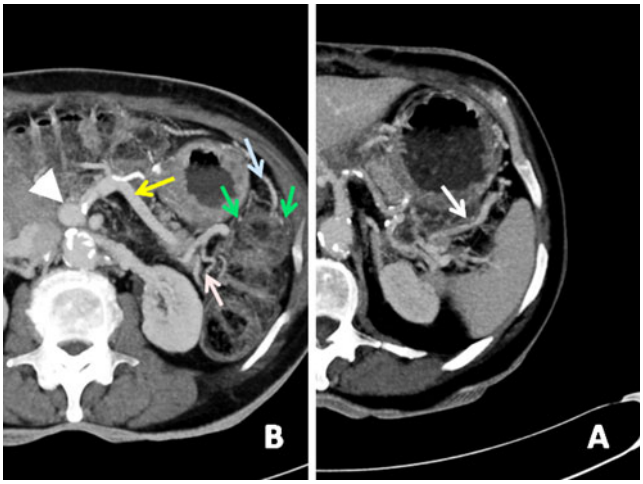

Fig. 5 **a** and **b** Patient 4. Transverse MIP postcontrast computed tomography. Veins from the area of the splenic hilum (*white arrow* in **a**) joined to those around the splenic flexure of the colon (*blue arrow* in **b**). These veins are connected to a fine network of veins around and in the colonic wall (*green arrows* in **b**). On the medial side of the splenic flexure, the fine network emanated into several distinct veins (*pink arrow* in **b**) that then formed a single large vein (*yellow arrow* in **b**) that travelled across the abdomen to join the superior mesenteric vein (*arrowhead* in **b**)

behind the duodenum, massive hemorrhage occurred due to a tear in the SMV/portal vein possibly due to traction. The pancreas was rapidly divided through the left side of the neck of the pancreas, the splenic vein was transected, the superior mesenteric and portal veins were clamped, and the SMA was dissected free. The portal and superior mesenteric veins were divided, and the specimen was removed. Venous continuity between the superior mesenteric and portal veins was restored with a graft. The splenic vein was not reconstructed. The inferior mesenteric vein was also ligated and divided. The resected tumor was 2.0 cm in greatest diameter, margins were negative, 6/37 lymph nodes were involved, and the stage was T4N1M0. There was invasion of the duodenum and peripancreatic soft tissue but no tumor invasion of the wall of the resected vein on microscopy. The patient remained in hospital for 19 days during which time she underwent an interventional radiologic procedure for a hepatic artery pseudoaneurysm.

Spleen Size and Vein Mapping The effect of splenic vein occlusion was evaluated 9 months after surgery by computed tomography. The vein anastomosis was patent but slightly narrowed. Spleen size was within normal limits, measuring 10.0 cm by 5.0 cm in maximum longitudinal and transverse diameters, respectively. The splenic vein was patent for 8.0 cm from the hilum of the spleen. Two collateral vein pathways had developed (Fig. 6). The first consisted of a network of fine veins around the body of the pancreas that coalesced into a vein that ran anteriorly then posteriorly into the portal vein (Fig. 6a, b). This was not the

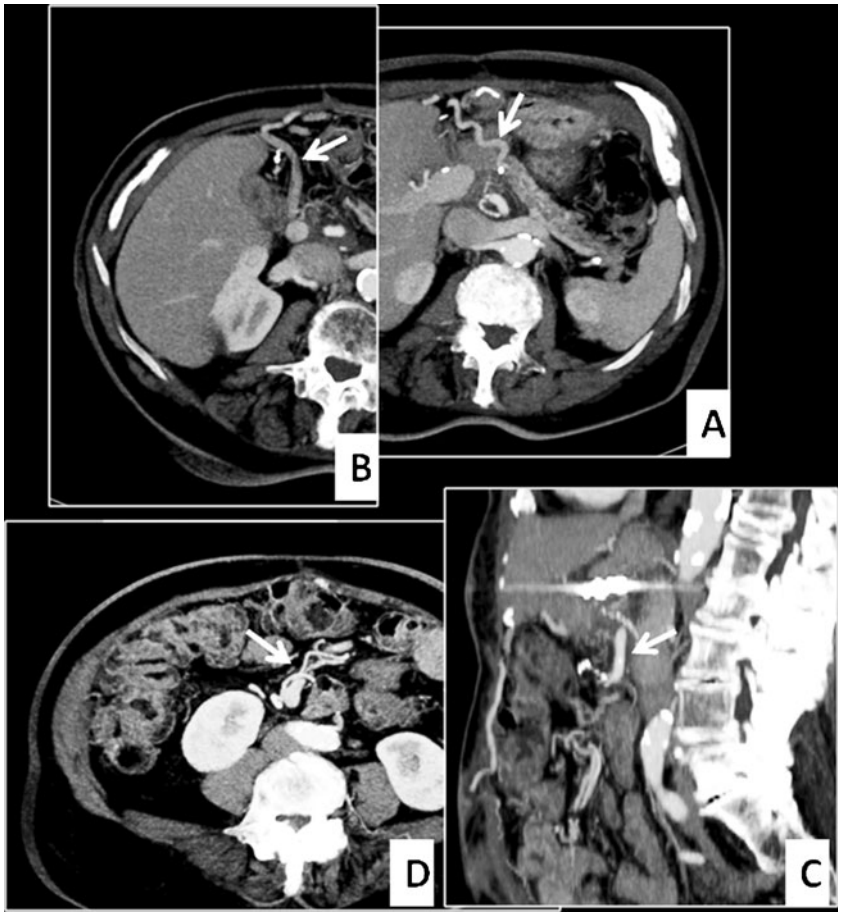

Fig. 6 Transverse and sagittal MIP postcontrast computed tomography. Two collateral vein pathways had developed. **a** and **b** A superior route consisted of fine veins around the body of the pancreas that coalesced into a single vein (*arrow* in **a**) that ran anteriorly then posteriorly (*arrow* in **b**) into the portal vein. This was not the coronary vein, and no coronary vein was detectable. **c** and **d** The second pathway ran inferiorly from the spleen (*arrow* in **c**) through the omentum and across the abdomen (*arrow* in **d**) to the right to end in the superior mesenteric vein

coronary vein, which was absent. The second pathway ran inferiorly from the spleen through the omentum and across the abdomen toward the right side to the end in the superior mesenteric vein (Fig. 6c, d). There were no visible veins in or around the esophagus or in the stomach.

Analysis of the Literature on Left-Sided Portal Hypertension as It Relates to the Present Study

Although left-sided portal hypertension is an uncommon condition, it has been the subject of three extensive reviews published between 1970 and 2007.[24–26] Of 450 patients, about 70% had splenomegaly and 70% upper gastrointestinal bleeding.[24–26] Pancreatitis was the cause of splenic vein occlusion in 66% of cases, with benign and malignant neoplasms accounting for most of the remainder.[24–26]

Virtually, all patients with sinistral portal hypertension described in the literature have developed a classical venous collateral pathway in which blood flow is from spleen into short gastric veins, then into perigastric and intragastric veins, and finally into coronary and portal veins.[26] We found only one exception in a case report by Burbige et al. in which a man, when young, had gastrectomy with division of the short gastric veins and later in life developed colonic varices when the splenic vein became obstructed.[27] Specifically, in the literature on sinistral portal hypertension, we found no other mention of an inferior route through omental, colonic, or mesenteric veins to the superior mesenteric vein such as we observed in several of our cases. Secondly, in terms of length of residual splenic vein (length of vein from spleen to obstruction), there were two types of cases. Most cases of sinistral portal hypertension are the result of pancreatitis, which causes diffuse splenic vein thrombosis. In these cases, there is no residual patent splenic vein.[24–26] Remarkably, this was also the case when the splenic vein obstruction was due to focal compression rather than diffuse thrombosis. Table 1 lists cases that clearly described the position of a localized obstruction leading to sinistral portal hypertension.[28–41] Strikingly, in every case, the obstruction was located near the tail of the pancreas so that the residual portion of splenic vein upstream from the site of obstruction was absent or very short. Again, this was very different from our cases in which the mean length of the residual vein was 7.6 cm (range 4.5–10.5 cm). Finally, none of the 450 cases listed

Table 1 Literature reports of left-sided portal hypertension which stipulate localized site of splenic vein obstruction

Reference number	First author	Year	Gender	Age	Presentation	Splenomegaly	Vascular findings	Type of lesion, location, and size
28	Gallardo-Navarra	1973	M	19	Malena	Yes	Varices of short gastric and gastroepiploic veins	Neuroendocrine tumor—300 gm; tail of pancreas
29	Wolloch	1974	F	50	Hematemasis	Yes	Varices of short gastric and gastroepiploic veins	Pancreatic cyst; tail of pancreas; 15 cm
30	Wolf	1977	M	66	Malena; hematemasis	Yes	Gastric varices	Neuroendocrine tumor; 6 cm; tail of pancreas
31	Hanar	1982	F	32	Hematemasis; bleeding esophageal varices	Yes	Varices around GE junction and dilated gastroepiploic vein	Focal pancreatitis; tail of pancreas; size not stated
32[a]	Chellappa	1986	F	39	Anemia; bleeding gastric varices	Yes	Esophagogastric varices	Neuroendocrine tumor of pancreas; 10 cm
33	Singh	1990		40	Hematemasis; malena		Esophagogastric varices	Jejunal TB; mass 5 cm extending to tail of pancreas
34	Sheen-Chen	1991	M	61	Malena	Yes	"Cardiac varices"	Acinar cell tumor; tail of pancreas; size not stated
35	Klopmaker	1993	F	27	Severe variceal bleeding	Not stated	Fundal varices	Hydatid cyst; tail of pancreas; size not stated
36	Seenu	1994	M	42	Hematemasis and malena	Yes	Gastric varices	Lymphoma splenic; flexure of colon; size not stated
37	Kimura	1996	M	51	Hematemasis	Yes	Varices between stomach and spleen	Celiac artery aneurysm; body of pancreas; 9 cm
38	Lewis	1998	M	59	Anemia	Not stated	Prominent gastric varices and gastroepiploic collaterals	Focal pancreatitis; tail of pancreas; size not stated
39	Tsuchida	2003	F	43	Splenomegaly; isolated gastric varices	Yes	Hepatopetal flow via coronary and gastroepiploic veins	Cystic tumor; tail of pancreas; 10 cm
40[b]	Thompson case 1	2006	F	57	Upper G.I. bleeding; gastric varices	Yes	Prominent veins around gastric fundus	Pseudocyst; tail of pancreas
40	Thompson case 2	2006	M	53	Malena; gastric varices	Not stated	Dilated veins around stomach	Neuroendocrine cancer; tail of pancreas; size not stated
40	Thompson case 3	2006	F	43	Upper G.I. bleeding; gastric varices	Yes	Dilated veins around stomach	Adenocarcinoma; tail of pancreas; size not stated
41	Ito	2007	M	68	Incidental; gastric varices on endoscopy	No	Hepatopetal flow via coronary vein	Serous cystadenoma; tail of pancreas; 8 cm

[a] This patient had a localized pancreatic resection of the tumor with the splenic vein in the tail of the pancreas but without splenectomy 11 years prior to treatment of the left-sided portal hypertension by splenectomy

[b] Four cases were presented in this report. The fourth patient had diffuse splenic vein thrombosis

in the review literature occurred following a Whipple procedure.

Discussion

The main finding in this study is that occlusion of the splenic vein about 2 cm from its confluence with the superior mesenteric vein did not result in splenomegaly or symptoms when evaluated after 6–8 months in five patients. Ligation of the splenic vein at this point also did not result in complete splenic vein occlusion. From 4.5 to 10 cm of vein measured from the spleen remained patent. This is very different from the pattern described in the literature on sinistral portal hypertension in which the length of patent splenic vein seems always to be negligible or very short. Furthermore, our patients developed some collateral pathways not described in the literature on sinistral portal hypertension. Some of the five patients developed the well-described superior collateral pathway

through the stomach associated with sinistral portal hypertension.[26] However, others developed an inferior collateral pathway in addition to or instead of the transgastric pathway. These inferior pathways run along the omental arcade (arc of Barkow), around and through the colon or through the mesentery, and usually terminate in the superior mesenteric as opposed to the portal vein. They may co-exist with the gastric pathway or be the preferred collateral route, even when the coronary vein is patent (patient 5). The absence of splenomegaly in our patients is also unlike the effect of occlusion near the tail of the pancreas (Table 1) in which case the spleen enlarges frequently—although an exact incidence cannot be stated. In sinistral portal hypertension, concomitant occlusion of the coronary vein leads to hepatofugal flow and esophageal varices.[26] In the two cases in which the coronary vein was also occluded in our series, this did not occur presumably because there were alternate pathways to shunt blood from the spleen to the superior mesenteric and portal veins. Finally, as noted, none of the 450 cases of sinistral portal hypertension that are described in the review literature occurred following a Whipple procedure. Sinistral portal hypertension after the Whipple procedure has been described, and it was due to thrombosis of the splenic vein after vascular reconstruction of the portal/superior mesenteric veins, i.e., without ligation of the splenic vein.[12] This raises the possibility that sinistral portal hypertension could occur after splenic vein ligation if the latter were to lead to diffuse thrombosis of the vein. This was not seen in our cases perhaps because the patients were lightly anticoagulated with heparin in the postoperative period. Figure 7 presents a comparison of the venous collateral pathways that develop in sinistral portal hypertension and that which was seen in our five patients. Presumably, the longer length of residual splenic vein upstream to an obstruction in our patients provided opportunity for alternate collateral pathways to develop.

As noted in the introduction, there is controversy in the surgical literature as to the safety of occluding the splenic vein in a Whipple procedure, with some authors claiming that it is safe and not associated with development of symptomatic portal hypertension,[1,6,11,22] while others describe complications related to this problem.[2,4,42] Misuta et al. studied postoperative venous drainage in patients with splenic vein occlusion but with an intact confluence of the splenic and inferior mesenteric veins.[11] When flow in the inferior mesenteric vein was downward, there was no splenomegaly, and venous congestion did not occur, but asymptomatic venous congestion and splenomegaly were observed in three patients when flow was upward. As noted previously, the inferior mesenteric vein was occluded in all our patients. Unfortunately, literature cases are not described in sufficient detail to permit close comparison to our own. Possibly, occlusion of the splenic vein can, on occasion, result in splenic vein thrombosis, which would be more likely to result in sinistral portal hypertension. Obviously, this study is too small to establish the safety of splenic vein occlusion during a Whipple procedure. One may only conclude at this point that sinistral portal hypertension is not inevitable when this is done, and an understanding of why this is so is now apparent.

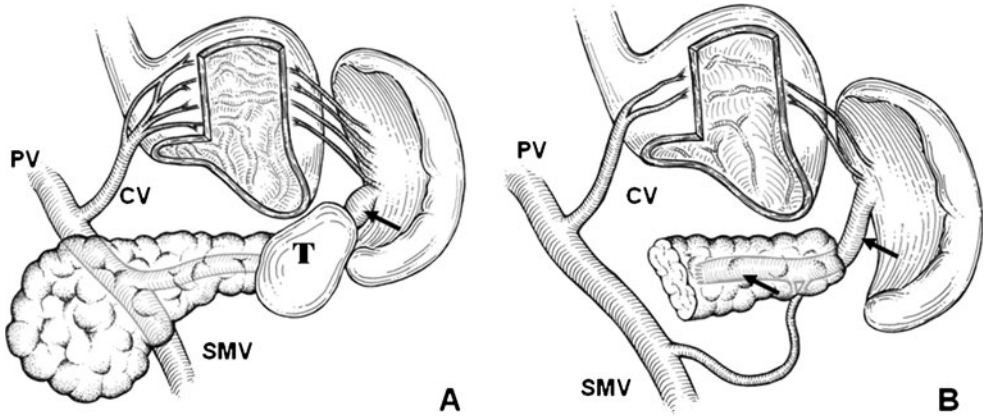

Fig. 7 Comparison between consequences of obstruction of the splenic vein in which the distance between the spleen and site of obstruction is short (**a**) or long (**b**). **a** shows the usual circumstance in which left-sided portal hypertension develops as a result of localized obstruction of the splenic vein. The length of the splenic vein between the spleen and the site of obstruction labeled "*T*" (for tumor) is short (*arrow*). Only one venous collateral pathway develops. This superior pathway travels through the short gastric veins, wall of the stomach, and coronary vein (*CV*). Splenomegaly and gastric varices develop commonly. **b** illustrates the consequences of obstructing the splenic vein (two *solid arrows*) close to its termination so that the length of patent vein between the spleen and the site of obstruction is long. In addition to the superior collateral pathway, development of inferior pathways may occur. Splenomegaly and bleeding gastric varices are probably less likely in these circumstances. *PV* portal vein, *SMV* superior mesenteric vein

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ORIGINAL ARTICLE

Endoscopic Transmural Drainage of Peripancreatic Fluid Collections: Outcomes and Predictors of Treatment Success in 211 Consecutive Patients

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Abstract
Objectives Endoscopy is a minimally invasive technique for the drainage of peripancreatic fluid collections. This study evaluated the clinical outcomes and predictors of treatment success in consecutive patients undergoing endoscopic transmural drainage of peripancreatic fluid collections.
Methods This is a retrospective study of patients who underwent endoscopic drainage of peripancreatic fluid collections over 7 years. Prior to drainage, an ERCP was attempted for stent placement in all patients with a pancreatic duct leak. Drainages were performed using conventional endoscopy or endoscopic ultrasound. Transmural stents and/or drainage catheters were deployed and endoscopic necrosectomy was undertaken when required. Data on clinical outcomes and complications were collected prospectively.
Results A total of 211 patients underwent drainage of peripancreatic fluid collections that was classified as pseudocyst in 45%, abscess in 28%, and necrosis in 27%. Mean diameter of the fluid collection was 100.6 mm, and 34.5% of patients had pancreatic duct stent placement. Median duration of follow-up was 356 days. Treatment success was 85.3% and was higher for pseudocyst and abscess compared to necrosis (93.5% vs. 63.2%, $p<0.0001$). Complications were encountered in 17 patients (8.5%) and was higher for drainage of necrosis than pseudocyst or abscess (15.8% vs. 5.2%, $p=0.02$). Treatment success was more likely for patients with pseudocyst or abscess than necrosis (adjusted OR=7.6, 95% CI [2.9, 20.1], $p<0.0001$) when adjusted for serum albumin and white cell count, type of endoscopic modality or accessory used, pancreatic duct stenting, luminal compression, size and location of fluid collection.
Conclusions Endoscopic therapy is a highly effective technique for the management of patients with non-necrotic peripancreatic fluid collections.

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Keywords Endoscopic drainage · Endoscopic ultrasound-guided drainage · EUS · Pancreatic fluid collections · Pancreatic pseudocysts · Pancreatic necrosis · Pancreatic abscess

Introduction

Peripancreatic fluid collections (PFCs) can arise as a result of acute or chronic pancreatitis, trauma, malignancy, or surgery.[1,2] Drainage of these PFCs may be necessary as they can result in abdominal pain, gastric outlet or biliary obstruction, infection, and rarely rupture.[3,4]

Endoscopic drainage of PFCs is a clinically effective and safe technique that was first reported in the late 1980s.[5,6] This method, with[2,7–11] or without[4,12–17] the concomitant use of endoscopic ultrasound (EUS), entails the creation of a fistulous tract between the PFC and the gastrointestinal lumen. When compared to the traditional surgical approach, not only are the clinical outcomes of endoscopic drainage comparable, but is also more economical and is associated with a shorter length of hospital stay.[18,19] Therefore, endoscopy is increasingly being regarded as a minimally invasive alternative to surgery for the management of PFCs.

While several studies have reported on the endoscopic outcomes of PFC drainages, they involved multiple operators, varying techniques, and a small sample size. In the two largest series published on endoscopic management of PFCs that included 113 and 116 patients,[2,12], respectively, not all subjects underwent transmural drainage as some were managed with only transpapillary pancreatic duct stent placement. In this study, we evaluate the clinical outcomes of endoscopy and determine the predictors of treatment success in 211 consecutive patients who underwent endoscopic transmural drainage of PFCs at a single center using a standardized technique.

Methods

Patients This study was conducted by retrospective analysis of prospectively collected data on consecutive patients who underwent endoscopic transmural drainage of PFCs between January 2003 and December 2010. Included in the study were patients aged more than 19 years with symptomatic PFCs measuring 6 cm or greater in size that was treated by endoscopic transmural drainage. Excluded were patients who underwent only an endoscopic retrograde cholangiopancreatography (ERCP) for transpapillary pancreatic duct stent placement, PFCs that were less than 4 weeks old, or were located more than 1.5 cm from the EUS transducer. Some patients in this study had been included previously in a pilot trial that evaluated the technical outcomes of endoscopic drainage.[11]

Informed procedural consents were obtained from all patients prior to undergoing endoscopic transmural drainage. This study received approval from the University of Alabama Medical Center Institutional Review Board.

Protocol for Peripancreatic Fluid Collection Drainage Prior to drainage, all patients underwent a contrast-enhanced computed tomography (CT) at our institution or already had a CT of suitable diagnostic quality at an outside institution within 1 week of planned intervention. Prior to drainage, inpatients were given 400 mg intravenous ciprofloxacin, which was continued for 48 h or until discharge, while outpatients were given 500 mg oral ciprofloxacin to be taken the night before and then continued twice daily for 5 days following drainage. All patients first underwent a routine ERCP prior to the drainage of PFCs. A pancreatogram was attempted to define the communication between the pancreatic duct and the pancreatic fluid collection, and in cases where the pancreatic duct was narrowed or obliterated, a transpapillary bridging stent was inserted, as long as the proximal duct could be reached with a guidewire. An ERCP was not performed in patients with a gastric outlet obstruction or with disconnected duct syndrome diagnosed by magnetic resonance cholangiopancreatography (MRCP).

Following ERCP, the duodenoscope was used to search for a luminal compression in the stomach and the duodenum. Once a luminal compression was found, transmural drainage of the PFC was undertaken by puncturing the gastric or the duodenal wall. If no luminal compression was identified or if the patient was at high risk for bleeding, an EUS-guided drainage was performed in the same endoscopic session.

Technique of Conventional Transmural Drainage (CTD) All PFCs were drained using a triple-lumen needle knife catheter (Microknife XL; Microvasive Endoscopy, Boston Scienctific Corp, Natick, MA, USA) to create a cyst-enterostomy fistula. After access to the PFC, dilation of the fistula was performed by using an 8- to 15-mm biliary balloon dilator, and two 10Fr double-pigtail endoprostheses were placed.

Technique of EUS-guided Drainage For EUS-guided drainage, a 19-gauge needle (EUSN-19-T; Cook Endoscopy, Winston-Salem, NC, USA) was introduced into the PFC. Before puncture, the cyst was evaluated by the EUS, and a color Doppler ultrasound was used to identify the regional vessels. A 0.035-inch guidewire was then introduced through the needle and coiled within the peripancreatic fluid collection under fluoroscopic guidance. The tract was sequentially dilated by first passing a 5Fr ERCP cannula and then an 8- to 15-mm biliary balloon dilator. Two to three 7Fr double-pigtail endoprostheses were then placed.

Technique for Drainage of Pancreatic Abscess/Necrosis In patients with pancreatic abscess or necrosis, a 7Fr nasocystic catheter was placed in addition to the stents to facilitate periodic flushing with 200 cc of nomal saline and vigorous aspiration every 4 h. Patients were placed in both the right and left lateral decubitus positions at the time of flushing to ensure thorough evacuation of the pancreatic abscess or

necrotic tissue. In patients with pancreatic necrosis, if the size of the PFC was 15 cm or more, two to three transmural tracts were created, and multiple 7Fr stents were placed in each track. Also, a nasocystic drainage catheter was placed in one tract to facilitate flushing with normal saline and for aspiration of the necrotic contents.

Technique for Drainage of Multiple PFCs In patients with pseudocysts, only the largest PFC was drained at index procedure. PFCs at other locations were drained subsequently within 48–72 h if the symptoms were persistent. In patients with pancreatic abscesses or necroses, all PFCs were drained at the index procedure. EUS guidance was used to perform transmural drainage in patients with multiple PFCs due to difficulty with identification of individual PFCs by conventional endoscopy.

Follow-up All patients who underwent transmural drainage of pseudocyts or abscess had a repeat contrast-enhanced CT and an outpatient clinic follow-up that included a history and physical examination at 8 weeks post-drainage. In patients with treatment success, all stents and feeding tubes were removed at this time. In patients with partial resolution of the fluid collection, they underwent a repeat endoscopy for placement of more transmural stents and were reassessed at 1 month. If clinical success was achieved at that time, all stents and tubes were removed. However, in patients with failed drainage, either the transmural drainage was re-attempted or they were referred for surgical management. In patients with necrosis who were intolerant of oral intake, a nasojejunal or gastrojejunostomy feeding tube was placed by interventional radiology for enteral nutrition. Also, at 72–96 h, a repeat CT of the abdomen was obtained in all patients with necrosis. If there was a decrease in size of the necrotic collection by >50% in association with improvement in patient symptoms and there was no necrotic fluid on aspiration of the drainage catheter, the nasocystic drain was removed. If symptoms were persistent, following interdisciplinary consultation with pancreatic surgeons, additional transmural drainage by placement of stents, endoscopic necrosectomy, or surgery was undertaken. The interval between endoscopy sessions and follow-up CT scans were not standardized and was dependent on the patient's clinical progress. A follow-up CT was obtained 8 weeks following patient discharge from the hospital. If the necrotic collection had resolved and the patients were symptomatically better, the transmural stents were retrieved by endoscopy. Patients with a persistent necrotic collection underwent surgery. For patients with a disconnected duct syndrome on ERCP or MRCP, the transmural stents were left in place indefinitely.

By protocol, we attempted to contact all patients by telephone at 6-month intervals for 18 months during which they were queried about the need for subsequent interventions for any pancreatitis-related complaints.

Definitions

Types of PFCs This was determined by the radiologist from examination of the CT images and followed the definitions outlined in the Atlanta Classification.[20]

Treatment Success Treatment success was defined as the complete resolution or a decrease in the size of the PFC to ≤2cm on CT, accompanied by the resolution of symptoms at 8 weeks follow-up.

Treatment Failure This was defined as persistence or worsening of symptoms occurring in association with PFCs that have increased in size or remaining greater than 2 cm in size on follow-up CT at 8 weeks post-drainage or requiring surgery for definitive treatment.

Outcome Measures The primary outcome measure was to evaluate the rate of treatment success for endoscopic drainage of PFCs. The secondary outcome measure was to identify predictors of treatment success for the endoscopic approach.

Statistical Analysis The data analysis was conducted using the SAS (version 9.1 Cary, NC, USA) statistical software. Patient characteristics related to transmural drainage of PFCs constituted continuous variables such as age, serum albumin level, and white cell count that were reported in terms of their medians (interquartile range). Categorical variables such as gender, etiology, and type of therapy were reported in terms of their frequency counts and proportions. Similar measures were adopted for reporting characteristics of PFCs and technical details of endotherapy. The abscess and pseduocyst groups were combined to form one group, and a nonparametric two-sample Wilcoxon rank-sum test was used to compare the continuous variables in this group with the necrosis group. The frequencies of the categorical variables in these two groups were compared using a chi-square test. The technical and clinical outcomes in these groups were also compared using a two-sample Wilcoxon rank-sum test, and a Fisher's exact test was deployed in cases where sample size was considered to be small. Multiple logistic regression was used to evaluate the predictors of treatment success at endoscopy and results obtained were reported by using adjusted odds ratios (OR) and their corresponding 95% confidence intervals (CIs) and p values. All tests were conducted at the 5% level of significance.

Results

Patient and PFC Characteristics Over the investigation period, of 231 patients referred, a total of 211 subjects underwent endoscopic transmural drainage of PFCs that comprised 95 pseudocysts (acute 23, chronic 72), 59 abscesses, and 57 necrosis. Reasons for not performing transmural drainage in 20 patients were establishment of an alternate diagnosis of mucinous cystic neoplasm by EUS in 6, the PFC was determined at EUS to be less than 6 cm in size in 9, and was beyond the reach of the echoendoscope in 5 patients. The median age of the 211 patients was 52 years; 61% were men, and alcohol was the most common etiology (34%) of pancreatitis (Table 1). While there was no difference in patient age, gender, etiology of pancreatitis, or prior interventions between the patient cohorts, patients with necrosis were more hypoalbuminemic and had elevated white cell count than those with pseudocyst or abscess (Table 1). The median size of the PFCs was 90 mm (interquartile range 70–120 mm) with the diameter of necrotic collections being significantly larger than pseudocysts or abscesses (Table 2). The majority of PFCs (58.7%) were located in the body followed by tail (22.7%) and head (18.6%) of the pancreas, and 23 patients (10.9%) had multiple PFCs.

Technical Outcomes Transpapillary pancreatic duct stents bridging the leak was successfully deployed in 72 (34.1%) patients. Placement of pancreatic duct stents was significantly more successful in patients with pseudocysts and abscesses compared to necrosis (40.2% vs. 17.5%, $p=0.002$). Reasons for not placing a pancreatic duct stent in 92 of 154 patients with pseudocyst or abscess were a normal pancreatogram in 41 patients, failed cannulation in 13, post-surgical altered anatomy in 7, gastric outlet obstruction in 11, pancreatic duct stricture or stone in 5, and a disconnected duct syndrome in 15 patients. Reasons for not placing a pancreatic duct stent in 47 of 57 patients with necrosis were a disconnected duct syndrome in 31 patients, gastric outlet obstruction in 6, failed cannulation due to pancreas divisum or ansa loop in 4, normal pancreatogram in 4, and pancreatic duct stricture that precluded stent placement in 2.

Most PFC drainages were undertaken via the trans-gastric route (81.6%), followed by the trans-duodenal (13.2%), trans-esophageal (4.2%), and trans-jejunal routes (1%). PFCs were drained under EUS guidance in 150 patients (71.2%) and by CTD in 61 (28.8%). A definitive luminal compression was evident at endoscopy in only 107 patients (50.7%) and was significantly more likely to be present in patients with necrosis than pseudocyst or abscess (63.2% vs. 41.6%, $p=0.02$). Of the 23 patients with multiple PFCs, 11 underwent EUS-guided drainage of more than one PFC. In 12 others, following EUS-guided drainage of the largest PFC, other PFCs were managed by percutaneous drainage ($n=9$) or by conservative measures ($n=3$). Reasons for not performing concomitant endoscopic drainage in these 12 patients were the presence of intervening vasculature in 3, fluid collection located within the splenic capsule in 4, and location of the PFC in the deep pelvis in 6 patients. While transmural stents were deployed in all patients, drainage catheters were more often placed in patients with necrosis than pseudocysts or abscesses (5.1% vs. 82.4%, $p<0.0001$). Of the 57 patients with necrotic collections, 12 had PFCs that measured more than 150 mm in diameter. In these 12 patients, multiple transmural tracts were created with placement of a nasocystic catheter in one tract and multiple 7Fr stents in others. The remaining 35 patients with necrosis were

Table 1 Characteristics of patients undergoing transmural drainage of PFCs

		PFCs			*p* values[a]
		Pseudocyst (*N*=95)	Abscess (*N*=59)	Necrosis (*N*=57)	
Age	Median (IQR)	49 (41–59)	55 (48–65)	41 (53–63)	0.49[b]
Males	*N* (%)	56 (59%)	32 (54%)	40 (70%)	0.08
Previous therapy	Endoscopy, *N* (%)	6 (6.3%)	5 (8.5%)	1 (1.8%)	
	Surgery, *N* (%)	5 (5.3%)	1 (1.7%)	4 (7%)	
	Radiology, *N* (%)	4 (4.2%)	13 (22%)	6 (10.5%)	
Etiology	Alcohol, *N* (%)	38 (40%)	10 (16.9%)	23 (40.4%)	0.21
	Gallstones, *N* (%)	23 (24.2%)	7 (11.9%)	10 (17.5%)	
	Idiopathic, *N* (%)	21 (22.1%)	4 (6.8%)	19 (33.3%)	
	Other, *N* (%)	13 (13.7%)	38 (64.4%)	5 (8.8%)	
Serum albumin, mg/dL	Median(IQR)	3 (2.2–3.6)	2.3 (1.9–3)	2.1 (1.8–2.8)	0.0002[+]
White cell count, mm^3	Median (IQR)	6.8 (8.1–12.8)	12.8 (8.1–18.9)	16.7 (9.1–18.9)	<0.0001[b]

[a] *p* values compare abscess+pseudocyst versus necrosis

[b] Wilcoxon rank-sum test was used

Table 2 Characteristics of PFCs and technical details of endotherapy

Variable		PFC			*p* value[a]
		Pseudocyst (*N*=95)	Abscess (*N*=59)	Necrosis (*N*=57)	
Long axis diameter mm	Median (IQR)	100 (80–120)	80 (60–100)	110 (80–120)	0.005[b]
Multiple PFC	*N* (%)	9 (9.5%)	6 (10.2%)	8 (14%)	0.37
PFC location	Head, *N* (%)	22 (23.2%)	7 (11.9%)	10 (17.5%)	0.83
	Body, *N* (%)	46 (48.4%)	37 (62.7%)	41 (72%)	
	Tail, *N* (%)	27 (28.4%)	15 (25.4%)	6 (10.5%)	
Luminal compression at endoscopy	*N* (%)	55 (57.9%)	16 (27.1%)	36 (63.2%)	0.02
Drainage modality	EUS, *N* (%)	59 (62.1%)	52 (88.1)	39 (68.4%)	0.60
	CTD, *N* (%)	36 (37.9)	7 (11.9%)	18 (31.6%)	
Transmural stents	*N* (%)	95 (100%)	58 (98.3%)	57 (100%)	
Transmural stents and catheters	*N* (%)	2 (2.1%)	6 (10.2%)	47 (82.4%)	<0.0001
Access route	Gastric	76 (80%)	48 (81.4%)	48 (84.2%)	0.54
	Duodenum	15 (15.8%)	4 (6.8%)	9 (15.8%)	
	Esophagus	2 (2.1%)	7 (11.9%)	–	
	Other	2 (2.1%)	–	–	
Pancreatic duct stents	*N* (%)	40 (42.1%)	22 (37.3%)	10 (17.5%)	0.002
Procedural duration	Median (IQR)	22 (18–35)	20 (15–41)	22 (15–40)	0.94[b]

EUS endoscopic ultrasound, *CTD* conventional transmural drainage

[a] *p* values compare "abscess+pseudocyst" versus necrosis;

[b] Wilcoxon rank-sum test was used

treated with a nasocystic drainage catheter and multiple stents, all placed in a single transmural tract.

Treatment Outcomes The overall treatment success was 85.3% and were higher for pseudocyst and abscess compared to necrosis (93.5% vs. 63.2%, $p<0.0001$) (Table 3). Twenty-four of 95 patients (25.2%) with pseudocysts had acute collections, and there was no difference in treatment outcomes between patients with acute or chronic pseudocysts. Reasons for treatment failure in 10 of 154 (6.5%) patients with pseudocyst or abscess were perforation in 2 patients, infection in 2, persistence of the PFC in 5, and death due to delayed bleeding in 1 patient. Nine of these ten patients underwent surgery with good clinical outcomes. Reasons for treatment failure in 21 of 57 patients (36.8%) with necrosis were persistence of PFC in 15, post-procedural infection in 5, and perforation in 1 patient. While two patients died of multi-organ failure (not procedure-related), 19 underwent surgery with good clinical outcomes in 17; 2 patients died of post-surgical complications. Of the 36 patients with necrosis who had successful treatment outcomes, 4 required endoscopic necrosectomy, as transmural drainage alone was ineffective. Of the 12 patients with necrotic collections that measured more than 150 mm in diameter who were treated by creation of multiple transmural tracts, treatment was successful in 11 patients; 1 patient required endoscopic necrosectomy due to persistence of necrosis and had good clinical outcomes.

The median number of re-interventions for patients with necrosis was significantly more than for patients with pseudocyst or abscess (Table 3). While only 16 of 154 (10.3%) patients with pseudocyst or abscess required more than one intervention, 18 of 57 (31.6%) patients with necrosis required re-interventions. The median duration of post-procedure hospital stay was significantly longer for patients with necrosis than for those with pseudocyst or

Table 3 Technical and clinical outcomes of endoscopic drainage of PFCs

Variable	PFC		*p* values
	Pseudocysts and abscesses (*N*=154)	Necrosis (*N*=57)	
Treatment success, *N* (%)	144 (93.5%)	36 (63.2%)	<0.0001
Complications, *N* (%)	8 (5.2%)	9 (15.8%)	0.02[a]
Number of re-interventions, Median (IQR)	1 (1–1)	1 (1, 2)	0.02[b]
Hospital stay in days, median (IQR)	2 (1–4)	5 (2–17)	<0.0001

[a] Fisher's exact test was used

[b] Wilcoxon rank-sum test was used

abscess (5 vs. 2 days, $p<0.0001$). Of the 180 patients with pancreatic pseudocysts or abscesses who had successful treatment outcomes at a median follow-up of 367 days (IQR, 136–545), 9 (5%) patients developed recurrence of PFCs that was managed by endoscopic drainage in 5, percutaneous drainage in 3, and surgery in 1. Nineteen patients were lost to long-term follow-up. Three other patients with persistent pain, but no recurrence of PFC had pancreatic duct strictures on ERCP that was managed by transpapillary pancreatic duct stent placement. One other patient with persistent pain underwent total pancreatectomy with auto islet transplantation. Of the 36 patients with necrosis who had successful clinical outcomes at a median follow-up of 345 days (IQR, 120–511), 32 patients were doing well, 2 experienced recurrent pancreatitis, and 2 were lost to follow-up. Currently, 62 patients in our database are on long-term follow-up.

While the double pig-tail transmural stents were removed at follow-up endoscopy in all patients with treatment success and an intact main pancreatic duct, they were left permanently in place in 50 patients with a disconnected duct syndrome or main pancreatic duct stricture/stone that was not amenable for pancreatic endotherapy.

Procedural Complications Complications were encountered in 17 patients (8.5%) that included perforation in 3, bleeding in 3, infection in 7, stent migration in 3, and death in 1 patient. The rate of complications was higher for drainage of necrosis than pseudocyst or abscess (15.8% vs. 5.2%, $p=0.02$) .Of the three perforations, two were encountered in patients with pseudocysts and in one with necrosis. All three patients underwent surgery with successful repair of the perforation. Bleeding was encountered in two patients with pseudocysts and one with necrosis. Two cases required embolization with interventional radiology, and the other was managed conservatively. Five patients with necrosis and two with pseudocyst developed post-procedural infection that was managed with surgical debridement in three patients and by placement of additional transmural stents in four. In two patients with pancreatic necrosis and a disconnected duct syndrome, the transmural stents migrated causing a small bowel obstruction. While one patient underwent surgery, the stents migrated spontaneously with conservative therapy in another. In one patient with a pseudocyst, the stent migrated into the PFC and was removed using a snare. One patient died due to delayed bleeding following conventional transmural drainage of a pseudocyst. Autopsy revealed bleeding within the pseudocyst in this patient.

Predictors of Treatment Success Multivariable logistic regression was performed to identify predictors of treatment success for endoscopic drainage (Table 4). Demographic, technical, and clinical factors of statistical significance were included in the model. The factors included were serum albumin and white cell count, type of PFC (pseudocyst and abscess versus necrosis), location of PFC (head vs. body and tail of pancreas), PFC size (<90 vs. >90 mm), presence or absence of luminal compression at endoscopy and type of endoscopic modality (EUS vs. CTD), and accessory (stents and drainage catheters vs. only stents) used for performing transmural drainage. Only the type of PFC remained significant with pseudocysts and abscesses having better treatment outcomes at endoscopy (adjusted OR=7.6, 95% CI [2.9, 20.1], $p<0.0001$) even after adjusting for all other factors in the model.

Discussion

In this study that encompassed a large cohort of patients who underwent endoscopic transmural drainage of PFCs, treatment outcomes were superior for patients with non-necrotic collections. Due to differences in the underlying pathology of various PFCs, differences in treatment outcomes are not unanticipated. In a study by Baron et al. of 113 patients,[12] PFC resolution was significantly better for patients with chronic pseudocysts (92%) than acute pseudocysts (74%), or necrosis (72%). In another study of 116 patients by Hookey et al.,[2] the treatment success rate for acute pseudocysts, chronic pseudocysts, abscess, and necrosis were 96.7%, 95.3%, 93%, 100%, and 25%, respectively. Similar to both reports, our treatment outcomes were better for patients with pseudocysts and abscesses.[2,12] The difference in treatment outcomes for pancreatic necrosis between our study and others may be due to variation in timing of the interventions and the technique adopted.[2,12] While the mean time to intervention in our necrosis cohort was 5 weeks, it was 3.2 and 7.2 weeks, respectively, in the other two reports.[2,12] Additionally, the technique adopted for drainage of necrosis in our study was different: rather than using an 8-mm balloon, we used a 15-mm radial expansion balloon for dilating the transmural tract. Also, when the necrotic collections were 150 mm or larger in size, we created multiple transmural tracts for facilitating better drainage of the necrotic contents. When a subgroup analysis was performed, 11 of 12 patients treated with multiple tracts had treatment success compared to 25 of 45 patients treated by conventional drainage technique (91.6% vs. 55.5%, $p=0.02$). Given these promising clinical outcomes, our current approach is to create multiple drainage tracts for patients with large necrotic collections. Four patients with necrosis who failed initial transmural drainage subsequently underwent endoscopic necrosectomy with good clinical outcomes.

Table 4 Predictors of treatment success at endoscopy

Variable	Odds ratio	95% CI	*p* values
Procedure (EUS vs. CTD)	0.614	[0.206–1.827]	0.39
Drainage catheter (yes vs. no)	0.585	[0.188–1.821]	0.35
Size in mm (short <90 vs. long >90)[a]	0.670	[0.229–1.965]	0.56
Location (head vs. body–tail)	1.083	[0.427–2.745]	0.90
Pseudocyst+abscess vs. necrosis	7.654	[2.909–20.138]	<0.0001
Albumin mg/dL	0.926	[0.488–1.757]	0.81
White cell count mm^3	1.010	[0.950–1.075]	0.73
Luminal compression (yes vs. no)	0.935	[0.324–2.696]	0.89
Pancreatic duct stent (yes vs. no)	1.699	[0.561–5.144]	0.34

EUS endoscopic ultrasound, *CTD* conventional transmural drainage

[a] Median size was 90 mm, thus short implies <90 and long implies >90

Two of these four patients had suffered an acute coronary event, and two others had severe obstructive lung disease. Three of these four patients required two sessions, and one required three sessions of necrosectomy. In a recent randomized trial that compared step-up approach and surgery for the management of pancreatic necrosis, patients treated by step-up approach had fewer complications and better clinical outcomes than those managed by surgical debridement.[21] Also, 35% of patients randomized to step-up approach did not require necrosectomy and were managed successfully only by percutaneous drainage. This emphasizes our study findings that better drainage of the necrotic cavity may preclude the need for more invasive interventions in a subset of patients. Moreover, an initial attempt at endoscopic drainage did not preclude subsequent surgery in any patient in this series. As endoscopic necrosectomy is resource consuming, requires multiple sessions, is of prolonged duration, and associated with a mortality rate of nearly 10%, our approach is to operate on patients who fail transmural drainage unless they are too sick to undergo surgery.[22] A major limitation of endoscopic necrosectomy is the lack of dedicated accessories to remove the necrotic material efficiently. Other authors have reported successful outcomes by using percutaneous drainage catheters for long-term flushing combined with endoscopic internal drainage of the necrotic cavity.[23] Placement of percutaneous drainage catheters may lead to fistula formation when a PFC communicates with the main pancreatic duct.[24] Also, these external catheters predispose to infection, cause patient discomfort, dislodge frequently, mandate prolonged hospital stay, and very often require other adjunctive treatment measures.[25]

The rate of PFC recurrence in this study was only 5% which is less than the 16% reported by other series.[2,12] While there was no difference in the rate of recurrence between the PFC cohorts in our study, Baron et al. reported a recurrence rate of 29% for necrotic collections versus only 9% for pseudocysts.[12] This difference may be due to the short duration of patient follow-up in this study (median 356 days). Another reason could be technique-related: Fifty-three of 211 (25.1%) patients in this study had a disconnected duct syndrome or main pancreatic stones or strictures that precluded pancreatic duct stent placement. In a majority of these patients, the transluminal stents were left in place indefinitely. We believe that these stents act as a conduit and facilitate drainage of pancreatic secretion from the disconnected gland. In a randomized trial that compared removal versus non-removal of transmural stents, the rate of PFC recurrence following stent removal was significantly higher.[26] One third of patients in that study had spontaneous stent migration on long-term follow-up. It is likely that PFC resolution leads to eventual adherence of the walls of the cavity, which in turn leads to gradual migration of the stent toward the GI lumen. On the contrary, stent retrieval occurring before complete collapse of the cavity might lead to PFC recurrence, particularly if a communication exists between the cavity and the pancreatic duct. Therefore, the duration of stent placement may be more important than whether the stents are still present or retrieved after an adequate stent placement period. It is logical to assume that a majority of plastic stents occlude within a few weeks after placement and most drainage occurs along the sides rather than the lumen of the stent. The rate of procedural complications in this study was 8.5% which is similar to the 11% reported by Hookey et al.[2] With the exception of one patient who died of delayed bleeding, other complications were identified and treated appropriately in most cases. Similar to the findings by Baron et al.,[12] we observed a higher rate of complications in patients undergoing drainage of pancreatic necrosis. Unlike pseudocysts, necrotic collections are more viscous with large amounts of debris and hence are difficult to drain. Ineffective instrumentation predisposes to infection in these patients. Although endoscopic necrosectomy and creation of multiple transmural tracts for drainage of necrotic contents are few therapeutic options, surgery is the only definitive therapy for many patients. Therefore, close collaboration with pancreatic surgeons is an absolute necessity for optimal treatment outcomes in this patient population.

Although we did not observe any difference in the rate of complications based on the modality (EUS vs. CTD) used for

transmural drainage (data not shown), we still believe that EUS is indispensible for the endoscopic drainage of PFCs as it enables identification of intervening vasculature, establishes an alternative diagnosis of cyst neoplasm in cases that mimic a pseudocyst, and facilitates safe access to PFCs that do not cause a luminal compression. In a randomized trial that compared EUS and conventional endoscopy for drainage of PFCs, conventional endoscopy was successful in only 33% of patients, whereas EUS guidance enabled PFC drainage in 100% of patients.[27] Patients with pancreatic necrosis are generally more hypoalbuminemic, and as a consequence, the gastric mucosal edema makes identification of PFC-induced luminal compression difficult at endoscopy.[28] Also, as some of these patients are on parenteral nutrition, the distension induced by the gallbladder can mimic a luminal compression caused by a PFC. In such instances, EUS is invaluable to facilitate safe access to the PFC. Prior studies have shown that EUS-guided drainage can be performed safely even at patient bedside and within 25 min in most patients.[11,29] Given these inherent advantages, we have increasingly used EUS for performing most endoscopic transmural drainages.

There are several limitations to this study. Firstly, the study design was retrospective thereby limiting the ability to investigate the effectiveness of several variables on treatment outcomes. Secondly, we included only those patients who underwent endoscopic transmural drainage of PFCs and not those treated by transpapillary pancreatic duct stent placement alone. Thirdly, these results pertain to one center and one endoscopist, and hence, the findings may not be generalized. Fourthly, the duration of follow-up was only medium term. Finally, the good clinical outcomes reported in this study could be secondary to selection bias as sicker patients may have undergone surgery or percutaneous drainage.

In conclusion, endoscopy is an effective and safe technique for the drainage of non-necrotic PFCs. Given the suboptimal outcomes in patients with necrosis, close collaboration with surgery is important to identify patients who will benefit from either treatment modality. Better accessories and techniques are required to improve the outcomes of patients undergoing endoscopic drainage of necrotic PFCs.

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REVIEW ARTICLE

Infiltrating Hepatocellular Carcinoma: Seeing the Tree through the Forest

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Abstract
Introduction Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide. It is traditionally difficult to cure, especially when discovered at later stages, making early diagnosis and intervention of paramount importance. HCC typically arises in the background of chronic liver disease and can have various morphologic appearances. One of the most difficult of these to recognize on early surveillance imaging is the infiltrative subtype, which can account for up to 13% of all HCC cases, and may be more closely associated with background hepatitis B infection.
Discussion Certain imaging characteristics can provide vital clues, including differing signal intensity on the T1 and T2 sequences of magnetic resonance imaging (MRI) and the presence/appearance of portal vein thrombus. Owing to the diffuse and infiltrating properties of this tumor, surgical resection and transplantation are rarely if ever viable therapeutic options. Other forms of liver-directed therapy have been attempted with limited success, having minimal efficacy and high morbidity. To date, there is no data available to determine if the various HCC subtypes respond to systemic therapy differently, so this may be the most reasonable approach. Left untreated, observed patients commonly progress to hepatic failure fairly rapidly.
Conclusion Infiltrative HCC can be extremely subtle, and therefore difficult to detect, especially in the background of cirrhosis. Providers caring for patients with hepatitis, chronic liver disease, and cirrhosis must be extremely vigilant in the evaluation of surveillance imaging in order to potentially discover this HCC subtype as early as possible and initiate a multidisciplinary treatment plan.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related death.[1] HCC most commonly arises in the background of chronic liver disease secondary to viral hepatitis or alcohol use, although other causes such as certain environmental exposures and non-alcoholic fatty liver disease have been implicated.[2] Strong geographic variations in the incidence of HCC have been well documented with the highest incidence being in Asia. In the USA, a rising incidence of HCC has been noted, which is believed to be related in part to an increase in the prevalence of hepatitis

C. The therapeutic options for HCC depend both on tumor- and liver-specific factors. In patients with advanced tumors and no or minimal evidence of hepatic dysfunction, hepatic resection is the mainstay of surgical therapy. In contrast, among patients with cirrhosis and early-stage HCC, transplantation may be the optimal therapy as it addresses both the neoplasm and the underlying liver disease.[3] For small HCC (<3 cm), ablation may also be a reasonable therapeutic option.[4] Unfortunately, most patients with HCC present with advanced stage disease in the setting of borderline or decompensated liver function, making them ineligible for potentially curative therapeutic options such as resection, transplantation, or ablation. Surveillance to detect early HCC, therefore, is a key component of the care of high-risk patients.

While the evaluation and diagnosis of HCC has become more standardized among high-risk populations, detection of early-stage disease can still be problematic. HCC can present with different morphological subtypes including "focal/nodular," "massive," and "diffuse/infiltrating."[5,6] These subtypes can behave differently with regard to etiology, response to treatment, disease progression, as well as presentation. Focal/nodular HCC most commonly presents as an arterially enhancing mass with well-defined margins and an expansive growth type. In contrast, infiltrating HCC can be difficult to identify as it presents as a spreading ill-defined mass that can blend into the background cirrhotic liver on cross-sectional imaging.[5–7] As such, infiltrating HCC is often not diagnosed until it has progressed to an advanced stage. While infiltrating HCC accounts for 7% to 13% of HCC cases,[6,7] making it not an uncommon HCC subtype, it remains not well-characterized in the literature. We herein review the current approach to the patient with infiltrating HCC. In particular, we highlight the presentation, natural history, and management options for patients with infiltrating HCC. In addition, we emphasize the potential pitfalls of diagnosing infiltrating HCC on cross-sectional imaging by elucidating and illustrating those radiographic criteria that can potentially aid in the earlier identification of infiltrating HCC.

Risk Factors for Infiltrating HCC

Factors specifically associated with the infiltrating subtype of HCC remain ill defined. There are, however, some emerging data that the etiology of the underlying liver disease and morphologic HCC subtype may be related. The carcinogenic pathway involved with hepatitis B virus (HBV)- and hepatitis C virus (HCV)-derived liver damage and tumorogenesis are distinct. HBV is a deoxyribonucleic acid (DNA) virus that integrates itself into the host cell DNA, allowing it to alter expression levels of various cellular proteins.[8,9] The integration of HBV double-stranded DNA into the host genome has been shown to enhance expression of the C-*myc* and N-*myc* oncogenes and to inactivate the tumor suppressor gene *p53*.[10] These alterations can adversely affect cell cycle control, signal pathways, and apoptosis, thereby leading to an increased risk of carcinogenesis.[11] In contrast to HBV, HCV is a positive-stranded RNA virus that does not integrate into the host DNA but rather most likely leads to carcinogenesis by inducing fibrosis and subsequent cirrhosis.[12,13] In turn, HBV-induced HCC may be less a function of a chronic inflammatory process,[9] while the chronic inflammatory process appears to be more central to HCV-induced carcinogenesis.[14] The varying mechanisms of HBV versus HCV carcinogenesis may in turn influence the development of different HCC subtypes.

Emerging data suggest that the infiltrating HCC subtype may arise more commonly in the setting of HBV infection. Benvegnu et al. prospectively followed 401 patients over a median duration of 84 months to compare the incidence, risk factors, and morphologic pattern of HCC development in HBV- and HCV-related cirrhosis.[15] During follow-up, 77 (19.2%) patients developed HCC, with a 5- and 10-year cumulative incidence of 10% and 27.5%, respectively. Of note, the pattern of HCC was nodular in 63 (81.8%) patients and infiltrating in 14 (18.2%). Interestingly, the authors found several factors that were not only associated with the incidence of HCC but also the specific morphological subtype. Patients with nodular HCC were more likely to be older, had a longer duration and severity of cirrhosis, but did not have a difference in the incidence of HBV relative to HCV. In contrast, development of infiltrating HCC was unrelated to age and duration of cirrhosis, but was more common among patients infected with HBV as well as HBV+HCV co-infection. The authors concluded that although HBV and HCV infection were both associated with the risk of HCC, distinct features in tumor development and in morphogenesis patterns can be identified, with HBV and HBV+HCV patients having a higher incidence of infiltrating HCC.

In a separate study, Myung et al. reported on 35 patients who had been newly diagnosed with infiltrating HCC.[16] Patients with infiltrating HCC were compared with patients who had other morphological subtypes of HCC who had been enrolled during the same period of the study. Similar to the study by Benvegnu et al.,[15] the authors found that patients with infiltrating HCC were more commonly positive for HBV than those with other subtypes of HCC. Of note, the authors also noted that during regular follow-up, infiltrating HCC tumors were less readily detectable.

Tumor Markers and Infiltrating HCC

Frequently, α-fetoprotein (AFP) is utilized to frame the level of clinical suspicion for an underlying HCC. The clinical usefulness of AFP to detect HCC and therefore assist in the management of high-risk patients is debatable. Farinati et al.[17] reported on a large multi-center Italian experience in which a total of 1,158 patients with HCC were analyzed with reference to serum AFP levels at diagnosis. When using the receiver operating characteristic (ROC) curve, the prognostic reliability of AFP was limited with an area under the curve (AUC) of 0.59. As such, while high AFP levels (i.e., >400 ng/mL) tended to be very specific, AFP was not a very sensitive marker of HCC (sensitivity of only 54%). As such, while an elevated AFP level should significantly heighten one's suspicion of HCC,[5,7] a normal AFP level does not exclude an underlying tumor.[7,17]

An elevated AFP level has been reported to be indicative of a large tumor burden (size and number), as well as more extensive disease. In the study by Farinati et al., statistical correlations with the AFP level were found for, among other things, tumor size and presence of thrombosis.[17] Given that infiltrating HCC frequently presents as a large, diffuse process that is often associated with portal vein thrombosis, one might expect that AFP may be a more sensitive indicator of disease in this subset of patients. Indeed, the infiltrating HCC subtype often may be associated with higher AFP levels perhaps owing to its diffuse permeation of the hepatic parenchyma.[5] AFP, however, is not a reliable indicator of the presence or absence of disease even among patients with infiltrating HCC. Rather, the range of AFP levels can be quite variable among patients with infiltrating HCC. Kanematsu et al. reported a small series of 15 patients with infiltrating HCC among whom 14 of 18 (78%) patients had an elevated AFP; in fact, 12 patients with infiltrating HCC had an AFP level >1,000 ng/mL.[7] However, as the authors noted, a sizeable subset of patients in the study (n=4; 22%) had a normal serum AFP level. In the study by Farinati et al., among the 1,105 included in the study, 97 patients had an HCC classified as an infiltrating morphological subtype.[17] The associated AFP levels in this cohort of patients were <20 ng/mL (36%), 21–400 ng/mL (28%), and >400 ng/mL (36%). Taken together, the data suggest that between one fifth and one third of patients with infiltrating HCC will have a completely normal AFP level and perhaps up to a full one half of patients with infiltrating HCC will have an AFP <400 ng/mL. These data have important implications as they strongly suggest that while AFP levels may be helpful in detecting infiltrating HCC, AFP is not a reliable surveillance or diagnostic tool.[7]

A host of other possible HCC serum biomarkers has been proposed including des-γ-carboxy prothrombin (DCP), glypican-3, transforming growth factor β1 (TGF), Golgi protein-73 (GP73), and Lens culinaris agglutinin reactive AFP (AFP-L3).[18] While each of these have varying degrees of sensitivity and specificity for HCC, AFP-L3 may be particularly relevant to infiltrating HCC. AFP-L3 is an alternative glycoform of AFP that differs in its binding affinity to lectins such as Lens culinaris agglutinin. The relative percent increase in AFP-L3 levels has been noted to be related to progression from moderately differentiated to poorly differentiated tumors.[18,19] The sensitivity of AFP-L3 changes with HCC tumor size, with a sensitivity of 80–90% when the tumor diameter is >5 cm.[18,20] AFP-L3 is also associated with vascular invasion, and therefore, AFL-L3 may be a marker for the aggressiveness of HCC.[18] Tada et al. investigated the pathological features of AFP-L3-positive HCC in order to correlate elevations in this serum biomarker with pathological and morphological variants of HCC.[21] Of the 111 patients included in the study, the authors identified 33 (29.7%) who were positive for AFP-L3 (i.e., >10%). The prevalence of HCC with an infiltrating growth pattern and portal vein invasion was significantly higher among patients with an elevated AFP-L3. In fact, patients with an infiltrating HCC had a seven-fold increased chance of having an elevated AFP-L3. The authors reported a sensitivity and specificity of AFP-L3 for infiltrating HCC of 75.0% and 73.8%, respectively.[21] Okuda et al. have similarly reported that HCC with an infiltrating growth pattern was often found in patients with elevated AFP-L3.[22]

Imaging of Infiltrating HCC

Although HCC typically has a very characteristic appearance on cross-sectional imaging, detection of the infiltrating HCC subtype can be a challenge. On computed tomography (CT) imaging, HCC generally presents as a mass that is hypervascular in the arterial phase, followed by relative "washout" in the portal venous phase.[23] With the advent of high-speed multi-detector CT scanners, even early nodular HCC can now be detected with a relatively high accuracy.[24,25] On magnetic resonance imaging (MRI), most HCC lesions have the classic characteristics of hypointensity on T1-weighted images, hyperintensity on the T2-weighted images, and arterial enhancement with washout in the portal venous phase.[26] Some studies have suggested that MRI is superior to CT in its sensitivity to detect HCC,[27] although the data are conflicting.[28]

While these "classic" cross-sectional characteristics of HCC apply to nodular HCC, infiltrating HCC is often much more difficult to detect on cross-sectional imaging studies. The imaging characteristics of diffuse HCC are poorly documented in the literature,[7,29] and therefore, radiologists may not be familiar with the radiologic findings associated

with this variant of HCC. Infiltrating HCC has a diffuse, permeative appearance on cross-sectional imaging and is difficult to detect in the setting of the heterogeneous background of a cirrhotic liver. This is in fact corroborated by histopathologic analysis, which has described tumor nodules having the same gross appearance as regenerative nodules in the cirrhotic liver.[5] Unlike nodular HCC, infiltrating HCC often blends into the background of the cirrhotic liver, and there is no discrete well-defined mass (Fig. 1).[7] Infiltrating HCC usually presents as a subtle poorly demarcated area within the liver characterized by heterogeneous or homogeneous abnormal signal intensity. Specifically, on MRI, infiltrating HCC often presents as predominantly hypointense on T1-weighted images. On T2-weighted images, infiltrating HCC usually is homogeneous and mild to moderately hyperintense (Fig. 2). Reflecting the histopathologic findings of extensive micronodules, the initial post-contrast images may show "miliary enhancement" of the area involved by the infiltrating HCC.[7] This enhancement can be particularly striking in the setting of portal vein thrombosis, which results in greater contribution of overall hepatic blood supply by the hepatic artery. On gadolinium-enhanced dynamic imaging, most infiltrating HCC will show inhomogeneous areas of enhancement on arterial phase images and corresponding washout on more delayed phases of contrast enhancement (Fig. 3).[29] HCC, due to the tightly packed cellular arrangement, causes restricted diffusion of water molecules. This manifests as increased signal on diffusion-weighted images (Fig. 2e) and corresponding low signal on the apparent diffusion coefficient (ADC) map.[30]

One prominent clue that can be used to identify infiltrating HCC is the presence of portal vein thrombosis, as most patients with infiltrating HCC will have this finding.[5,7,26,29] While many patients with cirrhosis and HCC may have portal vein thrombus, the characteristics of the portal vein

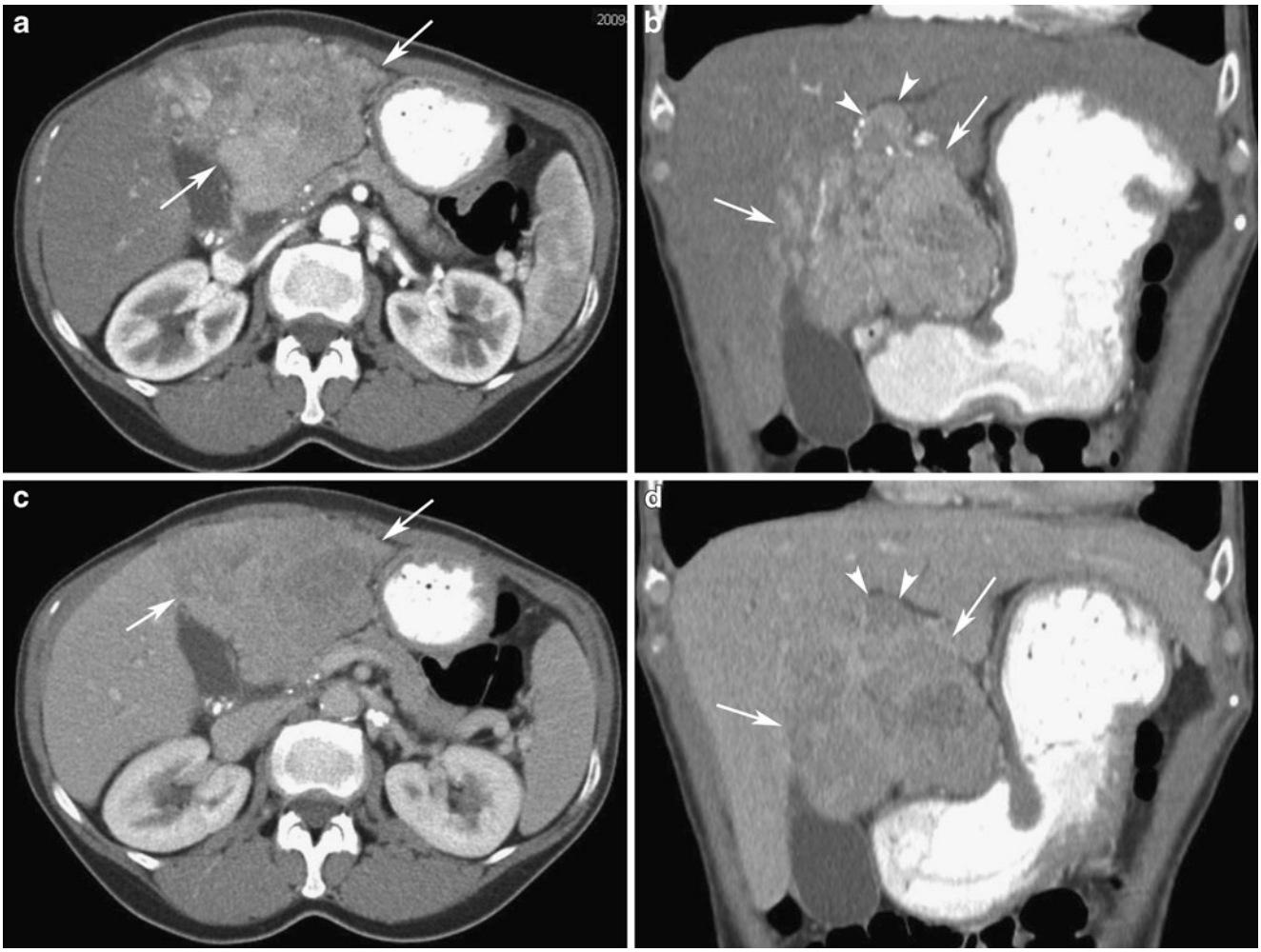

Fig. 1 Fifty-five-year-old woman with hepatitis C, cirrhosis, and hepatocellular carcinoma. Axial (**a**) and coronal (**b**) contrast-enhanced CT in the arterial phase shows a heterogeneously enhancing liver mass in the left hepatic lobe with ill-defined margins (*arrows*). There is enhancing tumor thrombus in the portal vein (*arrowheads*). Axial (**c**) and coronal (**d**) contrast-enhanced CT in the portal venous phase shows an infiltrative mass in the left hepatic lobe (*arrows*) with areas of washout consistent with hepatocellular carcinoma

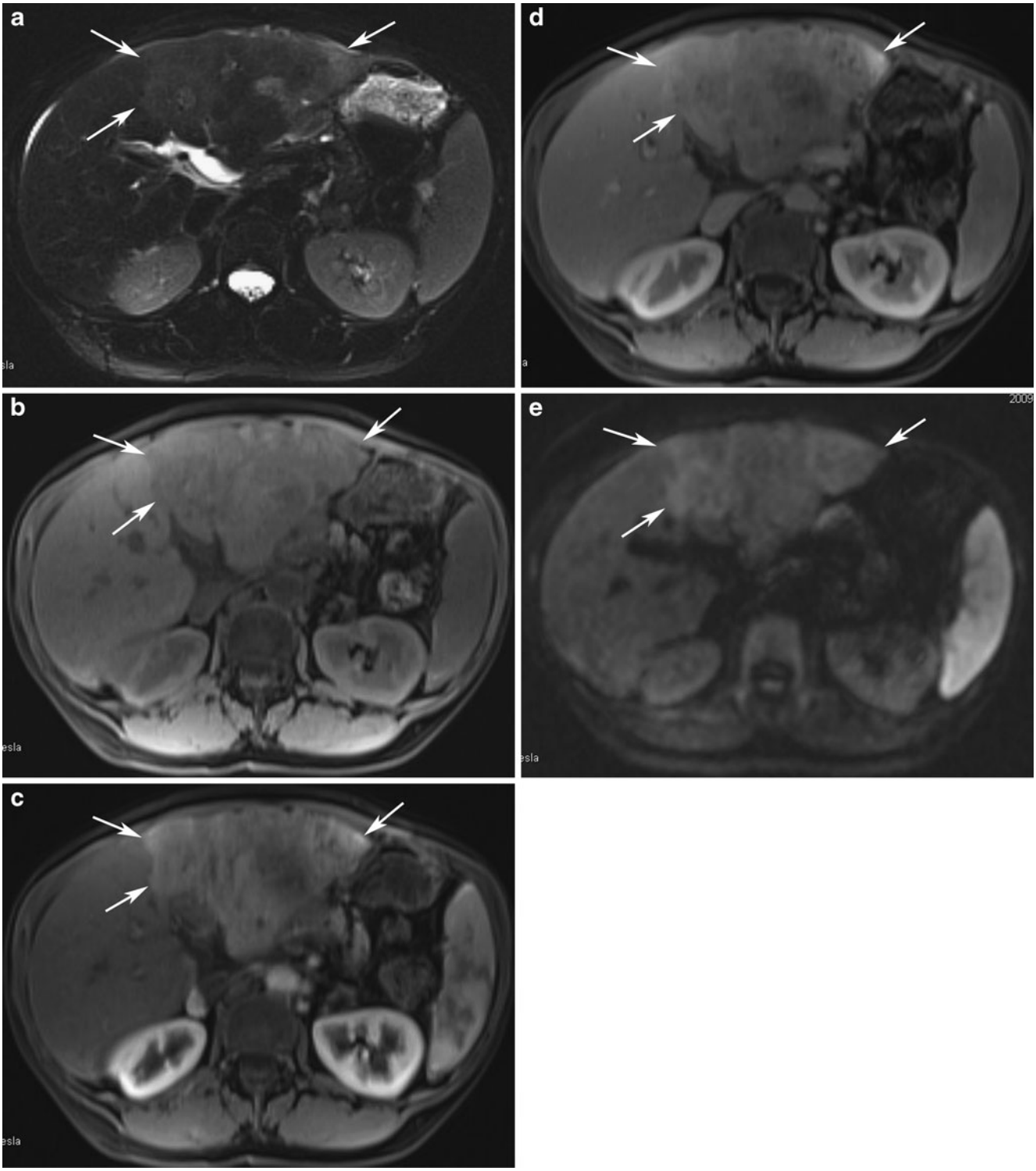

Fig. 2 MR images of the same patient as above. **a** Axial T2-weighted fat saturation image shows subtle T2 hyperintense signal within the infiltrative HCC in the left hepatic lobe (*arrows*). **b** Axial precontrast T1-weighted GRE image shows corresponding low T1 signal in the left hepatic lobe tumor (*arrows*). **c** Axial postcontrast T1-weighted GRE image in the arterial phase shows heterogeneous enhancement (*arrows*). **d** Axial postcontrast T1-weighted GRE image in the portal venous phase demonstrates patchy areas of washout within the tumor (*arrows*). **e** Axial diffusion-weighted MRI image shows restricted diffusion within the tumor (*arrows*)

thrombus in the setting of infiltrating HCC are often unique. The pattern of portal vein invasion with infiltrating HCC is commonly associated with gross distension of the portal vein. When portal vein invasion is extensive, it can fill the

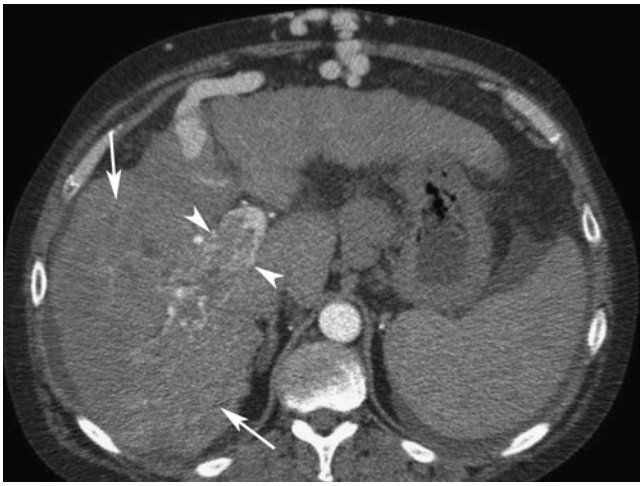

Fig. 3 Fifty-three-year-old man with alcoholic cirrhosis and hepatocellular carcinoma. Axial contrast-enhanced CT in the arterial phase shows thrombus in the right portal vein (*arrowheads*). Small enhancing vessels seen within the thrombus indicate the presence of tumor. The infiltrative HCC (*arrows*) in the right hepatic lobe is difficult to appreciate. Stigmata of portal hypertension are seen, including ascites and caput medusa

peripheral portal vein branches, creating a dilated tumor-filled "cast" of these vessels (Fig. 4). In addition, infiltrating HCC-associated portal vein thrombus commonly displays significant neovascularity or "arterialization" of the tumor thrombus. In fact, it is not uncommon for neovascularity of portal vein thrombus to be the only detectable initial imaging characteristic of an infiltrating HCC. On the corresponding portal venous phase images, tumor thrombus appears as a filling defect in the portal vein, similar to bland thrombus (Fig. 5). Diffusion-weighted images have also emerged as a method of detecting tumor thrombus and differentiating it from bland thrombus. On MRI, portal vein tumor thrombus, similar to the parenchymal mass, has subtle T2 hyperintense signal. The T1 signal is elevated compared to adjacent patent portal veins.

Treatment and Outcomes of Patients with Infiltrating HCC

The prognosis of patients with infiltrating HCC is considerably worse compared with patients who have a focal/nodular subtype. Benvegnu et al. reported that the cumulative probabilities of survival at 1 and 3 years after tumor development were 75.4% and 46.0% in patients with focal/nodular HCC versus 33.3% and 13.6% in patients with infiltrating HCC, independent of treatment received.[15] Given that most patients present at a late stage of disease with diffuse disease and associated major vascular invasion, the therapeutic options for infiltrating HCC are limited. Patients with infiltrating HCC are almost always outside the Milan criteria and are not candidates for transplantation. While surgical resection is feasible in patients with large HCC,[31] patients with major vascular invasion have a prohibitively poor prognosis with surgical resection.[32] In addition, most patients with infiltrating HCC also have advanced cirrhosis, making resection not a tenable option. Several studies have reported on patients who underwent resection or transplant in situations where the infiltrating subtype was underestimated (i.e., a seemingly small tumor nodule is seen, but the remainder of the disease blends into the cirrhotic background) or altogether unrecognized.[33,34] Han et al. reported a case involving a 41-year-old patient with HBV who was transplanted for advanced cirrhosis.[33] On pathological assessment of the explant, a previously unrecognized infiltrating HCC was detected. While the patient had yet to recur at 18 months of follow-up, the

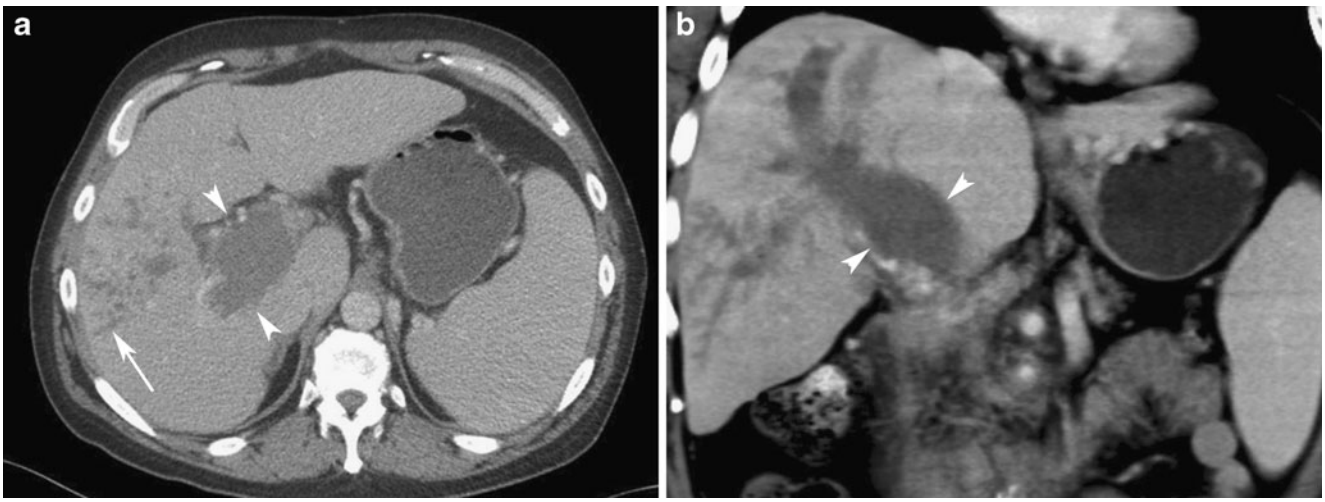

Fig. 4 Fifty-three-year-old man with hepatitis C, cirrhosis, and hepatocellular carcinoma. Axial (**a**) and coronal (**b**) contrast-enhanced CT in the portal venous phase shows expansion of the portal vein with tumor thrombus (*arrowheads*). The branching low attenuation structures in the right hepatic lobe represent dilated tumor-filled peripheral portal vein branches (*arrow* in **a**)

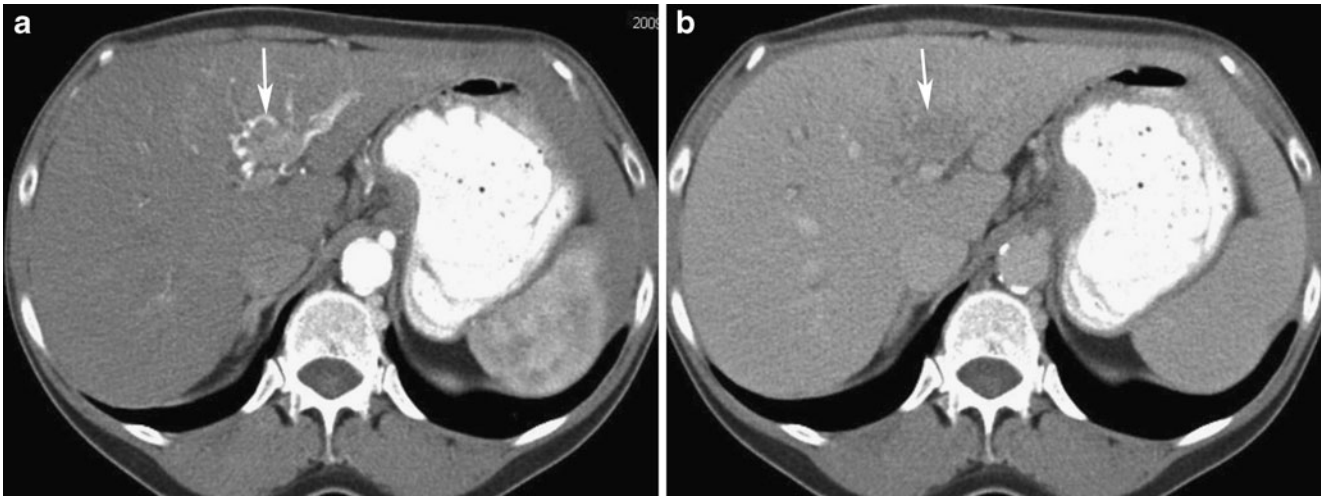

Fig. 5 Sixty-six-year-old man with infiltrative hepatocellular carcinoma. **a** Axial contrast-enhanced CT in the arterial phase shows early enhancement or "arterializations" of the left portal vein (*arrow*) indicating tumor involvement. **b** Axial contrast-enhanced CT in the portal venous phase demonstrates tumor thrombus in the left portal vein as a low attenuation filling defect (*arrow*)

authors noted that pathology revealed that virtually the entire liver parenchyma was replaced with malignant nodules. In a separate study, Ochiai et al. reported that the infiltrating HCC subtype, especially among those patients with an AFP >400 ng/mL, was associated with a very poor prognosis following surgical resection.[34] Specifically, patients with an infiltrating HCC subtype had over a three-fold increased risk of disease-specific death following resection with an associated 5-year survival of 16%. Patients with infiltrating HCC almost invariably do very poorly following transplantation or resection, and therefore, an infiltrating morphological subtype should be considered a strong or absolute contraindication to surgical therapy.

Given that surgical options are not applicable to patients with infiltrating HCC, there has been interest in intra-arterial therapy (IAT). IAT, largely in the form of trans-arterial chemoembolization (TACE), has been advocated as a potentially efficacious modality of liver-directed therapy for infiltrating HCC. IAT involves the delivery of cytotoxic agents via specific arterial tumor-feeding blood vessels, followed by induced ischemia secondary to embolization of those vessels.[35] Two randomized controlled trials have demonstrated a statistically significant improvement in survival using TACE as compared to supportive/symptomatic care for HCC—most of which was of the focal/nodular subtype.[36,37] The role and efficacy of IAT for diffuse, infiltrating HCC are less defined.

The poor demarcation and difficulty of defining the extent of infiltrating HCC on cross-sectional imaging may impact patient selection, the ability to adequately target the lesion as well as determine subsequent treatment response. Lopez et al. compared patients with unresectable infiltrating versus focal HCC who were treated with TACE.[38] In this study, patients in both groups underwent TACE using a drug combination of doxorubicin, cisplatin, and mitomycin. A total of 157 TACE treatments were performed in 88 patients with unresectable HCC: 132 treatments in 69 patients with focal HCC and 25 treatments in 19 patients with infiltrating HCC. Patients with infiltrating HCC did significantly worse following TACE. Specifically, after TACE, patients with infiltrating HCC had a longer hospital stay, more procedure-related mortalities, and a higher readmission rate. In fact, three out of the 19 (16%) patients with infiltrating HCC treated with TACE suffered from a procedure-related death (n=2, liver failure; n=1, tumor rupture). The long-term outcome following TACE for infiltrating HCC was similarly disappointing. While patients with focal HCC had a mean survival of 42.5 months and a 1-year survival of 63%, mean survival following TACE for infiltrating HCC patients was only 10.3 months, and no patient was alive at 1 year. Lopez et al. concluded that their data demonstrated that TACE for infiltrating HCC can be associated with significant morbidity, mortality, and yielded poor long-term outcomes. The authors cautioned that the poor outcomes were related to underestimation of the tumor burden and hepatic functional reserve among patients with infiltrating HCC.[38] As such, while IAT should be considered in situations where surgical intervention is not possible, the clinician needs to be cognizant of the possible increased risk of complications among patients with infiltrating HCC. Future studies will need to better define the role, safety, and efficacy of IAT therapy for infiltrating HCC.

While systemic chemotherapy has traditionally been largely ineffectual for HCC, data from the Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial showed an improvement in progression-free survival for HCC patients treated with sorafenib. The

median time to radiographic progression was 5.5 months in the sorafenib group and 2.8 months in the placebo group. Overall median survival was also significantly longer in the sorafenib group (10.7 months) than in the placebo group (7.9 months; hazard ratio, 0.69).[39] Based on these findings, sorafenib is approved for the treatment of advanced HCC. Whether sorafenib is safe and efficacious in the treatment of patients with infiltrating HCC remains, however, to be determined. It is important to note that only a minority of patients in the SHARP trial had HBV infection (19%) or macroscopic vascular invasion (36%), and most patients were Child-Pugh A. Given this, the role of sorafenib for patients with infiltrating HCC—most of whom have HBV, portal vein thrombosis, and more advanced underlying liver disease—is uncertain. While sorafenib and other emerging targeted agents hold some therapeutic promise, these agents will need to be better studied in patients with infiltrating HCC before the relative risks versus benefits can be determined.

Conclusion

Infiltrating HCC is relatively uncommon, representing 7% to 13% of HCC lesions. Infiltrating HCC appears to have a stronger correlation with HBV infection. Timely identification of infiltrating HCC can be challenging as AFP levels are unreliable and the tumor lacks a well-demarcated boundary on cross-sectional imaging. Infiltrating HCC often "blends" into the background of the cirrhotic liver, making it difficult to "see the tree through the forest". We have here highlighted the important radiologic features of infiltrating HCC. Specifically, infiltrating HCC most commonly is characterized by hypointensity on T1-weighted images and homogeneous, mild to moderately hyperintensity on T2-weighted images. Gadolinium-enhanced MR images usually show patchy contrast enhancement. Most patients with infiltrating HCC will also have portal vein thrombosis with characteristic distention of the vessel and "arterialization" of the thrombus. Due in part to the higher risk of being missed on cross-sectional imaging leading to a late diagnosis, treatment options for infiltrating HCC are limited. Surgery is almost always not a consideration for patients with infiltrating HCC. Unfortunately, liver-directed therapy with IAT is also difficult to apply given the difficulty assessing tumor extent and the reported increased rates of complications. As such, the prognosis of patients with infiltrating HCC is poor with most patients succumbing to disease progression and worsening of underlying liver function. Infiltrating HCC remains a challenging variant of primary liver cancer that demands more attention if we hope to improve the outcome of patients afflicted with this disease.

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HOW I DO IT

A Surgical Technique for Portal Vein Decompression in Retransplantation

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Abstract
Introduction Liver retransplantation is the only option for people who have a failing liver graft, but it can be technically challenging. Intraperitoneal adhesions often form after abdominal operations, which is true in liver retransplantation as well. Also, the liver hilum is scarred, which makes hilar dissection more difficult. In addition, dissection is further complicated in the setting of portal hypertension.
Discussion Venovenous bypass can be used for portomesenteric decompression. We describe an alternative technique for decompression of portal hypertension using an inferior mesenteric vein without placing the patient on venovenous bypass.

Keywords Liver retransplantation · Portal hypertension · Portovenous decompression

Introduction

Over the past years, liver transplantation techniques have been refined, and now, most centers use a relatively standardized approach. On the other hand, liver retransplantation is generally technically more challenging and requires a different set of surgical techniques. As with other abdominal surgeries, liver transplantation often leads to development of extensive adhesions in the abdomen, and these become even more challenging in the setting of a failing liver allograft with increased portal hypertension with numerous large variceal collaterals. As a result, significant blood loss can be encountered during adhesiolysis in order to reach the liver hilum.

In primary transplantation, the hilum is sequentially dissected, dividing separately the hepatic artery, bile duct, and finally the portal vein; however, this approach might not be possible or safe in retransplantation.[1] Often, in retransplantation, the liver hilum is scarred and is encased with multiple collaterals. If a difficult hilum is encountered, a clamp can be applied to the hilum and the structures transected en masse.[2,3] Subsequently, each structure is identified and reanastomosed to the donor structures to reestablish continuity.

In the past, the majority of centers routinely used venovenous bypass in orthotopic liver transplantation. In venovenous bypass, portal and femoral veins are cannulated to facilitate blood return to the right heart and to decompress portomesenteric venous system. With the popularization of the piggyback technique, venovenous bypass became nonessential. With this technique, the inferior vena cava is not clamped, and there is a continuous venous return to the right heart throughout the anhepatic phase. Presently, many centers do not use the venovenous bypass, some use it occasionally, and other centers continue its use in all liver transplants. Below we describe a technique of decompression of the portomesenteric system without placing the patient on venovenous bypass in retransplantation.

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Materials and Methods

During liver retransplantation, we enter the abdomen through a previous Chevron incision. The adhesions are taken down in order to reach the lower abdomen. The ligament of Treitz is mobilized, and the inferior mesenteric vein (IMV) is identified and exposed (Fig. 1). The blood is washed, centrifuged, resuspended in saline, and transfused into the patient via a rapid infuser (The Belmont®, Belmont Instrument Corporation, Billerica, MA) through a cannula placed in the internal jugular vein (Fig. 2). We have not experienced any clot formation in the cell saver circuit. However, since we use transesophageal echocardiography selectively to assess the cardiac function and filling status, small pulmonary emboli without significant hemodynamic impact may not be detected. Once the flow is established and the portal venous system is decompressed, the adhesions are taken down. The hilum is exposed, and the components of the porta hepatis are dissected. The native hepatectomy is completed, and the new liver allograft is reimplanted in a piggyback fashion. The original confluence of the right, middle, and left hepatic veins that was used in the primary transplant is used for the anastomosis to the suprahepatic vena cava in retransplantation. The liver allograft is flushed with 500 cc of normal saline with effluent exiting the inferior vena cava of the allograft. The portal vein of the graft is anastomosed to the recipient portal vein. Recirculation is initiated by releasing the portal vein clamp, allowing approximately 500 cc of blood to circulate through the allograft exiting at the inferior end of the allograft vena cava. Subsequently, the flow through the suprahepatic vena cava is reestablished, and the inferior vena cava of the allograft is ligated. The IMV cannula is removed, and the IMV is ligated. The operation is completed once the hepatic artery reconstruction and biliary drainage are completed.

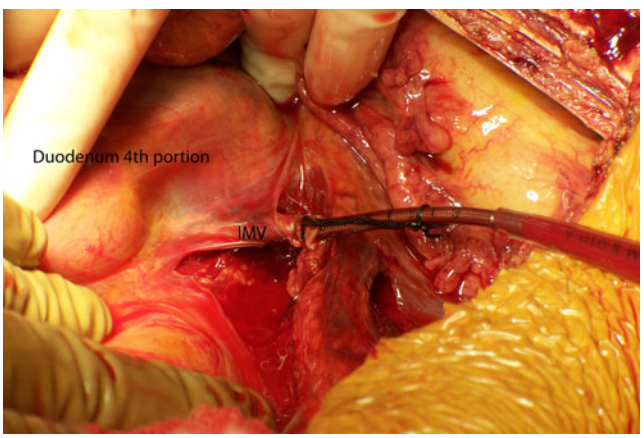

Fig. 1 10-Fr Fem-Flex femoral arterial cannula used for IMV cannulation

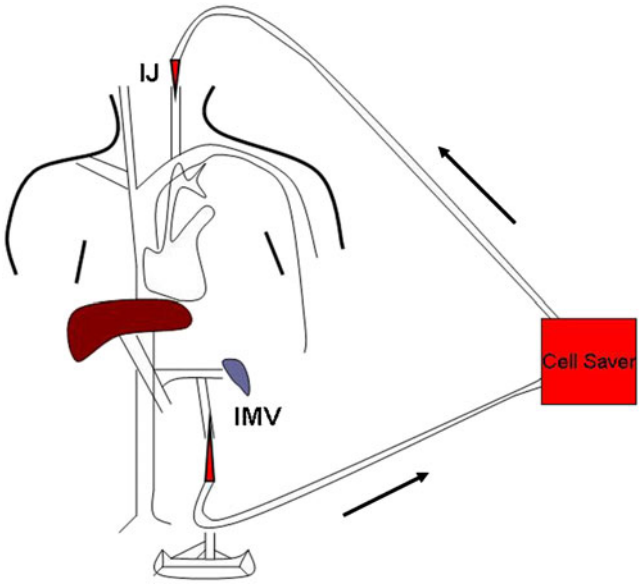

Fig. 2 Portomesenteric decompression with cell saver by inserting outflow cannulae into the IMV and inflow cannulae into the internal jugular vein

Discussion

Liver retransplantation is challenging but is the only option for people who have a failing liver graft. Adhesions, scarring, and venous collaterals from portal hypertension make the procedure more difficult than the primary transplantation. By diverting the flow away from the portomesenteric system through the IMV, the portal hypertension and its collaterals are decompressed, making the procedure more manageable. Using cell saver for decompression is an attractive alternative to venovenous bypass, especially for the transplant centers that do not utilize venovenous bypass in their practice and always use cell saver to collect the blood from the operative field. The advantage of using cell saver is that the decision to use it for this indication can be made once the abdomen is entered if the adhesions are encountered. This makes it more attractive than the venovenous bypass since when using venovenous bypass additional femoral cannulas have to be placed prior to initiation of transplantation.

At our center, we primarily utilize the piggyback technique without the use of a venovenous bypass in primary liver transplants and retransplantation. In a technically difficult retransplant, the IMV cannulation allows retrograde collection of the portomesenteric blood, which is then processed through the cell saver prior to being returned into a central vein (Fig. 2), allowing an effective decompression of the portomesenteric venous system. Our technique differs from the conventional use of IMV in venovenous bypass which requires an additional cannulation of the femoral vein to sustain the circulating volume of

blood required in venovenous bypass.[4, 5] The use of the cell saver to collect the IMV blood adds essentially no change in its primary use. We did not observe any obvious hemodynamic changes during the procedure when the cell saver was used for decompression. To determine how reinfusion of large amount of salvaged blood affects coagulation profile during the transplantation will require further investigations. In our experience, we found coagulopathy manageable and correctable with the help of thromboelastography monitoring.

Conclusion

We believe that diversion of flow away from the portal vein through the IMV using the cell saver without venovenous bypass is a safe and useful technique to be considered in liver retransplantation. This is an off-label use of the device, and randomized controlled trials are needed to better study the benefit of this technique.

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CASE REPORT

Gossypibomas Mimicking a Splenic Hydatid Cyst and Ileal Tumor

A Case Report and Literature Review

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Abstract
Background Gossypiboma is a term used to describe a retained surgical swab in the body after a surgical procedure. Gossypiboma is a rare surgical complication, but can cause significant morbidity and mortality. It may be a diagnostic dilemma with associated medico-legal implications, and is usually discovered during the first few days after surgery; however, it may remain undetected for many years.
Methods We present a gossypiboma case immigrating to small intestine, as well as a literature review of studies published in the English language on intraluminal migration of gossypiboma, accessed through PubMed and Google Scholar databases.
Results Case of a 51-year-old man who was admitted due to vomiting, abdominal distension, and pain. He had a history of abdominal trauma 8 years previously, and surgery had been performed at another hospital. The physical examination revealed muscular guarding and rebound tenderness in the right lower quadrant. A splenic hydatid cyst and ileal calcified mass were suspected based on results of abdominal computed tomography. Therefore, a laparotomy was performed. Segmental ileal resection, end-to-end anastomosis, and splenectomy were performed. The final diagnosis was gossypiboma in both the spleen and ileum. We performed a systemic review of the English-language literature between 2000 and 2010 in PubMed and Google Scholar, and we found 45 cases of transmural migration of surgical sponges following abdominal surgery. Three cases in which the gossypiboma was located in the spleen are also discussed.
Conclusion Gossypiboma should be considered as a differential diagnosis of any postoperative patient who presents with pain, infection, or a palpable mass.

Keywords Gossypiboma · Foreign body · Retained surgical sponge · Intraluminal migration · Spleen

Abbreviations

CT	Computed tomography
US	Ultrasonography
RSS	Retained surgical sponge

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Introduction

A retained foreign body in the peritoneal cavity after surgical intervention is an occasional complication in modern surgery. The most common retained foreign body is the surgical sponge.[1] Retained surgical sponge (RSS), also known gossypiboma, is used to describe a retained surgical swab in the body after a surgical procedure. It may lead to medico-legal problems and diagnostic dilemmas due to the necessity for invasive diagnostic procedures and operations.[2,3] Clinical symptoms both in the early postoperative period as well as in the months or years following the initial surgery are often nonspecific.[4] Although RSS is difficult to diagnose, a history of surgery, physical examination findings, laboratory results, and the utilization of a variety of radiologic instruments can help to arrive at the correct preoperative diagnosis.[3,5] Transluminal migration of

the RSS is rare and is due to the inflammatory process, which causes pressure necrosis of the bowel wall and extrusion of the sponge into the gastrointestinal luminal organs.[6] We report a case of retained surgical sponges mimicking an ileal calcified mass and a splenic hydatid cyst; we also review the English-language literature between 2000 and 2010.

Materials and Methods

In this study, we present a gossypiboma case imitating a splenic hydatid cyst and a calcified mass within the lumen of the small intestine. Additionally, for the review, the English-language literature between 2000 and November 2010 was searched in PubMed and Google Scholar using the terms "gossypiboma," "textiloma," "retained surgical sponge," "intraluminal migration of surgical sponge," "retained surgical swab," "retained surgical mop," and "transmural migration of surgical sponge." The full texts of all papers obtained were analyzed with respect to the aforementioned criteria. Gossypiboma cases immigrating to luminal organs within the gastrointestinal system, and located within the spleen, were included in the study, whereas cases located within the abdominopelvic cavity and retroperitoneum were excluded. Only appropriate cases based on our criteria were elected and included among papers, and reported in a case-series manner. Data regarding at least seven of all properties including age, sex, initial diagnosis, initial surgery, interval, clinical presentation, diagnostic methods, location, and surgical procedure must have been given for the patients to be included in the study.

Results

Case Report

A 51-year-old man was admitted to the Surgery Department of Diyarbakir Education and Research Hospital in September 2010, with the complaints of colicky abdominal pain, intermittent abdominal distention, constipation, nausea, and vomiting. He had undergone laparotomy twice at another center due to trauma 8 years previously. The physical examination revealed muscular guarding and rebound tenderness in the suprapubic region and the right lower quadrant. The results of a rectal examination were unremarkable. Laboratory investigations showed the following: blood urea nitrogen, 34 mg/dl; creatinine, 1.1 mg/dl; C-reactive protein, 23 mg/l. The blood cell count revealed leukocytosis at 12,500/dl, hemoglobin of 12.7 g/dl, and a platelet count of 335,000/dl. Other serum parameters were within normal limits. Plain abdominal radiographs revealed a small intestine with fluid levels. Computed tomography (CT) showed a heterogeneous calcified mass within the small intestinal lumen, suggesting the presence of tumor or foreign body. Additionally, CT showed a calcified mass of 10×6 cm located in the spleen, suggesting the presence of a splenic hydatid cyst (Fig. 1). The clinical symptoms were thought to be consistent with a foreign body or mechanical intestinal obstruction caused by an ileal calcified mass; therefore, an operative decision was made. Exploratory laparotomy was performed, revealing gross adhesions over a loop of small bowel and a segment 50 cm proximal to the ileocecal region containing an intraluminal hard mass approximately 25 cm in length, without external communication to the other surrounding viscera. Segmental ileal resection and anastomosis were performed. Upon opening the specimen, a 30×30-cm surgical sponge was found. In addition, a splenectomy was performed because a portion of the sponge was located in the spleen (Fig. 2a–c). The abdominal cavity was drained and closed. The postoperative period was uneventful and the patient was discharged on the eighth postoperative day. He has been free of symptoms during the last 2 months.

Literature Review

The English medical literature published up to November 2010, in the PubMed and Google Scholar databases were reviewed, and 42 reports concerning 48 cases meeting the aforementioned criteria were included in this review.[1–42] Thirty-six of these were written as case reports, three as letters to the editor, two as original articles, and one as a literature review. Thirty-eight patients were female and ten were male, with ages ranging from 3 to 75 years (median, 41.8±16.2 years). The time from the causative operation to presentation with a retained surgical sponge ranged from

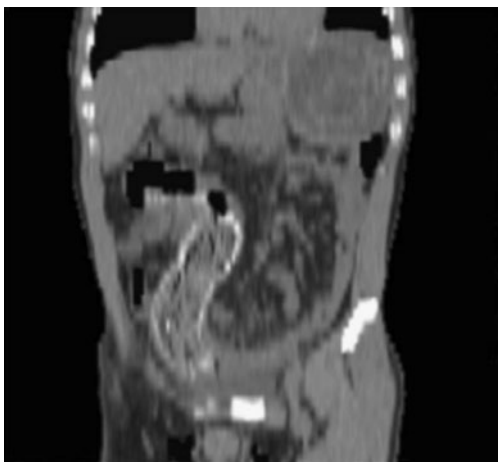

Fig. 1 Contrast-enhanced computed tomography showing two foreign bodies located both ileum and spleen

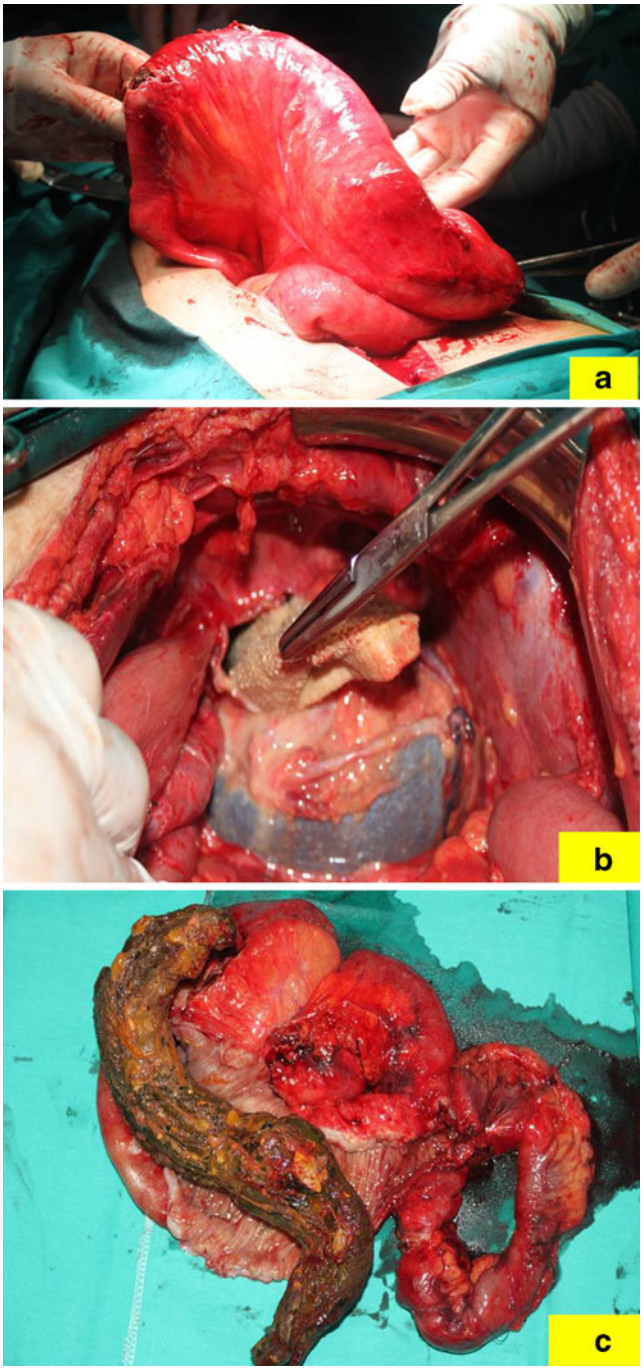

Fig. 2 Peroperative photographs of gossypibomas. **a** View of a mass, about 25 cm in length, extending into ileum. **b** Removal of retained surgical sponge into the spleen. **c** Gross specimen of gossypiboma in an opened ileal lumen

10 days to 43 years. Various radiological and endoscopic modalities were used as diagnostic tools. The most frequent site of impaction in 45 of 48 cases was the gastrointestinal luminal organs, especially the ileum (14 cases). Eight sponges migrated into the colon, six into the jejunum, five into the stomach, five into the duodenum, two into the ileocolic region, and two into the ileojejunal region, one into the both jejenum and colon; three were unnoted. We found three cases in which a surgical sponge had adhered to the spleen. In eight patients, the surgical sponge passed spontaneously through the rectum, while in 34 of 48 patients, the retained sponge was removed by different surgical procedures. In six of 48 patients, surgical sponges were extracted endoscopically. The demographic features of these patients are summarized in Table 1.

Discussion

RSS is not uncommon in surgical practice; it has been under-reported and rarely discussed because of medico-legal problems for surgeons.[7,8] The incidence of an RSS is difficult to estimate, but it has been reported to be 1 in 100 to 3,000 for all surgical procedures and 1 in 1,000 to 1,500 for abdominal surgery.[2,3,8–13] RSS is frequently located in the abdominopelvic cavities, but it can also follow thoracic, orthopedic, urological, and neurosurgical procedures.[5,12,14–16]

Despite improvements in surgical techniques and operating room facilities, and awareness of the importance of check counts at the end of operations, retained foreign bodies remain a problem in many surgical clinics. Many risk factors, such as duration and complexity of surgery, excessive blood loss in trauma patients, surgery under emergency conditions, unplanned procedural changes, a change in operating room teams during the course of the operation, and a failure to count surgical instruments and sponges, were identified. The three most important risk factors are emergency surgery, unplanned change in the operation, and body mass index.[2,15,17,18]

Two types of foreign body reactions occur in patients with retained sponges. The most common reaction consists of an aseptic fibrous response resulting in adhesion, encapsulation, and granuloma formation. Patients usually remain asymptomatic and the retained sponges are detected incidentally, or they present with a pseudotumor syndrome. The other foreign body reaction in retained sponge cases involves an exudative inflammatory reaction with abscess formation or chronic internal or external fistula formation. The latter is believed to be associated with transmural migration of retained sponges.[9,19–22]

The clinical presentation of gossypiboma is variable and depends on the location of the sponge. Common symptoms and signs of gossypiboma are abdominal distention, ileus, tenesmus, pain, a palpable mass, vomiting, weight loss, diarrhea, abscess formation, fistula formation, and rectal bleeding.[3–5,15,23] Clinical symptoms may appear in the postoperative period or even after weeks, months, or years. The interval between the probable causative operation and

Table 1 Transmural migration of retained surgical sponge to the gastrointestinal luminal organs and splenic sponge: review of the literature (2000–2010)

References	Year	Age	Sex	Initial diagnosis	Initial surgery	Interval	Clinical presentation	Diagnostic methods	Location	Surgical procedure
Yakan	2010	61	F	P. Ulcer	UN	23 years	Palpable mass	CT	Spleen	Splenectomy
Sumer	2010	54	F	Pregnancy	Caesarean	23 years	AP	CT+MR	Ileum[9]	Segmental resection+Primary repair
Patil	2010	23	F	Pregnancy	Caesarean	3 months	V+C+AP	CT	Ileum	Enterotomy
Allegre	2010	48	F	Cholelithiasis	Cholecystectomy	2 years	Palpable mass+AP	Endoscopy	Stomach	Gastrostomy
Gupta	2010	50	F	UN	TAH	9 months	RIO	US+CT+Sigmoidoscopy	Sigmoid colon, Ileum	Segmental resection+Sigmoid resection
Sharma	2010	30	F	Cholelithiasis	Cholecystectomy	10 months	V+Rectal bleeding	Barium gr+US	Jejunum[1]	Segmental resection
Govarjin	2010	35	F	Pregnancy	Caesarean	5 months	Cuteness fistula	Fistulography	Ileocecal [2]	Ileotomy+Right hemicolectomy
De Compos	2010	58	F	UN	TAH+USO+UO	16/13 years	AP, Weight loss	CT+Colonoscopy	Ileum	Segmental resection
Ulucay	2010	22	F	Pregnancy	Caesarean	7 months	Palpable mass	Barium+US+CT	Sigmoid colon, Ileum	Segmental resection+Sigmoid resection
Tandon	2009	30	F	Pregnancy	Caesarean	2 years	AP+AD	Barium enema+US+CT	Colon, Jejenum	Segmental jejunal and colonic resection
Ivica	2009	73	F	Ectopic pregnancy	Laparatomy	40 years	Fever+AP	USG+CT	Spleen	Splenectomy
Akbulut	2009	33	F	Trauma	Splenectomy	4 years	V+C+AP	Endoscopy	Ileum	Enterotomy
Dakubo	2009	44	F	Bleeding	TAH	4 years	C+Foreign body in rectum	UN	Rectum	Spontaneous discharge
Ozyer	2009	58	F	Cholecystitis	Cholecystectomy	3 months	V+AP	US+CT+MR+Barium+ Sigmoidoscopy	Sigmoid colon	Sigmoidoscopic extraction
Grassi	2008	75	F	Rectum ca	Anterior Resection	3 years	AP+Fever	CT	Ileum	Enterotomy
Agarwal	2008	40	F	Cholelithiasis	Cholecystectomy	18 months	Obst.	X-ray	Jejunum	Enterotomy
Kansakar	2008	55	F	Cholelithiasis	Cholecystectomy	14 years	AP	US+CT+Barium enema+ Colonoscopy	Ileum[4]	Segmental resection
Zantvoord	2008	39	F	Pregnancy	Caesarean	3 months	Palpable mass	CT	Rectum	Spontan discharge
Erdil	2008	55	F	Cholelithiasis	Cholecystectomy	12 months	GI Bleeding	US+ERCP	Duodenum	Endoscopic extraction
Peyrin	2007	62	M	Colon cancer	Hemicolectomy, Left	6 months	V	CT	Duodenum	Endoscopic extraction
Sinha	2007	38	M	Blunt trauma	Laparotomy	12 months	AP	US+CT+Barium enema+ endoscopy	Duodenum	Endoscopic extraction
Disu	2007	42	M	Ovarian cyst+ Menorrhagia	Cystectomy+ Myomectomy	16 years/ 18 months	Palpable mass	US+CT	Ileum	Segmental resection
Alis	2007	44	F	Cystotomy	Hidatid cyst	2 months	AP	Endoscopy+CT	Duodenum	Conservative Managent[6]
Sarda	2007	26	F	Cholelithiasis	Cholecystectomy	2 months	V+AP	US+Endoscopy	Stomach	Endoscopic extraction
		40	F	Fibroid Uterus	TAH	Few day	C+Rectal mucoid discharge	Colonoscopy+US+Barium enem+CT	Sigmoid[5]	Segmental resection+Sigmoid resection
Choi	2006	29	F	Pregnancy	Caesarean	3 months	V+C+AP	CT	Colon	Spontaneous discharge
Yildirim	2006	35	F	Peptic Ulcer	Dist.Gastrectomy	14 months	V+Weight loss	Endoscopy	Stomach	Gastrotomy
		52	F	Myoma Uteri	TAH	22 months	Obst.	X-ray	UN	Segmental resection
Godara	2006	19	M	Blunt trauma	Laparotomy	16 months	AP	USG+CT	Splenic flexure	Spontaneous discharge

Table 1 (continued)

References	Year	Age	Sex	Initial diagnosis	Initial surgery	Interval	Clinical presentation	Diagnostic methods	Location	Surgical procedure
Tiwary	2006	35	F	Cholelithiasis	Cholecystectomy	3 months	V+Lump	Endoscopy+Barium	Stomach	Gastrotomy
		30	F	Cholelithiasis	Cholecystectomy	4.5 months	V	Endoscopy+Barium	Stomach	Gastrotomy
Sarker	2006	35	F	Pregnancy	Caesarean	9.5 months	V+AP+Lump	US	Ileum	Segmental resection
Ukwenya	2006	42	F	Fibroid Uterus	TAH	8 months	V+AP	US	Jejuno-ileal	Segmental resection
		25	M	Acute abdomen	UN	2 weeks	Enterocutanous fistula	US	UN	Spontaneous discharge
		3	M	Anorectal anomaly	Pull-through operation	10 days	Sacral discharge from sacral incision	Fistulography	UN	Spontaneous discharge
		36	M	Typhoid perforation	Laparatomy	UN	Enterocutanous fistula	Fistulography	Ileum	Segmental resection
Bani-Hani	2005	45	F	Appendicitis	Appendectomy	24 months	AP+Distension	US+Barium enema	Ileum	Spontaneous discharge
Keymeulen	2004	73	M	Tuberculosis	Nephrectomy	43 years	AP+Weight loss	CT	Spleen	Splenectomy
Yeung	2004	61	F	Leiomyoma	TAH	15 years	Palpable mass	CT	Ileum	Segmental resection
Cruz	2003	41	M	Gunshot trauma	Laparatomy	3 months	Obst.	CT	Descending Colon	Right hemicolectomy
Gencosman	2003	74	F	Cholelithiasis+ Umbilical hernia	Cholecystectomy+ Hernia repair	3/1 years	AP+V	CT	Jejenum[7]	Segmental resection
Hinrichs	2003	5	F	Appendicitis	Appendectomy	7 months	AP+Bloody stool	CT+Colonoscopy	Cecum	Colonoscopic extraction
Turan	2003	54	F	Renal cell carcinoma	Nephrectomy+ Appendectomy	1 month	V+C+AP	US	Jejenum	Segmental resection
Puri	2002	32	F	Cholelithiasis	Cholecystectomy	8 months	Palpable mass+Obst. +anemia	US+CT+Barium enema	Jejenum	Segmental resection
Dux	2002	47	M	Cholelithiasis	Cholecystectomy	10 months	Obst.	USG+CT	Jejunum	Segmental resection
Manikyam	2002	44	F	Cholelithiasis	Cholecystectomy	2 years	V+AP	US+Barium+ Endoscopy	Duodenum[8]	Right hemicolectomy+ Duodenoraphy
Dhillon	2002	35	F	UN	TAH	11 months	V+AP	US	Ileum	Segmental resection
Silva	2001	24	F	Pregnancy	Caesarean	4 months	V+C+AP	US	Ileum	Segmental resection

AP abdominal pain, *V* vomiting, *C* constipation, *TAH* transabdominal hysterectomy, *Obst* intestinal obstruction findings, *UN* unnoted, *CT* computed tomography, *US* ltrasonography

1 Jejunocolic fistulae, *2* ileocecocutaneus fistulae, *3* ileojejunal fistulae, *4* ileoileal fistulae, *5* ileosigmoidal fistulae, *6* spontaneous discharge, *7* jejunojejunal fistulae, *8* duodenoileocolic fistulae

the diagnosis of RSS is reportedly from 1 day to 28 years.[5,10,20,33] Cruz et al.[18] found this interval to be 6 months to 33 years, while it was found to be 10 weeks to 35 years by Zantvoord et al.[20] This interval was found to be 10 days to 43 years in our study.

The main complications of abdominal gossypiboma are bowel or visceral perforation, obstruction, peritonitis, adhesion, abscess development, fistula formation, sepsis, and migration of the sponge into the lumens of gastrointestinal or urinary systems.[15,23]

According to the literature, migration of a sponge into the bowel is rare compared with the formation of an abscess, chronic fistula, or foreign body granuloma.[4,19] Abdominal gossypibomas can migrate into the stomach, duodenum, jejunum, ileum, colon, or bladder without any apparent opening in the wall of these luminal organs**.** The ileum is the most common part of the intestine into which migration takes place, followed by the jejunum and duodenum.[24] Cruz et al.[18] retrospectively analyzed a total of 21 gossypiboma cases reported in the English literature between 1940 and 2001 and showed that of the cases analyzed, 11 migrated to the ileum while seven migrated to the jejunum, one to the duodenum, one to the rectum, and one to the stomach wall. Zantvoord et al.[20] found the migration rates following an analysis of a total of 65 gossypiboma cases reported in different languages between 1960 and 2007 to be as follows: 22 to the ileum, seven to the jejunum, six to the duodenum, five to the colon, and two to the stomach. The results of our literature study also support the results of these two studies.

The diagnosis of RSS is difficult to reach because the clinical symptoms are nonspecific and the imaging findings are often inconclusive. However, plain radiography, barium studies, endoscopy, ultrasonography (US), CT, and magnetic resonance imaging (MRI) are useful for diagnosis.[4,11] Plain radiographs suggest the diagnosis if the surgical sponge is calcified or when a characteristic "whirl-like" pattern is present. In the presence of radiopaque markers, surgical sponges can be easily diagnosed by direct radiography. However, if surgical sponges penetrate and migrate to the inside of the small bowel or bladder, it is difficult to locate them.[1,5]

Barium studies are helpful in cases of intraluminal migration of the textile in which the exact location can be ascertained. Perforation of the bowel wall and fistulous communication with the cavity containing the foreign body or adjacent bowel loop is best demonstrated by this modality.[6,7,14,16,25–28] US images can be classified into two groups: cystic and solid. The mainstay of investigation is considered to be US images that show a hyper-reflective mass with a hypoechoic rim, along with a strong posterior shadow. However, ultrasonic sensitivity may be low in the early postoperative period because of intestinal gas distension.[5,16] CT scans may show air trapped between surgical sponge fibers, calcification of cavity walls and contrast-enhanced rims, which may not be distinguishable from other intra-abdominal abscesses.[2,3,5–7,15,23] MRI usually shows a well-defined mass with a fibrous capsule that exhibits low signal intensity on T1-weighted images and high signal intensity on T2-weight images.[23]

Endoscopy (panendoscopy and colonoscopy) is a method used in both the diagnosis and treatment of intraluminal gossypiboma cases.[15,26,29,30]

A correct preoperative diagnosis is made in about one-third of cases. Depending on the form of presentation, differential diagnoses are proposed. The differential diagnoses of gossypiboma include fecaloma, hematoma, abscess, and tumor.[5,28]

RSSs should be removed as soon as diagnosed. Various techniques are used for the removal of RSSs, depending on the clinical presentation and facilities available: percutaneous techniques, laparoscopy, and laparotomy.[7,15,26,29–31] However, a few cases have been reported in the literature in which the RSS spontaneously discharged during defecation.[8,16,17,32,33] Prognosis is excellent if the RSS is removed immediately after diagnosis.[17] However, a mortality rate of 10% to 17.6% has been reported in the older medical literature and is associated with delayed diagnosis and treatment.[18,20]

In conclusion, RSS should be considered as a differential diagnosis of any postoperative patient who presents with pain, infection, or a palpable mass. Also, we strongly advise using only sponges with radiopaque markers during operations and additional systematic wound/body cavity examinations, even when the sponge count is reportedly correct.

Author's contributions AS, AZ and YY performed the surgical procedures; AS and SH contributed in writing the article and review of the literature as well as undertaking a comprehensive literature search; SA and AZ contributed in the design and manuscript preparation.

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GI IMAGE

A Case of Obstruction Due to Jejunoileal Diverticula

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Abstract
Objective The objective of this study is to discuss the presentation and diagnosis of a complicated jejunoileal diverticuli.
Case Report The case of a 94-year-old woman with small bowel obstruction secondary to an impacted enterolith from a jejunoileal diverticulum is presented to illustrate the clinical picture and radiographic findings of complicated small bowel diverticula.

Keywords Small bowel diverticula · Enterolith · Small bowel obstruction

Clinical Presentation

A 94-year-old female was hospitalized for mild lower abdominal pain for 2 days with associated nausea and vomiting and a 3-day history of constipation. Past medical history includes a statin for hypercholesterolemia, stents for coronary artery disease, and colace for constipation with no prior abdominal surgeries. Physical exam is significant for mild abdominal distention and tenderness in the bilateral lower quadrants, and there were no peritoneal signs and no palpable umbilical or inguinal masses. Laboratory values indicate leukocytosis of 14,400 with 91% neutrophils. Blood chemistry results are consistent with a hypokalemic, hypochloremic metabolic alkalosis and mild BUN and creatinine elevation. Liver enzymes and amylase are normal, but the troponin is elevated to 2.7. Computed tomographic scan of the abdomen shows multiple contrast-enhancing rings off the loops of small bowel consistent with the diverticula (Fig. 1).

Discussion

Reports of small bowel diverticula (nonmeckelian jejunoileal diverticula, JID) have peppered the literature since the 1700s, primarily as anatomic peculiarities rather than anything of clinical significance. Usually asymptomatic and difficult to diagnose, the true incidence of these diverticuli are likely underestimated and vary by identification technique. Incidence is estimated to be over 7%[1,2] and are most frequently seen in the elderly population, although they may occur at any age.[1,3]

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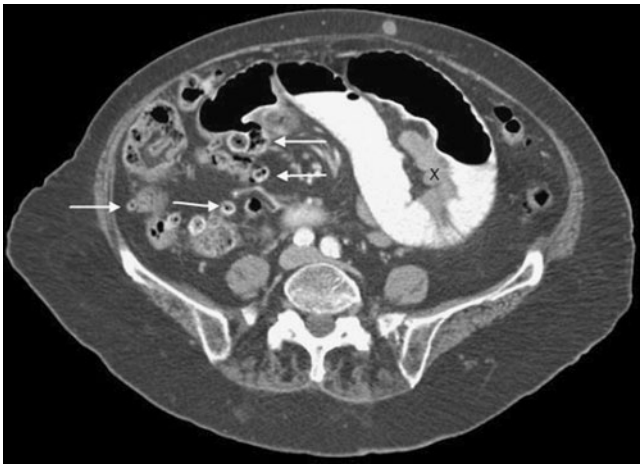

Fig. 1 CT of abdomen with oral and IV contrast. The loop of jejunum containing the phytobezoar in the diverticula is marked with a *black X*. Note the lack of penetration of the oral contrast into the mesenteric diverticula. In addition, note the multiple diverticula adjacent to a loop of small bowel appearing as small contrast-enhanced ovoid masses containing mottled gas (*white arrows*)

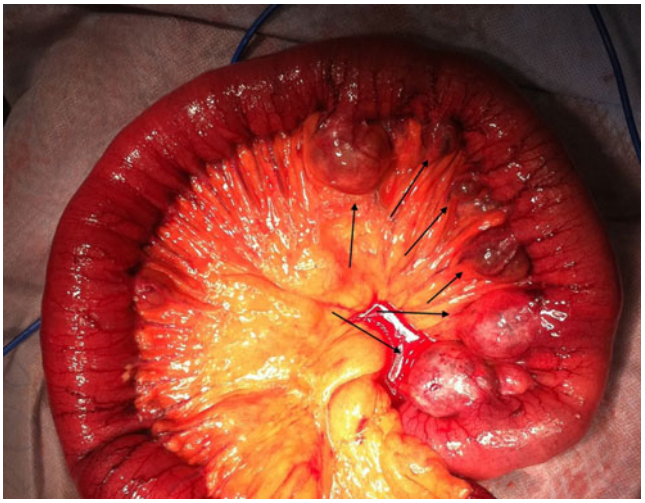

Fig. 2 Intraoperative photo of the jejunal diverticula (*black arrows*). Note the location on the mesenteric border. Phytobezoars were present within several of the diverticula

As opposed to a true (i.e., Meckelian) diverticula, JID are false diverticula, having only mucosa and submucosa acquired by increased intraluminal pressure due to gut hypomotility.[3] They are located on the mesenteric side of the small bowel and found preferentially in the jejunum where the penetrating vasa recta provide opportunity for the two layers to herniate through these areas of weakened bowel wall.[3]

Most JIDs are asymptomatic and may only be found incidentally during laparotomy or imaging. In these cases, no intervention is necessary, and they are reported as incidental findings.[3] However, JIDs may become complicated, presenting as chronic pain or malabsorption, or with an acute abdomen from a gastrointestinal (GI) hemorrhage, diverticulitis, perforation, abscess, or obstruction. The gold standard for diagnosis is by laparotomy, though enteroclysis and upper GI series with barium swallow are radiologic options with high sensitivity for JID.[3,5] Generally, complicated JID requires surgical resection.[3]

Obstruction is one of the complications of JID. This may be a mechanical obstruction, such as compression from a distended or inflamed diverticula, intussusception, volvulus, adhesions from prior diverticulitis, or enterolith, or functional obstruction from uncoordinated peristalsis.[3]

Though a rare complication, an enterolith may form in the diverticula, subsequently dislodge and cause a small bowel obstruction distally (Fig. 2). Enteroliths may form around a nidus (called bezoars) composed of food particles, stool content, and physical or chemical foreign material.[1,5–7] Enteroliths may also form de novo from choleic acid stasis (from bacterial deconjugation of choleic salt) in the diverticula and rarely calcify.[3–7]

Obstructing small bowel enteroliths are usually very difficult to diagnose preoperatively, unless calcified.[8] However, abdominal CT of our patient (Fig. 1) shows several IV contrast-enhancing ovoid masses off the small bowel that appear to contain air. A round mass with mottled gas is the most common finding on CT for phytobezoar detection,[10] making these rings a key radiographic find. It should be noted, however, that this gas may not always be present, which may pose some difficulty in accurate diagnosis since the bezoars could appear like soft tissue masses (i.e., tumor),[9] or the gas may be mistaken as pneuomoperitoneum caused by perforation.[10]

Once found intraoperatively, the enterolith should be manually lysed and milked either towards the cecum or towards an enterotomy.[3,4] Failing this, segmental resection and primary anastomosis is warranted, followed by a thorough search for additional enteroliths in the bowel and gallbladder.[1–4]

In summary, complicated small bowel diverticula are rare but potential etiologies for small bowel obstruction or any acute abdomen presentation. As illustrated by this case, JID should be suspected particularly in elderly patients with no prior abdominal surgeries, gallbladder disease, or hernias.[4] Radiologic imaging usually does not provide preoperative JID identification;[8] however, an experienced radiologist may observe clues to assist in the diagnosis preoperatively. Treatment is surgical removal of the obstruction by milking or by bowel resection, if symptomatic, with careful search for multiple enteroliths throughout the bowel.

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GI IMAGE

Multiple Caeco-Appendiceal Fistulas and Diverticulosis: A Newly Defined Congenital Anomaly of the Appendix—Report of the First Case

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Abstract
Introduction Congenital anomalies of the appendix are extremely rare. They are usually found incidentally during operations other than appendectomies. Congenital appendix diverticula are even less frequent.
Discussion Congenital caeco-appendiceal fistulae have not been reported until today. Herein, we present real diverticula of the appendix with multiple caeco-appendiceal fistulae which, to our knowledge, is the first in the literature.

Keywords Appendix anomaly · Diverticula · Caeco-appendiceal fistulae

Case Report

A 23-year-old woman was diagnosed and operated on because of acute appendicitis. The appendix was not a retrocecal one and was not attached to the cecal wall. There were nothing but a total of three macroscopically visible and individual connecting channels in the form of ordinary fistulas (like a network) running out between the walls of the appendix and cecum. Additional three diverticular dilatations of the appendix as if trying to form extra connections were also detected (Fig. 1) and sections of the specimen confirmed the findings (Fig. 2). Colonic mucosa lining the additional lumens contain without any inflammation (Figs. 3 and 4). Since two of the three diverticula contained muscle layers, in addition to mucosal, submucosal and serosal layers, the decision of real congenital diverticula was made (Fig. 5). There was no inflammation in the diverticula and fistulas. There was only one location presenting acute and focal inlammation at the tip of the appendix far away from the congenital fistulas and diverticula (Fig. 6).

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Discussion

Congenital diverticulum of the appendix is a very rare anomaly. About 50 cases have been reported until today.[1] It classically has two variants: congenital and acquired.[2] Congenital diverticula are real diverticula including mucosa, submucosa, serosa, and, most importantly, the muscular layers. Acquired diverticula are false structures which do not have a muscular layer.[3,4] Congenital appendiceal diverticula are thought to be developmental abnormalities. These anomalies include failure of appendiceal luminal rechannelization, appendix duplication, epithelial inclusion cyst residues in the wall

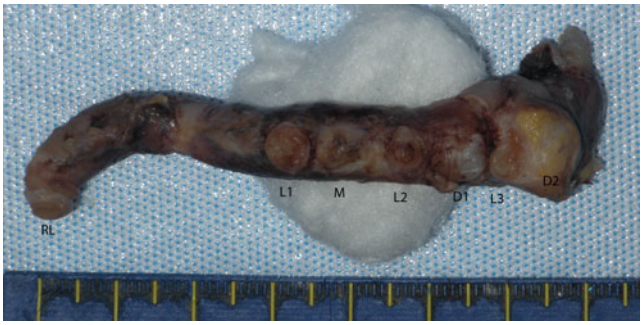

Fig. 1 Macroscopic anatomy of the appendix with multiple orifices. *RL* real lumen, *L1–L2–L3* additional orifices, *M* mucous pool, *D1–D2* diverticula

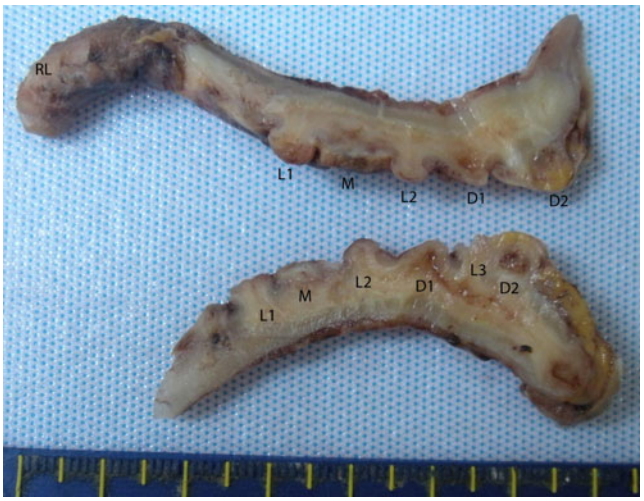

Fig. 2 Sectioned specimen showing the relationship of the additional diverticula with luminae and the real lumen

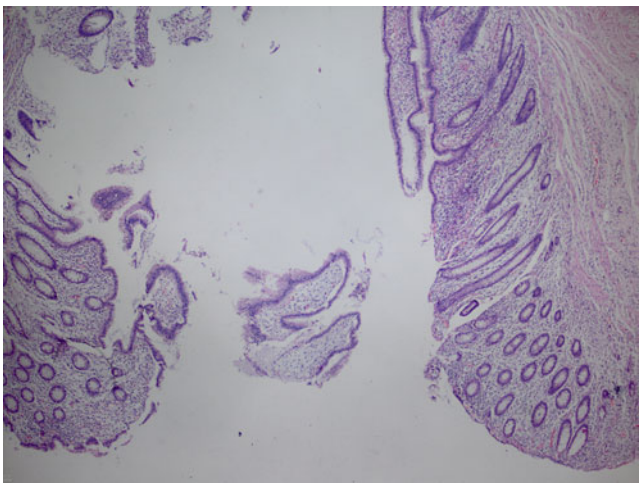

Fig. 3 Colonic mucosa lining the additional lumens. Haematoxylene & Eosine (H & E), ×40

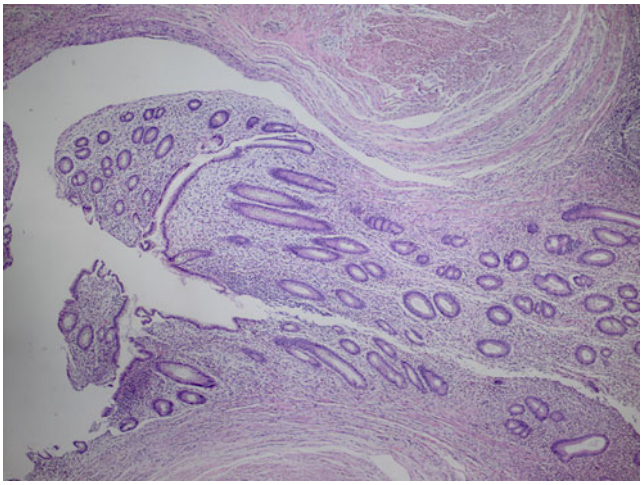

Fig. 4 Colonic mucosa lining the additional lumens, without contain any inflammation. H & E, ×40

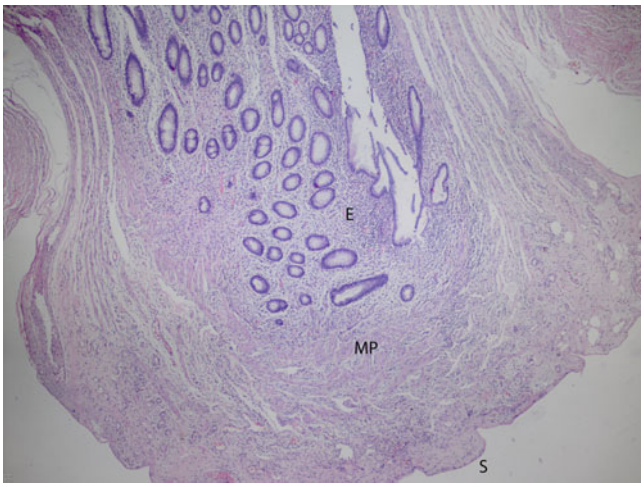

Fig. 5 Congenital diverticula with muscular layer within the wall (H & E, ×40). *E* colonic epithelium, *MP* muscularis propria, *S* serosa

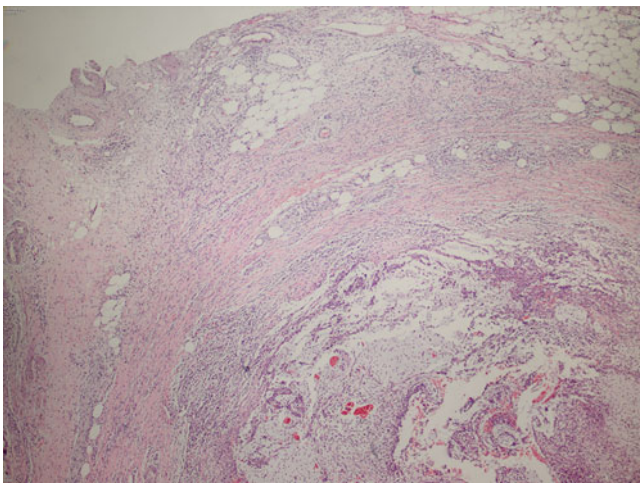

Fig. 6 Dissecting acellular pool of mucous and focal purulent peritonitis and periappendicitis. H & E, ×40

of the appendix, failure of vitelline duct obliteration and/or wall retraction due to adhesions.[4] Diverticula are seen in 2.2% to 0.3% of the population, the majority of which is acquired.[2,5] Congenital diverticula are very rare with a 0.014% of incidence.[3,6] Acquired diverticula are often multiple and are seen in the mesoappendix.[7] Congenital diverticula are generally single and are seen at the antimesenteric side of the appendix.[2,6]

On the contrary to the literature, in our case, the diverticula were both multiple and located unexpectedly at the mesenteric side of the appendix. Furthermore, on the walls of all fistulas tracts, there were layers of serosa and muscle, in addition to colonic epithelium according to the microscopic examination. There were no acute or chronic findings of any inflammation as well as sequela such as scar or fibrosis which would force us to think about a previous inflammation.

All of the features described supported the fistulas and diverticula to have been congenital in the present case, and this special and unique condition was described as "congenital multiple caeco-appendiceal fistulas and diverticula" for the first time in the literature.

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LETTER TO THE EDITOR

Preoperative Detection of Novel Predictors for Lymph Node Metastasis in Early Colorectal Cancer

Jung Wook Huh · Young Jin Kim

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Dear Editor,

We thank Dr. Shukla and colleagues for their interest in our paper.[1] Due to the recent advances in endoscopic techniques, T1 or T2 tumors may potentially be cured by non-invasive resection of the tumor with the appropriate selection of patients. Preoperative detection of novel predictive factors for lymph node metastasis from early colorectal cancer may be the most important issue for obtaining a better prognosis in this group of patients. Unfortunately, the recent preoperative clinical studies that have employed imaging modalities or histopathological examination have fallen short of our expectations in terms of detecting high risk factors in a preoperative setting.

In last year's August issue of the *Journal of Gastrointestinal Surgery*,[2] we observed that the incidence of lymph node metastasis for all the patients with early colorectal cancer was a considerable figure at 21.0% (14.5% for T1 and 23.9% for T2). As we mentioned in our study, the presence of lymphovascular or perineural invasion was associated with lymph node metastasis, and the latter was the only independent factor that could predict the survival of patients with early tumor. Therefore, the preoperative identification of high risk factors for lymph node metastasis in patients with early tumor cannot be emphasized too strongly. We agree with the comment of Dr. Shukla and colleagues that both lymphovascular and perineural invasion are best detected by pathological examination after surgical resection, and no imaging modalities that can detect them are currently available. Furthermore, developing new technologies for enhancing the accuracy of detecting these high risk factors in preoperative biopsied specimens may be essential in the future clinical setting. New research in the field of pathology as well as radiology is needed to facilitate the evaluation of the high risk factors for survival in patients with colorectal cancer in the preoperative setting.

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LETTER TO THE EDITOR

The Clinical Significance of Lymphovascular and Perineural Invasions in Patients with Colorectal Cancer

Parul J. Shukla · Junjun Ma · Rhonda K. Yantiss · Jeffrey W. Milsom

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We read with interest the study of Huh et al. regarding the relationship between the presence of lymphovascular or perineural invasion and likelihood of detecting lymph node metastases in patients with T1 and T2 colorectal cancer.[1] The authors reported that lymphovascular or perineural invasion was an independent predictor of lymph node metastasis, which, in turn, was the only significant independent predictor for both overall and disease-free survival in their patient cohort.

The significance of perineural invasion and lymphovascular invasion in node-negative colorectal cancer has been described by Desolneux et al.[2] They suggested that these parameters could be used to identify patients with high-risk node-negative colorectal cancer, in whom adjuvant therapy should be considered.

While vascular invasion, perineural invasion, and postoperative CEA level have been reported to be significant predictive factors for early relapse of colon cancer postoperatively, only perineural invasion is considered to be a significant predictor among rectal cancer patients.[3] Perineural invasion may also be a source of distant tumor spread well beyond the extent of any local invasion and may be the sole route of metastatic spread in some tumors.[4] Recognizing patients at high risk for early relapse is important, and detection of perineural invasion may help identify patients for enhanced follow-up and a therapeutic program.[3]

It is likely that lymphovascular and perineural invasions are currently underreported by pathologists. A recent study that evaluated the predictive value of perineural invasion showed that the presence of perineural invasion was noted in less than 0.5% of initial pathology reports, but 22% of tumors were found to show perineural invasion upon re-review of the original tissue sections.[5] Detection of lymphovascular and peritumoral invasions may be particularly problematic if histologic examination is largely limited to areas rich in infiltrating glands owing to destruction of tissue architecture by the tumor as well as desmoplasia and inflammation. For this reason, pathologists should examine a minimum of four sections obtained from the advancing front of the tumor where nerves, blood vessels, and lymphatic channels are readily identified and evaluated for the presence of invasion.

Unfortunately, both perineural and lymphovascular invasions are best detected by pathological examination, and no imaging modalities to detect them are currently available. For this reason, it is not feasible to preoperatively determine which patients would benefit from radical surgery, rather than limited resection (as has been suggested by the authors). The implications of these findings are chiefly of prognostic value and may impact the decision to consider postoperative chemotherapy in a select group of patients.[6]

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LETTER TO THE EDITOR

Regarding "Laparoscopic Repair of Large Hiatal Hernia Without Prosthetic Reinforcement: Late Results and Relevance of Anterior Gastropexy"

Stavros A. Antoniou · George A. Antoniou · Rudolf Pointner · Frank Alexander Granderath

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Dear Editor,

We read with great interest the article by Poncet et al., reporting their results of laparoscopic repair of large hiatal hernias without mesh reinforcement.[1] In a prospective series of 89 patients, the authors achieved early and late recurrence rates of 4.5% and 15.7%, respectively, over a follow-up period of more than 4 years. The authors concluded that large hiatal defects may be repaired by simple cruroplasty with satisfactory results.

However, there are several shortcomings of the study that need to be addressed, in order to evaluate the outcomes and make objective conclusions. Although the study included a fairly large number of patients with a long follow-up, the authors failed to report on the proportion of patients who underwent barium esophagogram at long-term follow-up. Although many patients with anatomical recurrence present with recurrent or new onset foregut symptoms, up to 21% may be asymptomatic.[2] Furthermore, a significant percentage of 12.3% was lost to follow-up, raising questions on whether the results were biased by "non-comers". If we exclude four patients who died during the follow-up period, the overall recurrence rate is as high as 21.2%.

Current data support that mesh application significantly reduces recurrence rates after laparoscopic antireflux surgery. There are currently three available high-quality randomized trials and numerous prospective and retrospective observational studies which demonstrate significantly higher recurrence rates for patients undergoing non-mesh repair.[3–5] Furthermore, there are no randomized studies disputing these results.

Indeed, mesh hiatoplasty carries significant risks, and routine application cannot be recommended. Dysphagia seems to occur more frequently following prosthetic hiatal reinforcement, although it seems to relinquish with time. Moreover, revisional surgery for failed antireflux surgery with mesh application is a difficult task with high morbidity and the potential need for esophagectomy or gastrectomy.[6] Mesh erosion may have been overestimated in the past, considering that this complications occur in 0–0.49% of patients in large series.[7,8]

Considering these facts, it seems reasonable to weigh the advantages and disadvantages of mesh application according to the underlying pathology, the patient's age and functional status, co-morbidities, the size of the hiatus, and the structural quality of the crural pillars. Identification of patient groups which will more likely benefit from hiatal reinforcement remains a continuing field of investigation.

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LETTER TO THE EDITOR

Dor Against Toupet Fundoplication After Heller Myotomy. Laparoscopic Technical Improvements and Endoscopic Support

Stefano Pontone · Paolo Urciuoli · Paolo Pontone · Filippo Custureri

Received: 28 January 2011 / Accepted: 20 June 2011 / Published online: 1 July 2011

To the Editor:

We read with great interest the review by Patti and Herbella[1] published in your journal regarding the identification of the best fundoplication technique after laparoscopic Heller myotomy for esophageal achalasia in order to effectively prevent gastroesophageal reflux. We congratulate the authors that performed a very exhaustive analysis of the various surgical techniques in order to highlight the most appropriate one. The authors' conclusions—that emphasize surgery versus other minimally invasive techniques—do not give a conclusive answer. Thus, we have some questions for the authors to deepen conclusions and justify their technical choice.

First of all, previous studies show that the Dor fundoplication, against Toupet fundoplication, should be preferred[2, 3], because it does not require posterior dissection, and it covers the exposed mucosa. Furthermore, the surgical technique, also in the Dor fundoplication, adopted standardized key points in order to maintain the myotomy margins well separated as follows: (1) isolation of the gastroesophageal junction limited to the anterior aspect and avoiding the division of the short gastric vessels, (2) extension of the myotomy to the gastric lesser curvature, (3) suturing of the apex of the fundus to the apex of the myotomy, and (4) fixation of the anterior aspect of the gastric fundus to the two edges of the myotomy with two rows of six to eight stitches each.[4] However, the operating time and incidence of complications related to the different surgical procedures are not taken into account.

The authors did not specify the endoscopic procedures performed before surgery (balloon dilatation and botulinum toxin injection). It would be important to know the incidence of intraoperative complications (perforation, bleeding, etc.) in relation to previous endoscopic treatment. Surgical procedures for achalasia, in most cases, have been indicated for failure or recurrence after attempted multiple pneumatic dilatation or botulinum toxin injection that may induce a transmural stricture that had involved the normal anatomic planes with scar formation. Several studies[5] suggest that, considering the low morbidity of the operation versus only temporary relief offered by botulinum toxin injection and the increased risk of pneumatic dilation, the clinician should choose a laparoscopic Heller myotomy as the primary treatment for achalasia and that the other two modalities should only be used for patients who cannot tolerate an operation.

In our experience, intraoperative endoscopy is performed simultaneously with the myotomy to assess the adequacy of the myotomy and to detect esophageal mucosal tears. In addition, when previously placed over the cardia, the endoscope allows a correct visualization of incidental perforation margins. Thus, when this complication occurred, it is not necessary to convert into laparotomy, but laparoscopic repair is facilitated.[6, 7] Furthermore, intraoperative endoscopic pneumatic testing during laparoscopy, which permits the evaluation of air leaks, could be a safe and rapid means of testing esophageal integrity after myotomy and timely repairing any complication.

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In conclusion, although endoscopic treatment today plays a key role in the minimally invasive treatment of achalasia, surgery, thanks to recent technical improvements, should be considered as the first-line treatment. The late results of myotomy are also significantly better than those of forceful dilation because, with the latter method, most patients need subsequent dilations for recurrences of the symptoms. Thus, endoscopy could be a valid support to the laparoscopic approach reducing the incidence and relevance of complications.

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LETTER TO THE EDITOR

Patti MG, Herbella FA. Fundoplication After Laparoscopic Heller Myotomy for Esophageal Achalasia: What Type? J Gastrointest Surg. 2010 Sept.;14(9):1453–8

Marco G. Patti · Fernando A. M. Herbella

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Dear Editor,

We would like to thank Dr. Pontone and his colleagues for their interest in our review paper[1] and their letter to this esteemed journal. They raise some important questions that we will be glad to answer even though they are unrelated to the manuscript we wrote. Our goal was not to review the treatment of esophageal achalasia, but rather to assess the role of fundoplication after the myotomy, and to identify the best procedure that limits postoperative reflux while avoiding recurrent dysphagia.

Dr. Pontone et al. raise three points: (1) the superiority of the Dor fundoplication over the Toupet fundoplication, (2) the influence of previous endoscopic therapy on the outcome of the myotomy, and (3) the use of intra-operative endoscopy. There is no definite evidence that shows the superiority of the Dor fundoplication over the Toupet fundoplication. Since both procedures seem to be very similar in terms of clinical outcome and complications, the choice is based on surgeons' preference. Although we prefer an anterior wrap, others have excellent results with a posterior wrap.[2]

Many studies have shown that previous therapy, either intra-sphincteric injections of botulinum toxin or pneumatic dilatation, makes the myotomy more difficult to perform because of the loss of the normal anatomic planes. In addition, the results are less predictable and often worse than those obtained in patients who have never been treated before the myotomy.[3,4]

We agree that intra-operative endoscopy may help identify the esophago-gastric junction, guiding the extent of the myotomy.[5] However, with more experience, this step can be avoided in most cases.

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LETTER TO THE EDITOR

D2 Lymphadenectomy (Over-D1 Dissection) for Advanced Gastric Cancer Is an Evidence-Based Procedure

Federico Bozzetti

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Dear Editor,

I read with interest the excellent review by Maduekwe and Yoon[1] on the evidence-based literature regarding the surgical treatment of gastric adenocarcinoma, and I appreciated the way the authors carefully scrutinized the literature to find robust data supporting their conclusions.

However, I wonder that in the section concerning the lymph node dissection, the authors did not mention the recent update of the Dutch Gastric Cancer Group trial[2] which involved 711 patients. Songun et al.[2] reported that, after a 15-year follow-up, gastric cancer-related death rate was significantly higher (p=0.01) in the D1 group (48%, 182 patients) compared with the D2 group (37%, 123 patients), whereas death due to other diseases was similar in both groups. Local recurrence was 22% (82 patients) in the D1 group versus 12% (40 patients) in D2, and regional recurrence was 19% (73 patients) in D1 versus 13% (43 patients) in D2, a difference that was statistically significant (p=0.01).

I think that the oncologic advantage of the D2 lymphadenectomy is now validated by a randomised clinical trial, and the likely explanation of the delayed appearance of such benefit is related to two major problems with the study, namely, the higher postoperative mortality of the D2 versus the D1 procedure (10% versus 4%, respectively) and the non-negligible percentage of contamination and noncompliance (6% and 51% in D1 and D2, respectively). This means that the trialists have effectively compared a D1 procedure with a D1.5–2 dissection.

Many western surgeons now accept that the rationale of an extended lymphadenectomy is finally evidence based even if there is some reluctance to properly define this procedure as a formal D2 dissection. In fact, since there is an objective difficulty of performing a complete dissection of all the second lymph node tier (even in a prospective study with a superb quality control as the Dutch Gastric Cancer Group trial), several pathologic studies reported that a D2 dissection usually removes at least 30–35 lymph nodes.[3–6] Accordingly also the TNM classification places a higher emphasis on the number of retrieved lymph nodes rather than on their anatomical site,[7] and it may be preferable to define such extended dissection as "over-D1"[8] to avoid confusion with the Japanese terminology.

In conclusion, it should be clearly acknowledged that a lymphadenectomy extended beyond the first tier, a procedure originally performed and popularized in Japan but finally validated in Europe through a large randomised clinical trial, should now represent the standard surgical approach for advanced gastric cancer, regardless of its denomination.

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LETTER TO THE EDITOR

Conservative Management of Isolated Sectoral Duct Injury With Bile Leak (Type C Injury): Important and Essential Initial Step in the Management, Not an Option

Vishal Gupta · Abhijit Chandra

Received: 29 April 2011 / Accepted: 8 August 2011 / Published online: 16 August 2011

Dear Editor,

We read the article by Mazer et al.[1] with great interest. This study adds to the emerging evidence for the conservative management of isolated sectoral duct injury.[2] Isolated injury to the right sectoral duct may (Strasberg type C) or may not (Strasberg type B) present with bile leak. There is no universally accepted single modality of treatment for these injuries.[3] Detected intraoperatively, these ducts may be ligated safely, thus actually converting type C injury into type B injury, with the patient usually remaining asymptomatic and the undrained liver becoming atrophied without major sequelae.[4] However, some advocate repair in all the cases irrespective of the size of the duct.[5]

Few points need to be clarified before it can be concluded that conservative management is an important *option* for patients with an isolated right posterior bile duct injury as suggested by Mazer et al.[1]

First, follow-up is very short with a mean of 8.2 months (2 to 14 months). Even after surgical repair, a minimum follow-up of 5 years is considered optimum.[6] Second, three patients underwent biliary stenting. How stenting is useful in such cases, where by definition of Strasberg type B or C (all cases in this report), hepatoenteric continuity of aberrant sectoral or right hepatic duct is lost. These injuries are classically suspected when the biliary system is apparently normal on ERCP, in the presence of biliary leak. Did the biliary fistula respond to stenting in these cases? Third, results of this study are considered as "excellent". Results of surgical repair are considered as excellent when liver enzymes and the biliary ductal system are normal in an asymptomatic patient.[7] Three out of five patients had elevated serum alkaline phosphatase on follow-up. This may be due to ongoing liver atrophy, and in such cases, gamma glutamyl transpeptidase may be more informative regarding the development of biliary stricture.

Lastly, it is concluded that the conservative management is an important *option* for patients with an isolated right posterior bile duct injury. In fact, conservative management with radiological and endoscopic interventions is an *essential initial step* in the management of all patients presenting with bile leak even if surgical repair is planned later on. This allows the local sepsis to subside allowing safe repair.[5] In addition, delayed approach in such situation allows the fistula to close by itself, and if repair is deemed necessary, it can be performed on the dilated duct.[7] In this series, all patients had bile leak, i.e. type C injury.

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LETTER TO THE EDITOR

Response to Gupta et al. Regarding Non-operative Management of Right Posterior Sectoral Duct Injury

Laura M. Mazer · Elliot Tapper · Juan M. Sarmiento

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Dear Editor,

Thank you for the opportunity to reply to the letter received from Gupta et al. regarding our paper (Non-Operative Management of Right Posterior Sectoral Duct Injury Following Laparoscopic Cholecystectomy). We appreciate their comments and agree with much of their analysis.

1. Gupta et al. suggest that conservative management is best viewed as an "initial step" rather than a definitive treatment option. We appreciate the distinction they are drawing, and we do agree that a period of conservative management to allow sepsis to subside is essential in all patients with an isolated sectoral duct injury. As we mention in our Discussion section, the first patients we describe were treated conservatively as a step towards surgical management. The surgery was delayed, however, and in the interim, the patients experienced complete symptom resolution. We agree that all patients should be given a trial of conservative management, which in most cases is indicated due to the local inflammatory consequences of the bile leak. However, we caution against considering this trial as strictly an initial step towards more definitive management. The purpose of our small case report series is to suggest that for some patients, this initial conservative phase may be the only treatment required. Obviously, this treatment cannot go on forever, and a surgical option should be entertained in case of failure.
2. The authors also point out that the follow-up in our series is short. We agree that long-term management is desirable and will continue to follow these patients in clinic as long as possible.
3. Gupta et al. also question the value of biliary stenting for a Strasberg type B or C injury. As we are a major referral center, we receive these patients after initial stenting in outside institutions. We have described this in detail for data accuracy, and we agree that the value of stenting in this setting is very limited.
4. Finally, the authors ask whether gamma glutamyl transpeptidase (GGT) might be a better indication of biliary stricture. We do not routinely check GGT in our patients, but we had alkaline phosphatase data in every one of them. We agree with the authors that the elevated alkaline phosphatase seen in three of our patients likely represents ongoing liver atrophy with compensatory hypertrophy, as evidenced by the imaging and the clinical data we present. One point of caution is the fact that many patients with successful bile duct repair will go on to have abnormal (higher) values on their liver function tests. In a very recent series by Fialkowski et al.[1], up to 29% of

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patients in their series of consecutive bile duct repairs (n=113) had a higher than the upper reference value of alkaline phosphatase at some point in their postoperative surveillance, a number that is clearly higher than their postoperative failures and suggests that new (higher) reference values need to be defined for this population and in no way implies anastomotic failures. Furthermore, the "abnormal" values will decrease as the length of the follow-up extends. The clinical and imaging data need to be taken into consideration to judge operative results. In our series, we follow these numbers, but the clinical evidence has been strong enough to continue non-operative therapy.

Again, we thank Dr. Gupta and colleagues for their thoughtful comments on our paper.

Sincerely,

Laura Mazer

Elliot Tapper

Juan M. Sarmiento

Reference

1. Fialkowsli EA, Winslow ER, Scott MG, Hawkins WG, Linehan DC, Strasberg SM. Establishing "normal" values for liver function tests after reconstruction of biliary injuries. J Am Coll Surg 2008;207:705–9.