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The Ileal Pouch Anal Anastomosis: To Divert or not to Divert? The Case for Diversion

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Abstract The ileal pouch anal anastomosis is a high-risk anastomosis with a high rate of complications. Because of this proximal diversion has often been done when performing this operation. Recently the practice of proximal diversion has been questioned, noting the high rate of complications associated with the stoma and stomal reversal. However, the cumulative data does suggest that an undiverted ileal pouch anal anastomosis has a higher leak rate and is associated with increased pelvic sepsis. Because of the severity of this complication proximal diversion is still advocated in the majority of cases.

Keywords Ileal pouch anal anastomosis · Diversion · Risk management

The decision to perform proximal diversion following an ileal pouch anal anastomosis (IPAA) is an exercise in risk management. The major advantage of a one-staged procedure (i.e., no diversion) is the avoidance of a stoma and all of its associated complications. Furthermore, there is no second procedure, thus avoiding these associated costs and cumulative complications. However, when patients are left undiverted following an IPAA, they are at risk for the most dreaded complication: an uncontrolled anastomotic leak with the potential for life threatening sepsis. Proponents of the one-staged procedure focus largely on the associated morbidity and costs of a second procedure while advocates of the two-staged procedure are more concerned with implications of an uncontrolled anastomotic leak. Ironically, while much is written in the literature on this question, the majority of these procedures are still done with proximal diversion.

Anastomotic leak remains a major source of morbidity and the leading cause of mortality following elective colon and rectal surgery. Known risk factors for an anastomotic leak include a low pelvic anastomosis, hypoalbuminemia, recent weight loss, and high-dose steroids. Since nearly 90% of patients having an IPAA have chronic ulcerative colitis, many patients having this operation will have some or all of these risk factors. Tjandra et al.[1] from the Cleveland Clinic reported on a case matched series of 50 patients without proximal diversion compared with 50 patients who were proximally diverted. It is important to note that these patients were not randomly selected and were assumed to be at relatively low risk based on preoperative and intraoperative criteria. Nevertheless, 14% of patients left undiverted developed pelvic sepsis compared with 4% in the diverted group. Furthermore, 6% of the patients not diverted required a laparotomy due to uncontrolled sepsis, compared with 0% in the diverted group. An additional 10% of patients undiverted had a prolonged ileus or fever of unknown origin, compared with 4% in the diverted group, which may have represented a low-grade leak. These differences seemed particularly pronounced in patients on high-dose steroids (>20 mg/day

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prednisone). These data lead authors to conclude that a single-staged procedure should only be done under highly selected circumstances. Williamson et al.[2] also reported on 100 patients, 50 with diversion and 50 without. Similarly, these patients were not randomized so the patients without diversion were actually a favorable group. While overall complication rates were similar, of the seven patients with pelvic sepsis in the diverted group, none required surgery. This was in contrast to the 11 patients with pelvic sepsis in the undiverted group, seven of which required surgery and three of which had diffuse peritonitis. Based on these concerning data, the authors expressed concern that routine omission of a diverting stoma may lead to increased operative mortality. While an increased mortality has never been shown in other series, this may be due to underpowered studies. However, based on our knowledge from other colon and rectal procedures, it would stand to reason that uncontrolled sepsis may increase operative mortality, although large numbers may be needed to fully assess this concern. Even in reports supporting a one-stage operation anastomotic leak rates in the 10–12% range [3] are common, and in a recent meta-analysis, the risk of anastomotic leak was 2.5 times more likely for undiverted patients.[4] This higher rate of anastomotic leak after a single-staged procedure is very concerning and is the major reason that most IPAA are still done with proximal diversion.

Pelvic sepsis may have profound effects on pouch function and quality of life. Farouk et al.[5] from the Mayo Clinic reported on 1,508 patients having an IPAA. Approximately 5% of these patients experienced pelvic sepsis. When compared with the 95% of patients without pelvic sepsis, patients with an intact pouch who had experienced pelvic sepsis were more likely to be incontinent, were more likely to wear a pad, and were more restricted according to certain quality of life parameters. Furthermore, patients with pelvic sepsis were approximately five times more likely to experience pouch excision. Based on these data, these authors concluded that avoidance of pelvic sepsis was critical to success and therefore also advocated the use of proximal diversion.

What about the ileostomy reversal? In 1999, the University of Minnesota reported on 366 ileostomy closures, 70% after an IPAA.[6] In this group, 28% experienced a complication, which was higher than most expected and suggested that this procedure was more morbid than previously appreciated. However, the authors concluded that while the overall complication rate seemed high, the rate of serious complications was less than 5% and therefore continued to advocate the loop ileostomy for a high-risk pelvic anastomosis. More recently, the Cleveland Clinic reported an 11% complication rate for over 1,500 patients having an ileostomy reversed with a median length of stay of only 3 days, which are very favorable numbers.[7] Furthermore, 80% of these procedures were done through a small peristomal incision. In general, therefore, the reversal of a loop ileostomy can be done with low morbidity. Furthermore, even when serious septic complications do occur, the sepsis is usually in the upper abdomen and can be fixed without affecting the pouch and its ultimate function. This is in stark contrast to pouch complications, which are notoriously difficult to operatively repair.

In summary, the IPAA is a complicated operation that is often performed on patients who are chronically ill. Complications are common. Even under the best of circumstances, anastomotic leaks are not uncommon and seem to be significantly higher in patients after a single-staged procedure. The sequelae of an uncontrolled anastomotic leak should not be underestimated with the potential to even be life threatening. If a single-staged procedure is to be done, the patient needs to be fully informed of the potential complications and the increased risk of anastomotic leak. I personally have found that once informed of the reason for proximal diversion, most patients are understanding and prefer the conservative approach. Furthermore, the loop ileostomy is reasonably well tolerated and can be reversed with relatively low morbidity. Remember, while the decision to divert is an exercise in risk management, it is ultimately the patient who is assuming the risk. I favor diversion.

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Diverting Ostomy with Pouch Procedure: "Causes More Morbidity Than It Prevents!"

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Abstract Temporary diverting ileostomies are routine performed as a "protective" adjunct to ileal pouch procedures. The need for routine diverting ileostomies has been challenged because of the risks associated with their management. A review of the available data and my personal experience demonstrates that diversion results in lower pouch leaks but a higher instance of pouch failure and strictures. The creation of ileal pouches without an ileostomy is preferable under selective conditions with quite acceptable results.

Keywords Diverting ostomy with pouch procedure · Chronic ulcerative colitis · Morbidity

Since its original description by Parks and Nicholls in 1978, restorative proctocolectomy (RPC) with an ileal pouch–anal anastomosis (IPAA) has become the gold standard in the surgical management of chronic ulcerative colitis (CUC) and familial polyposis (FAP). As the operation is lengthy, requiring many suture lines under varying tension, and is frequently performed in a less-than-healthy patient population, perioperative septic and anastomotic complications are, unfortunately, relatively common. Pelvic sepsis accompanying this operation has been associated with poor pouch function, anastomotic stricture, greater infertility in females, and death. In an effort to minimize the risks for septic complications, a temporary loop ileostomy is traditionally formed at the initial operation, diverting the fecal stream away from the newly created pouch. The ileostomy is ultimately taken down in a second operation 6 weeks to several months after the initial operation once the pouch has been demonstrated to have "healed." As surgeons have become more experienced with the procedure and stapling techniques have advanced, the need for the creation of the temporary ileostomy has been challenged.

Proponents for the diverting ileostomy feel its benefits outweigh the risks. Namely:

- There is minimum morbidity associated with the stoma.
- The consequences of a pouch leak are minimized.
- Diversion allows for sphincter recovery.
- The patients have a better appreciation of the operation after having lived with a stoma.

Those favoring the omission of the ileostomy feel quite differently; the risks outweigh the benefits. A single-stage operation:

- Requires one hospitalization
- Avoids complications of the stoma
- Avoids complications of ostomy takedown (leak, anastomotic stricture, bowel obstruction, etc.)
- Avoids potential vascular compromise to the pouch
- Avoids disuse atrophy effect on pouch and anastomosis

One way to ask the question as to the relative need for a diverting stoma is:

> is the need for diversion intrinsic to the operation itself because of technical aspects of pouch creation, anastomotic healing, and/or recuperation of sphincter function

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is the need for diversion determined by the conditions under which it is performed (malnutrition/weight loss, hypoalbuminemia, anemia, steroid use and immunosuppressants)?

As one would expect when competing opinions continue for years, the scientific literature has not reached a definitive conclusion on this topic. To date, there have been 18 studies that have addressed the issue of the need for diverting ileostomy. Among these, there was only one randomized control trial, 11 prospective nonrandomized studies, five retrospective reviews, and a recent meta-analysis.[1] A major stumbling block in designing, conducting, and analyzing these studies is the inability to control for matching criteria in this diverse patient population (age, sex, diagnosis, previous colectomy, surgeon, immunosuppressant therapy, colitis activity, pouch design and anastomotic technique, and follow-up).

The results from these less-than-perfect analyses can be summarized as follows:

- A diverting ileostomy results in an approximate twofold decrease in pouch leak without an improvement in "pouch related sepsis."
- There does appear to be detrimental consequences of the ileostomy. Pouch failure and anastomotic strictures occur up to three times more frequently in diverted patients and total length of hospital stay is longer.

In my practice, I approach each patient individually considering them for one of several operative approaches. For the 5-year period (2002 thru 2007), I performed 306 RPC–IPAAs for CUC or FAP in the following distribution:

- 30% single stage—for well patients
- 39% standard two-stage procedure (RPC–IPAA with ileostomy, then ileostomy takedown)—for moderately ill–immunosuppressed patients
- 26% *variant* two-stage (colectomy–end ileostomy, then completion proctectomy–IPAA *without* ileostomy) done for ill, debilitated patients
- 5% three stages (colectomy–ileostomy, then completion proctectomy–IPAA with ileostomy, and then ileostomy takedown) for patients who, for technical issues, could not have the variant two-stage.

In order to answer the question I raised earlier, "is it the operation itself or the patient which poses the risk and need for diversion," I combined the variant two-stage group with the single-stage group. As the completion colectomy and pouch were performed in this group >6 weeks after their colectomy, at a time when they were now well, not taking immunosuppresants, and either no longer taking steroids or on a low dose, the pouch was created in these patients without stomal diversion. Hence, these patients received a *single-stage pouch*.

Of the 176 patients (56% of total) who had an ileal pouch created *without* a diverting ileostomy, there were only four leaks (2.3%). Of these, one patient required subsequent ileostomy diversion and three required prolonged TPN (3–5 months). All pouches are intact.

As to the answer to the question as to whether the need for diversion is intrinsic to the operation itself or the conditions under which it is performed, I believe it is clearly a combination of both. RPC–IPAA *without* ileostomy is preferable under selective conditions with quite acceptable results. Although leaks may occur, function and longevity is preserved. RPC–IPAA *with* ileostomy is appropriate for those patients at risk for perioperative infectious and wound healing complications realizing that ileostomy creation, management by the patient, and its takedown are not without risk. IPAA with ileostomy is associated with higher anastomotic strictures, a greater pouch failure rate, and longer hospitalizations.

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Colonic Trauma: Indications for Diversion vs. Repair

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Abstract
Introduction The management of colonic trauma has evolved considerably over the past several decades. An appreciation of best-evidence practices is paramount to the optimal management of these injuries.
Materials and Methods Literature review of pertinent clinical literature regarding the management of colonic trauma was performed.
Results Based on available level I evidence, primary repair of all colorectal injuries should be attempted, irrespective of associated risk factors. Diversion should only be considered if the colonic tissue itself is deemed inappropriate for repair, as in the setting of prohibitive edema or questionable perfusion of the tissues. Diversion does remain the standard of care for the management of extra-peritoneal rectal injuries, although this practice is under active investigation.
Conclusion Level 1 evidence has failed to demonstrate that routine proximal diversion, once considered the standard of care for the treatment of all colorectal trauma, affords benefit for victims of the injuries. While utilization of these practices may prove beneficial in select circumstances, the routine utilization of proximal diversion for the treatment of colorectal injuries is unwarranted.

Keywords Colonic trauma · Diversions · Repair

The mortality associated with colonic trauma has decreased considerably over the last half century; from 40% during World War II to 1–3% over the last several decades. Colon-related morbidity, however, remains a significant concern following these injuries. Abdominal complication rates of 24% are still reported,[1] even as the surgical management of colonic trauma has continued to evolve. In the period after World War II, diversion techniques were routinely employed in the treatment of these injuries, with the rationale that this practice would decrease the rates of subsequent abdominal complications. Following success with selective utilization in the 1970s and more liberal use at academic centers beginning in the 1990s, however, primary repair has replaced routine diversion as the modern operative management of choice for colonic trauma. This evolution has been fueled by contemporary research demonstrating that the use of diversion versus primary repair increases the risk for subsequent abdominal complications.

Several factors have been considered important for the decision between diversion and primary repair in the surgical management of colon injuries. The location of injury, once believe to be an important issue in this decision, is now known to be of little significance. The mechanism of injury has also been proven to be of lesser importance. Other proposed risk factors have included transfusion requirements, physiologic condition of the patient, and antibiotic utilization. Of all the proposed considerations in surgical management, however, the

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degree of colon injury has been among the most widely discussed. Traditionally, investigators have divided these injuries into destructive (>50% of the colonic circumference compromised or colonic vascular compromise) or non-destructive subtypes for consideration.

For non-destructive lesions, it has now been widely accepted that primary repair should be attempted whenever possible. Class I evidence has demonstrated that the use of diversion for these injuries, irrespective of associated risk factors, is associated with an increased incidence of complications.[2] In fact, no study in the modern era has ever linked the use of diversion for non-destructive colon lesions to any patient benefit. Considering that the complication rate of subsequent colostomy closure is reported as 15%,[3] it is only reasonable to accept the rationale for primary repair of all non-destructive colon injuries.

The optimal surgical management of destructive colonic lesions was once a more contentious topic. Based on recent studies, however, the traditional practice of routine diversion has now largely been replaced by that of primary repair. The result of one of the largest of these trials was reported by the AAST in 2001.[1] In this multicenter, prospective examination of 297 patients with destructive colon injuries, the authors found that abdominal complications occurred in 24%. When they further evaluated 41 potential risk factors for these adverse events using logistic regression analysis, they found that only (1) blood transfusion requirement of greater than four units over 24 h, (2) single generation cephalosporin prophylactic antibiotic use, and (3) severe contamination at the time of operation were independent risk factors for abdominal complications. The type of surgical management was not found to affect the incidence of these adverse events. In fact, even among "high risk" patients (shock, penetrating abdominal trauma index >25, operative delay >6 h, at least 6-unit transfusion or severe contamination), colon-related deaths occurred in 4.5% of patients undergoing diversion and none of those undergoing primary re-anastamosis after resection (p=0.03).

In 2003, a subsequent Cochrane review[2] was conducted to further investigate the role of operative management for colonic injuries. The investigators included six trials, consisting of 705 patients in their review. Their intensive analysis confirmed that the use of primary repair, compared to diversion, was associated with a significant decrease in (1) overall complication rate, (2) total infectious complications, (3) abdominal infections including dehiscence, and (4) wound complications excluding dehiscence. These findings further support the position that primary repair of all colon injuries should be attempted at initial operation, irrespective of present risk factors.

Although routine attempts at primary repair of all colon injuries are supported by well-designed studies, the data supporting this practice for rectal injuries is less well established. The traditional principles of management for rectal trauma consisted of colostomy, rectal washout, and presacral drainage. None of these practices, however, are supported by class I, II, or even III evidence. In fact, this approach has been shown to be of no benefit.[4,5] Most trauma surgeons have, subsequently, abandoned the routine use of these traditional practices. At our own institution, we utilize diversion only in cases of rectal injury in which the repair is deemed tenuous or in the setting of an unrepaired extraperitoneal rectal injury. Even the latter indication is controversial. An ongoing AAST prospective, multicenter trial for non-diversion management of extraperitoneal penetrating rectal injuries may provide significant information regarding the optimal surgical management for these injuries in the future.

Based on available level I evidence, routine primary repair should be attempted in the initial surgical management of all traumatic colon injuries, irrespective of associated risk factors. Diversion of colonic injuries should only be considered if the colon tissue itself is deemed inappropriate for repair, as in the setting of severe edema or questionable ischemia after damage control procedures. Primary repair of all intraperitoneal rectal injuries should also be attempted, with proximal diversion utilized only for repairs that are deemed tenuous. The role of diversion in the management of unrepaired extraperitoneal rectal injuries is presently an accepted standard of care, although this practice is being actively investigated.

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The Incidental Asymptomatic Pancreatic Lesion: Nuisance or Threat?

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Abstract
Introduction Although asymptomatic pancreatic lesions (APLs) are being discovered incidentally with increasing frequency, their true significance remains uncertain. Treatment decisions pivot off concerns for malignancy but at times might be excessive. To understand better the role of surgery, we scrutinized a spectrum of APLs as they presented to our surgical practice over defined periods.
Methods All incidentally identified APLs that were operated upon during the past 5 years were clinically and pathologically annotated. Among features evaluated were method/reason for detection, location, morphology, interventions, and pathology. For the past 2 years, since our adoption of the Sendai guidelines for cystic lesions, we scrutinized our approach to *all patients* presenting with APLs, operated upon or not.
Results Over 5 years, APLs were identified most frequently during evaluation of: genitourinary/renal (16%), asymptomatic rise in liver function tests (LFTs; 13%), screening/surveillance (7%), and chest pain (6%). APLs occurred throughout the pancreas (body/tail 63%; head/uncinate 37%) with 48% being solid. One hundred ten operations were performed with no operative mortality including 89 resections (distal 57; Whipple 32) and 21 other procedures. Morbidity was equivalent or better than those cases performed for symptomatic lesions during the same time frame. During these 5 years, APLs accounted for 23% of *all* pancreatic resections we performed. In all, 22 different diagnoses emerged including non-malignant intraductal papillary mucinous neoplasm (IPMN; 17%), serous cystadenoma (14%), and neuroendocrine tumors (13%), while 6% of patients had >1 distinct pathology and 12% had no actual pancreatic lesion at all. Invasive malignancy was present 17% of the time, while carcinoma in situ or metastases was identified in an additional eight patients. Thus, the overall malignancy rate for APLs equals 24% and these patients were substantially older (68 vs 58 years; $p=0.003$). An asymptomatic rise in LFTs correlated significantly ($p=0.009$) with malignancy. Furthermore, premalignant pathology was found an additional 47% of the time. Seven patients ultimately chose an operation over continued observation for radiographic changes (mean 2.6 years), but none had cancer. In the last 2 years, we have evaluated 132 new patients with APLs, representing 47% of total referrals for pancreatic conditions. Nearly half were operated upon, with a 3:2 ratio of solid to cystic lesions. This differs significantly ($p=0.037$) from the previous 3 years (2:3 ratio), reflecting tolerance for cysts <3 cm and side-branch IPMN. Surgery was undertaken more often when a solid APL was encountered (74%) than for cysts (32%). Some solid APLs were actually unresectable cancers. Due to anxiety, two patients requested an operation over continued observation, and neither had cancer.
Conclusion APLs occur commonly, are often solid, and reflect a spectrum of diagnoses. Sendai guidelines are not transferable to solid masses but have safely refined management of cysts. An asymptomatic rise in LFTs cannot be overlooked nor should a patient or doctor's anxiety, given the prevalence of cancer in APLs.

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Keywords Pancreatic incidentaloma · Pancreatic cyst · Pancreatic resection · Pancreatic malignancy · Precursor lesions · IPMN

Introduction

The topic of incidentally identified lesions of the pancreas is rapidly coming to the forefront in pancreatology.[1] While seemingly excessive at times, the increasing use of computed tomography (CT), magnetic resonance imaging, ultrasound (US), and even endoscopy has allowed for the detection of asymptomatic pancreatic lesions that would previously have gone unrecognized. For instance, it is estimated that roughly 150,000 asymptomatic cysts alone are identified yearly in the US,[2] and this probably is an underestimate. For pancreatic practitioners, this phenomenon provides an important opportunity to understand the natural history of these various lesions and any threat they may bring.

Understanding of the asymptomatic pancreatic lesion (APL) is sparse compared to already well-defined "incidentalomas" in organs such as the kidney, lung, or adrenal gland. Other than limited case reports or series,[3–5] the few extended series thus far have focused on either certain topography (proximal gland) or discrete morphology (cysts) of the pancreas. One paper suggests that, when compared to symptomatic disease, early detection and resection of incidental pancreatic head lesions result in more favorable pathologic features and improved long-term survival.[6] Another report advises that asymptomatic cystic lesions of the pancreas, while smaller than symptomatic lesions, still harbor malignant or premalignant features up to 60% of the time.[7] The Sendai Conference guidelines have taken a necessary step in refining the approach to mucinous cystic lesions.[8] A "resect-first" approach is giving way more often today to an evidence-based acceptance of surveillance for select types of cysts. Yet, guidance for management of solid lesions and other cystic entities remains elusive.

The concern is pancreatic malignancy. Long-term survival from adenocarcinoma of the pancreas after pancreaticoduodenectomy is only 10% to 20% with a median survival of no better than 40 months.[9] The possibility of eradicating threatening pancreatic lesions in their earliest stages, as advocated in these preliminary studies, is sensible. However, pancreatic resections are morbid procedures and, in some cases, cause long-term side effects.[6] There are other important considerations. Can we achieve better diagnostic accuracy of both non-mucinous cysts and malignancy? How do we conduct the process of surveillance in the most efficient, safe, and cost-effective manner? What is the optimal timing for intervention for premalignant pathologies? How will minimally invasive surgery apply to incidental lesions? How can we best help anxious and worried patients presenting with an APL?

To date, the full scope of asymptomatic pancreatic lesions has not been completely delineated. Patients and their doctors continue to face real uncertainty and are challenged by decisions which might be made too early or too late. Hoping to understand better the full spectrum and significance of these lesions, we characterized all APLs that have recently presented to our pancreatic surgery practice.

Methods

Using our Institutional-Review-Board-approved prospective database, we reviewed the medical records of all patients who had operations for incidentally identified pancreatic lesions during the 5-year period September 2002 until September 2007. A lesion was defined as incidental if encountered on workup for symptoms not normally associated with pancreatic disease (most notably: obstructive jaundice, acute or chronic pancreatitis, acute epigastric pain, boring back pain, or evidence of steatorrhea). All lesions were felt to arise possibly from the pancreas based on the best interpretation by skilled pancreatic radiologists in conjunction with the surgeons' impressions. Lesions were identified through a variety of methods but can be broadly grouped as either radiologic identification, endoscopic identification, or via abnormal laboratory values (liver function tests, LFTs). All patients were evaluated, and operations were performed by one of the two fellowship-trained pancreaticobiliary surgeons (CMV, MPC) in a high-volume practice (>200 major procedures per annum) for both benign and malignant pancreatic and biliary diseases.

All lesions, solid and cystic, were considered, as was the complete topography of the gland (proximal, central, and distal). Specifically, we looked at the: (1) initial method of detection, (2) subsequent diagnostics employed, (3) location of lesion within the pancreas, (4) predicted size, (5) morphologic considerations, (6) specific interventions chosen, and (7) final pathology. Patients with APLs were also directly compared to those patients presenting with symptomatic pancreatic lesions (SPLs) in our practice over the same 5-year period. The two groups were clinically annotated to age, gender, diagnostics utilized, and final pathologic diagnoses. Characteristics for solid and cystic lesions were also detailed and compared.

Contemporary outcome measures for pancreatic surgical procedures were calculated.[10] Operative mortality was considered as during the index hospitalization and/or up to 30 days postoperatively. Postoperative morbidity was also closely examined for up to 90 days following the procedure. Pancreatic fistula was classified according to the International Study Group on Pancreatic Fistula (ISGPF)

scheme.[11,12] For purposes of classification, the term malignancy was considered to be any lesion harboring either carcinoma in situ (CIS), invasive, or metastatic features. Malignancy occurring within the background of premalignant conditions (e.g., intraductal papillary mucinous neoplasm (IPMN), mucinous cystadenoma (MCA), ampullary neoplasms) was upgraded and classified within the malignant category.

We next extended our analysis by scrutinizing *all* of those patients who were referred with the diagnosis of an APL over the most recent 2-year period, whether they received an operation or not. This time frame (September 2005–September 2007) coincides with the general adoption of Sendai criteria for mucinous cystic lesions among our multidisciplinary team.[8] Since that point, each patient referred with an APL has been collectively evaluated by our team which includes a medical pancreatologist, an advanced gastroenterology endoscopist, a surgeon, specialty pancreatic radiologists, and pathologists. Through this collaboration, the capture of *all referrals for* APLs was consistently annotated. This had not always occurred in the prior 3 years when these patients were more arbitrarily, and unilaterally, assessed. This overall population was divided into two distinct groups who received either operative or non-operative therapy. These cohorts were assessed for the aforementioned criteria and compared to one another.

All statistical analyses were performed using Statistical Package for the Social Sciences 16.0 for Windows (SPSS, Inc. Chicago, IL, USA). Analyses of changes within groups were compared using the χ^2 statistical test. Analyses of changes between groups were compared using the standard Student *t* tests. Statistical significance was accepted at a p value <0.05 for all analyses.

Results

Operative Cases (2002–2007)

Over this 5-year period, 110 patients were operated upon for APLs. Forty-eight percent were solid (n=53). Lesions were identified most commonly during the evaluation of genitourinary and renal symptoms (16%), analysis of asymptomatic elevation of liver function tests (13%), screening or surveillance processes (7%), and assessment of chest pain (6%; Table 1). Vague abdominal symptoms constituted the primary complaint in five patients whose presentations ranged from right lower quadrant pain suspicious for appendicitis, distention after colonoscopy, abdominal pain in the setting of polymyalgia rheumatica, generalized abdominal discomfort, and persistent bloating. These symptoms were not felt to correlate with the actual pancreatic radiographic findings nor were there documented biochemical abnormalities indicative of biliary obstruction, cholangitis, or pancreatitis in these five patients.

Table 1 Most Common Initial Presentations of Asymptomatic Pancreatic Lesions

Presentation	Number	Percent
Genitourinary/renal	17	16
Elevated liver function tests	14	13
Screening/surveillance	8	7
Chest pain	7	6
Cholangitis/cholecystitis/colic	7	6
Postoperative/follow-up	7	6
Trauma/emergency	5	5
Vague abdominal symptoms	5	5
Diverticulitis	4	4
Gastroesophageal reflux	3	3
Anemia	3	3
Integumentary	3	3
Others	27	25
Total	110	100

APLs were found as a result of either radiologic (n=80) or endoscopic (n=16) means and also by abnormal laboratory values (n=14). Within the radiologic group, CT was the leading initial modality, utilized in 63% of patients, followed by endoscopic retrograde cholangiopancreatography (ERCP; 19%), ultrasound (13%), magnetic resonance imaging (MRI; 5%), and, lastly, X-ray (1%). Asymptomatic LFT elevation was further worked up with: US (n=6), esophagogastroduodenoscopy/ERCP (n=4), CT (n=3), or MRI (n=1).

Patients received a median of three radiologic exams (mean 2.7, range 1–4) for workup prior to an operation. Endoscopic ultrasound (EUS) was employed in 21 patients (19%). Of these patients, 15 were ultimately diagnosed with malignant or premalignant conditions. Table 2 reflects the general lack of accuracy of EUS aspiration cytology in determining true malignancy. For instance, atypical or malignant cytology was called on six of the 21 patients (29%), yet only one of them was actually an invasive cancer, and this had been read definitively as *malignant* by the cytologist. However, the other five *atypical* findings were all malignant precursors. Elevation of the carcinoembryonic antigen (CEA) tumor marker (>200 ng/mL) in the aspirate occurred seven times, always in the setting of mucinous cystic pathology.

There was an equal distribution of solid to cystic lesions (48% to 52%). Lesions, when actually derived from the pancreas, were identified throughout the whole gland, with nearly two thirds (63%) occurring in the body and tail and the remainder (37%) occurring in the head or uncinate process. Nearly 12% of patients had no pure pancreatic-based lesion identified after all. These ranged from ampullary and duodenal neoplasms to mesenteric cysts,

Table 2 Operative APLs from 2002 to 2007 Evaluated by EUS

Lesion	IPMN	SCA	MCA	NET	Adenocarcinoma	PanIN	Splenule	GIST
Patients (n=21)	9	2	1	2	4	1	1	1
CEA aspirate >200 ng/mL (n=7)	5	0	1	0	1	0	0	0
Abnormal amylase aspirate (n=8)	6	0	1	0	1	0	0	0
Malignant on cytology (n=1)	0	0	0	0	1	0	0	0
Atypia on cytology (n=5)	3	0	0	0	0	1	0	1

retroperitoneal tumors, and even gastrointestinal stromal tumors (GISTs).

Of the 110 operations, 89 (81%) were pancreatic resections of various degrees. Most of these were distal/subtotal pancreatic resections (n=42) and pancreatoduodenectomies (n=32). The three total pancreatectomies were only performed in the setting of total involvement of the gland by IPMN, and one harbored invasive malignancy. During the same time frame, 381 major pancreatic resections were performed for *all* indications in our practice, so APLs represented 23% (89/381) of the overall resection volume. Operations for APLs constituted a significant proportion of *all* central pancreatectomies (70%), cyst enucleations (56%), and distal or subtotal pancreatectomies (35%) performed in the 5-year span (Table 3). The remaining 21 operations spanned a spectrum from diagnostics (seven laparotomies/laparoscopies) to procedures performed on organs or structures peripheral to the pancreas (stomach, duodenum, retroperitoneum). In all, 11 different sorts of operations were needed as illustrated in Table 4. Of resections performed, only five (6%) were felt suitable for a laparoscopic approach (based on concerns over presumed malignancy, position in the gland, prior abdominal surgery, body habitus, etc.). Three distal pancreatectomies (all spleen preserving) and an enucleation were achieved in this fashion. The fifth, a distal pancreatectomy, was converted to open for failure to progress.

There was no operative mortality. Overall morbidity was 28% (n=31), predominated by eight pancreatic fistulas. Of these, one was biochemical alone (ISGPF grade A); five required therapeutic interventions (grade B), and two required reoperation (grade C). While these fistulas represent 9% of the resection cases performed for APLs, that level is markedly lower than our fistula rate for all resections performed in the practice over the concurrent timeframe where all grades=30% and clinically significant (grades B/C) fistulas equal 14%.[12] Other distinct morbidities encountered were related to respiratory issues (N=8), wound infections (N=5), ileus (N=4), and cardiac concerns (N=3). Median estimated blood loss for the 89 resection cases was 275 cm^3 (mean 414; 10–1,500). Blood products were transfused 20% of the time. Intensive care unit care was required, at any point in the postoperative period, in five patients (5%). Median duration of stay for the major pancreatic resections was 7 days (average 9.21: range 4–26). Eight patients (7%) were readmitted within 90 days postoperatively. In each case, these metrics equaled or exceeded recent historical outcomes for pancreatic surgery.[10]

In all, 22 distinct diagnoses were identified on final pathology with the most prevalent being non-malignant IPMN (17%), serous cystadenoma (SCA; 14%), and pancreatic neuroendocrine tumors (PNETs; 13%; Table 5). Seven patients (6.4%) had >1 distinct histologic diagnosis in their resection specimen, and ten others demonstrated various degrees of pancreatic intraepithelial neoplasia (PanIN) in areas remote from the primary pathology identified (Tables 6 and 7).

Table 3 Pancreatic Resections Performed for Incidental Lesions as a Percentage of Total Resections Performed for all Causes Over 5 Years

Operation	APL	Total	Percent of total
Distal/subtotal pancreatectomy	42	120	35
Pancreatoduodenectomy	32	228	14
Central pancreatectomy	7	10	70
Cyst enucleation	5	9	56
Total pancreatectomy	3	14	21
Totals	89	381	23

Table 4 Type of Operations for Incidental Pancreatic Lesions Performed Over 5-Year Period

Operation	Number
Resections	
Distal/subtotal pancreatectomy	42
Whipple	32
Central pancreatectomy	7
Cyst enucleation	5
Total pancreatectomy	3
	89
Other operations	
Diagnostic laparotomy/laparoscopy	7
Ampullectomy	4
Partial gastrectomy	3
Retroperitoneal cyst excision	3
Excision mass	2
Diversion	2
	21
Totals	110

Table 5 Pathologic Diagnoses of all Pancreatic Lesions Operated Upon Between Sept 2002 and Sept 2007, Broken Down by Separate Periods of Analysis

Diagnosis	2002–2005	2005–2007	Totals
Invasive malignancies			
Adenocarcinoma	7	10	17
Adenosquamous carcinoma	0	1	1
Non-invasive malignancies			
CIS in IPMN	3	0	3
CIS in mucinous cystadenoma (MCA)	1	1	2
CIS in duodenal adenoma	2	0	2
Melanoma	0	1	1
Lesions with malignant potential			
Intraductal papillary mucinous neoplasm (IPMN)	9	10	19
Pancreatic neuroendocrine tumor (PNET)	6	8	14
Mucinous cystadenoma (MCA)	4	1	5
Ampullary adenoma	1	3	4
Gastrointestinal stromal tumor (GIST)	1	4	5
Solid pseudopapillary tumor	1	1	2
Carcinoid	0	2	2
Intraductal oncocytic papillary neoplasm (IOPN)	0	1	1
Malignant precursor lesions			
Pancreatic intraepithelial neoplasm	0	1	1
Benign lesions			
Serous cystadenoma	9	6	15
Fat necrosis	2	1	3
Simple cyst	0	2	2
Pseudocyst	0	2	2
Benign multiloculated cyst	0	2	2
Splenule	0	2	2
Pancreatitis	0	2	2
Normal tissue	1	0	1
Ectopic tissue	0	1	1
Inflammatory tissue	1	0	1
Totals	48	62	110

Invasive malignancy was found in 17% of patients overall, with 17 having adenocarcinoma and one having adenosquamous cancer. Moreover, seven patients were found to harbor carcinoma *in situ* in the setting of IPMN, MCA, or ampullary adenoma. Yet another patient had metastatic melanoma to the pancreas. Therefore, the *overall malignancy rate* was 24% for APLs. Patients with malignancy averaged 10 years older (68 vs. 58 years) and this was statistically significant ($p=0.003$). Furthermore, an asymptomatic rise in LFTs was found to correlate significantly ($p=0.009$) with malignancy. In addition, almost half (47%) of all lesions had the capacity for malignant transformation (e.g., IPMN, MCA, PNET, GIST) with the majority of those being IPMN (Table 5). Therefore, the total number of patients with either malignant or premalignant pathology was 78, accounting for 71% of all APLs. An

Table 6 Resected Specimen's Carrying >1 Distinct Pathology

Primary pathology	Secondary pathology
Ampullary adenoma	IPMN
Pancreatic adenocarcinoma	IPMN (separate lesion)
GIST	Serous cystadenoma
IPMN	Serous cystadenoma
PNET	Carcinoid
PNET	Carcinoid
PNET	Serous cystadenoma

PNET pancreatic neuroendocrine tumor, *GIST* gastrointestinal stromal tumor, *IPMN* intraductal papillary mucinous neoplasm

Table 7 Specimens with Additional Pathology of Pancreatic Intraepithelial Neoplasia (PanIN) Identified

Primary pathology	PanIN level
IPMN	III
IPMN	III
Mucinous cystadenoma	III
IPMN	II
Pancreatitis	II
Pancreatitis	II
Serous cystadenoma	II
Serous cystadenoma	I
Serous cystadenoma	I
Serous cystadenoma	I

additional 6.4% of the total revealed PanIN lesions—a diagnosis of debatable malignant potential—either alone (N=1) or in conjunction with a benign serous cystadenoma or pancreatitis (N=6). Of the 18 patients with invasive disease, 94% were solid lesions. Of these, 65% (n=11) were proximal lesions and 35% were found in the body or tail.

Over the 5-year period, seven patients (6.3%) on our surveillance protocol ultimately opted for surgery due to changes in morphology or size on imaging at a mean of 2.6 years of observation (range 1.2 to 6.8 years). None had overt cancer on final pathology. Three had non-malignant IPMN; two had benign multiloculated cysts, one a serous cystadenoma, and one a pseudocyst.

Solid vs Cystic Morphology

Lesions were classified by morphology as either primarily solid (N=53) or cystic (N=57). There was no significant difference in age (solid 59.9 years vs cystic 62.3 years) or gender between the two groups. Radiographic lesion size was similar (solids=3.45 cm; cysts=3.58 cm).

For solids, 30% of lesions were adenocarcinoma; 23% were PNETs; 9% were GISTs, and 9% were ampullary adenomas (with an additional 4%—two patients—being adenomas harboring CIS). In all, malignancy was present in 22 patients or 38% (34% invasive + 4% CIS); lesions with malignant potential accounted for an additional 49%, leaving only 13% of these APLs as purely benign lesions.

Of cystic APLs, one third consisted of non-invasive IPMN. Beyond that, 26% were SCAs, and 12% were MCAs. There was only one cystic APL (out of 57, 1.7%) with invasive cancer. This large 4.6-cm lesion was situated in the pancreatic tail and removed via a distal pancreatectomy. There were an additional five patients with cystic processes who were found to harbor carcinoma in situ (three IPMN, two MCA), and their average size was 6.42 cm. One of these was a 1.8-cm IPMN—representing the *only case* of any form of malignancy in a cyst <3 cm in size. Thus, the total malignancy rate for cystic APLs is 10.5% (6/57). Furthermore, there were *no* cases of cystic disease which were unresectable, unlike solid lesions in which there were seven. Over half of the cystic lesions were benign (58%), composed mostly of SCAs.

The occurrence, between solids and cystic APLs, respectively, of invasive malignancy (34% vs 1.7%), overall malignancy (38% vs 10.5%), malignant precursor lesions (49% vs 33%), and benign lesions (13% vs 58%) varied dramatically. All comparisons were statistically significant at p values <0.001.

Incidental vs Symptomatic Presentation

When APLs were compared to symptomatic patients (SPLs) over this 5-year span, there was no difference found between age (APL 61 years old vs. SPL 60 years old) or gender (APL 46% male vs. SPL 51% male). The groups differed in their diagnoses (Fig. 1), with pancreatitis, pseudocysts, and benign strictures being far more common in SPLs. Most importantly, invasive malignancy was far more prevalent within the symptomatic group (43% vs 17%; p<0.0001) than the asymptomatic group. Also of note, the diagnosis of any form of IPMN was over three times more frequent in APLs (21% vs 6%).

All APLs Referred from 2005 to 2007

In the most recent 2-year period since the adoption of Sendai Criteria, 132 new patients with APLs were referred for surgical evaluation. This represented almost half (47%) of total referrals (n=281) for all pancreatic conditions seen in our practice. Of these, 62% were cysts and 38% were solid. These patients were divided into operative and non-operative groups. Of the patients presenting with APLs, 47% were operated upon (n=62), while the rest (n=70) underwent surveillance. Surgery was undertaken more often for solid APLs (74%) than for cystic lesions (32%; Fig. 2). The majority of solid APLs which were not operated upon (n=7) was actually cancers deemed unresectable by imaging due to concurrent metastases or local–regional factors.

Of those patients operated upon in this contemporary period, solid masses predominated by a 3:2 ratio over cystic lesions. This differed significantly (p=0.037) from the previous 3 years in which the opposite ratio (2:3) was seen. In the last 2 years, the frequency (as well as rate) of operations for solid lesions has almost doubled (37 cases vs 19), regardless of lesion size, compared to the previous 3-year span. However, the same does not hold true for cystic lesions where 29 lesions were operated on in the former 3-year era, decreasing to 25 operations

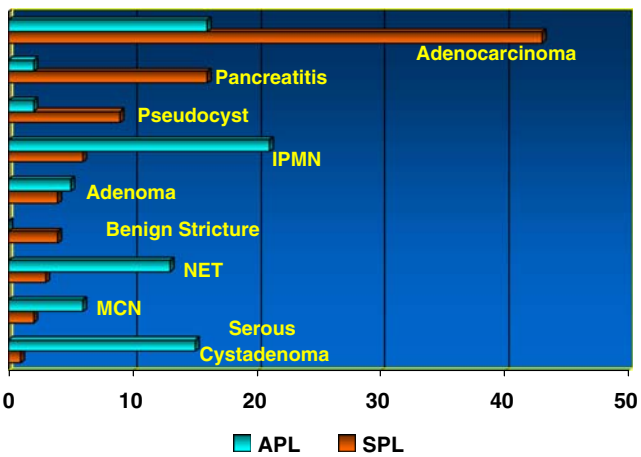

Figure 1 Comparison between asymptomatic (APL) and symptomatic (SPL) pancreatic lesions with regard to most common diagnoses.

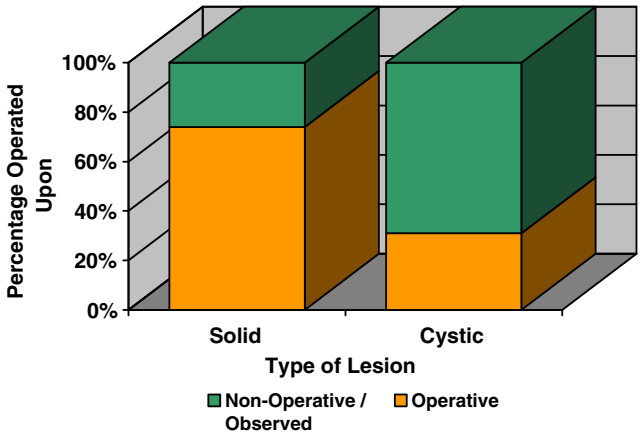

Figure 2 Percentage of solid and cystic lesions operated upon from 2005 to 2007. Solid APLs not operated upon consisted of inoperable cancers ($n=7$), cases of a splenule, inflammatory tissue, normal tissue (one each), and a patient on high-dose steroids. Two patients were lost to follow-up.

in the last 2 years. Most notably, cystic lesions <3 cm that were operated upon have dropped from 16 (2002–1005) to ten cases (since 2005), whereas the number of cysts >3 cm resected in the last 2 years has risen (13 to 15; Fig. 3). Indeed, operations for cysts >3 cm increased from 4.33 to 7.5 per year—a 1.7-fold increase most recently.

Size of operative lesions as they presented in the two time frames (2002–2005 and 2005–2007) was not different. Cystic lesions on average have been slightly larger (3.12 to 3.93 cm) between the respective periods, and solids also increased from 3.19 to 3.61 cm. Neither of these trends were statistically significant.

Due to anxiety and despite thorough counseling regarding risks and benefits, two patients in this cohort requested operation over continued observation. Neither had cancer. Both had low-grade IPMN resected by distal pancreatectomy.

Discussion

This study uses the prospective database of a high-volume pancreatic surgery practice to understand the occurrence and impact of APLs. The results uniquely reveal the scope of these lesions according to morphology(solid/cystic), location in the pancreas, and frequency. Most notably, APLs now account for half of our practice's total referrals and a quarter of our major pancreatic resections. They are equally as likely to be solid or cystic (48% vs 52%) and the lesion size (mean 3.5 cm) and demographics are equivalent between each morphology. No less than 22 distinct diagnoses were encountered (most commonly IPMN, serous cystadenoma, adenocarcinoma, and PNETs), and in 6% of patients there were more than one diagnosis within the same resection specimen. Of greatest importance, APLs were associated with overt malignancy up to a quarter of the time and are malignant precursor lesions in another half of our cases reported. Many operations were required to either diagnose or definitively address these incidentally identified lesions. Within the last 2 years, management of many cysts has transitioned from operation to observation, but longer follow-up is required to know that this is safe. Like most, we still operate usually for solid lesions.

In this series, APLs were initially discovered during clinical evaluations of a wide variety of symptoms. Most commonly, these stemmed from renal or genitourinary problems—usually hematuria, kidney stones, or surveillance of renal masses, all in concordance with the series by Bruzoni et al.[5] Axial imaging, particularly computed tomography, has often been implicated in the identification of more incidentalomas. We found the same but also point out their frequent discovery through other means including endoscopic procedures and biochemical abnormalities (exclusive of those associated with pancreatitis). While elevated liver function tests have been shown to correlate with malignancy in symptomatic patients,[13] we now find this can also be true for APLs. In fact, this series demonstrates a strong correlation of abnormal LFTs with malignant pathology, all occurring in otherwise asymptomatic patients. While this may reflect a distinct referral/practice bias, it does emphasize that asymptomatic elevations in LFTs should not be overlooked. Over time, as increasingly common APLs assume their position for this differential diagnosis, caretakers at all levels will need to be aware.

The number of radiologic tests utilized prior to intervention (median=3) reflects the challenges of reaching a diagnosis and plan for many of these lesions. We usually obtained valuable complementary information with each modality, however. Endoscopic-ultrasound-guided fine-needle aspiration (FNA) was infrequently used overall

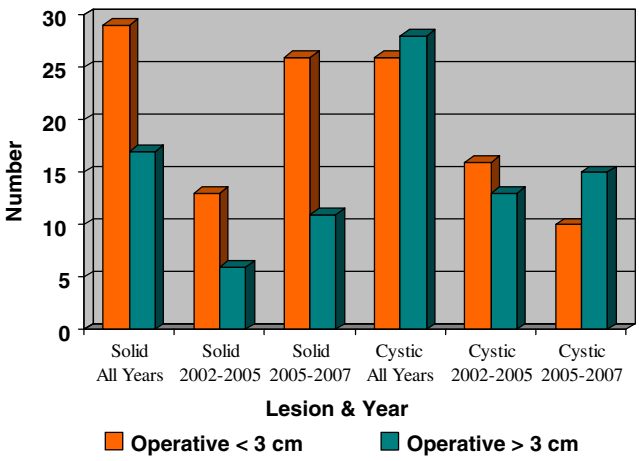

Figure 3 Ratio of operative solid to cystic lesions in the years prior to (2002–2005) and subsequent to (2005–2007) the establishment of Sendai Criteria for management of cystic pancreatic lesions.

(around 20%) for the operative patients but proved valuable for predicting mucinous cyst etiology.[14] While not always predictive of *invasive* malignancy, findings of *atypical* aspiration cytology were always associated with malignant precursor lesions. As such, we now utilize EUS more frequently in the initial analysis of both solid and cystic APLs.

The operations required to address these APLs covered the spectrum of pancreatic surgery from diagnostic interventions to palliative procedures and traditional resections. A previous report suggests that Whipple's resections, at least for APLs, should be undertaken with caution due to the potential for higher rates of complications, particularly pancreatic fistulas.[6] The authors suggest that these operations are more often performed in the setting where protective factors for fistula are absent (firm gland, large duct, pancreatitis). Fortunately, in our series, there were no deaths and other operative and postoperative outcomes compared favorably with established benchmarks and our own larger simultaneous cohort of symptomatic patients. Specifically, pancreatic fistula has been less frequently encountered.

While resection procedures were often used, parenchymal preservation procedures (central pancreatectomy, enucleation) were used as well, more often for APLs rather than for SPLs. Similar to previous reports, laparoscopic procedures were sometimes performed in our series, especially for cases in which the diagnosis remains equivocal despite extensive radiographic and endoscopic workup.[15] Frequently, this was merely securing a diagnosis of malignancy through laparoscopic biopsy. We found limited occasions (5/132) where planned laparoscopic resection procedures were either indicated or feasible. This is likely to change going forward as our own laparoscopic pancreatic surgical skills evolve and improve. For example, now with better predictive guidelines that temper concerns for malignancy in cystic neoplasms, laparoscopic resections may become more common and preferred. Their efficacy for invasive malignancies, however, remains in question and must be proven. Some patients may well choose minimally invasive operations over the long realities (cost, convenience, etc.) of surveillance.

The *threat* of APLs is obviously the frequent occurrence of malignancy in this series. Taken together, any form of malignancy was present in almost a quarter of these APL cases. These were more often situated in the proximal pancreas and were almost always solid lesions (94% of the time). In seven cases, the cancer was advanced and, in fact, inoperable. The sad truth remains that many pancreatic cancers are asymptomatic until incurable. Finding them while still asymptomatic is no guarantee of better outcome. Our study suggests that predictive factors for true malignancy in APLs are advanced age and of abnormal LFTs. These findings now drive our aggressive stance towards intervening on APLs, particularly solid ones, since malignancy occurred in them over a third of the time (38%). Conversely, benign histology is encountered in only 13% of solids but is far more often the case for cysts. Invasive cancer is a rare event (1.7%) in such incidentally identified cystic APLs. This occurred in a large 4.6-cm lesion and, while five other patients harbored CIS in their cysts, their average size was quite large (6.42 cm) with only one being <3 cm in diameter. Also, in contrast to some solid APLs, all cystic lesions were resectable.

The *nuisance* of APLs refers to the fact that we cannot yet assuredly diagnose benign lesions nor reliably predict the conversion of a premalignant APL to an invasive malignancy. One such trouble with APLs, the diagnosis of the benign serous cystadenoma, is highlighted by its common occurrence in this (14%) and other series.[6,7] Unfortunately, this diagnosis is too often made by the pathologist, rather than the radiologist, and therefore leads to unnecessary resections. Another problem is that changes on radiographic or endoscopic surveillance, including advancing size, cyst morphology, presence of nodules, or atypical aspirates have driven us (and the patients) to abandon surveillance. Thankfully, no invasive cancers were identified. The clinical driver in essence was patient and doctor anxiety.

While symptomatic patients from our overall surgical series had distinctly unique diagnoses *vis-à-vis* APLs, there was no difference in demographics such as age or gender. One might intuitively conclude that APLs would present earlier in their natural history and in younger patients. We did not find this. This may instead be explained by the fact that APLs are most often discovered via radiology or endoscopy techniques and these are applied more liberally to patients as they age. It is worth emphasizing two other findings when comparing symptomatic versus asymptomatic lesions. First, invasive malignancy is far more prevalent in symptomatic patients (43% vs 17%). Yet, so too is benign pathology (pancreatitis, pseudocysts, benign strictures, etc.), which is symbolic of so many pancreatic diseases. Secondly, IPMN is more than three times more likely to present in an asymptomatic fashion, reflecting the overall predominance of the more indolent side-branch variant.

Prior to the Sendai Conference Guidelines, management of cysts of the pancreas ranged from conservative[16] to those who advocated excision of all lesions regardless of size. Since then, we have seen more cysts at an ever accelerating pace (now 62% of APL referrals) and have operated less frequently on them (only a third of the time). Though with limited follow-up duration, our most recent experience reflects our tolerance of cystic lesions less than 3 cm in size, which has led to a reversal of proportion cystic/solid lesions we now operate for. There will be variable adoption

of the Sendai Guidelines going forward, however, until years of study and proper follow-up prove their safety. When analyzing a potential pancreatic cystic neoplasm and especially if symptomatic, most will consider important criteria beyond cyst size alone. These include any solid component within the lesion, atypical or malignant cytology, significant increases in cyst size over time, or radiographic evidence of ductal obstruction. Furthermore, an anxious patient is no longer truly asymptomatic in any case. Two patients stated a subjective decline in their quality of life strictly attributable to persistent uneasiness with their diagnoses and requested operation.

We adhere to a multidisciplinary strategy for clinical evaluation and decision making when confronted with an APL. Surgeons, pancreatologists, endoscopists, radiologists, and pathologists become a valuable team for the patient. It is probably more efficient and cost-effective, though this study does not measure that. Baseline imaging is reviewed from the original source of referral, and all prior imaging is sought to determine a potential evolution of the APL over time. Together, we decide on the next step. CT angiography is often preferred as an initial exam for solid lesions, with MRI being used preferentially for cystic lesions, though this can change. EUS with cyst or lesion aspiration is more frequently employed now than previously. Our team members all know and agree on the onerous clinical features for cystic lesions as noted earlier and recognize the heightened risk of malignancy for solid lesions. We work to consensus before presenting to the APL patient the choices of operation or rigorous long-term surveillance and observation. Hopefully, this "same-page" approach can help mitigate the understandable anxiety for any individual patient with an asymptomatic pancreatic lesion.

Conclusion

The incidental discovery of asymptomatic pancreatic lesions (APLs) is increasing. Treatment decisions pivot off concerns for malignancy but must be tempered by the short and long-term realities of major pancreatic surgery. Today, in this practice, almost half of total referrals and one quarter of the operations are performed for APLs. Many diagnoses are in play, with 24% being shown to be overt malignancies with another 47% being malignant precursor lesions (most commonly IPMN). Half of the lesions identified are solid and these are far more likely malignant (38%) than are cystic APLs, mandating an aggressive diagnostic and therapeutic approach. An asymptomatic rise in LFTs cannot be overlooked given a strong correlation with cancer. Consensus guidelines for the management of smaller cysts and side-branch IPMN may well be safe, but universal adoption will await more study and long-term follow-up. A multidisciplinary management approach is helpful and makes sense and can be reassuring to patients.

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Discussion

The Incidental Asymptomatic Pancreatic Lesion: Nuisance or Threat

Craig P. Fischer, M.D. (Houston, TX): Once again, a nice paper from a high volume pancreatic surgery center in Boston. Asymptomatic pancreatic lesions are increasingly observed because of high utilization of cross-sectional imaging for unrelated abdominal complaints. As a result, physicians are often in a quandary—is this lesion really a threat? The International Association of Pancreatology met in Sendai Japan, and published guidelines for management of cystic lesions of the pancreas in 2004. A larger percentage of cystic lesions are now being observed when specific criteria are met. We don't have similar guidelines for solid, asymptomatic pancreatic lesions. These authors examine patients referred with asymptomatic pancreatic lesions—and examine two time periods—before and after the international consensus publications from Sendai. They show a very high percentage of solid lesions that are asymptomatic and nearly 17% of all resected specimens harbored invasive malignancy. We are still left however with the same quandary—how do preoperatively determine who is at risk, and who can be observed.

My first question. The frequency of invasive disease observed in solid APLs was about 30%. Are there any solid pancreatic lesions which should be observed, and if so, is EUS with FNA a good discriminate test? Or is the false negative rate high enough that all suitable patients should undergo operation.

My second question. Since the Sendai criteria, you have observed more pancreatic cysts that are less than 3 cm. What criteria do you use for surgery in the patients who are being observed? Is it change in diameter, the patient becomes symptomatic? Development of a mural nodule?

Lastly, how do you balance the risk and benefit ratio for patients with asymptomatic lesions? An 86-year-old patient with multiple comorbid conditions is not somebody you really want to operate on. Are you observing any of these folks, and if so, are you going to report back to our association the natural history of what happens to those patients.

Thanks very much.

Teviah E. Sachs (Boston, MA): Very poignant questions, Dr. Fischer. Certainly your first question, the solid lesions that are being observed, we do have a few. In the study, as I mentioned, 74% of those patients who had solid lesions were resected, and the ones that weren't were often due to comorbidities. However, in some of our patients who are being followed after receiving EUS analysis for solid lesions, it is often they need to have something like a splenule workup, so that some of those lesions that wouldn't need to be operated upon due to the possible morbidity of resection. We find EUS very useful in categorizing these lesions.

As for the last 2 years, in the patients were following whose lesions are under 3 cm, we are using radiographic findings as the major determinant in deciding on who to subsequently resect. Certainly changes in size on imaging or the new appearance of any solid elements or nodules would heighten our concern and perhaps lead to the resection.

And as for the risk/benefits ratio in those patients who have multiple comorbidities, the resections can be morbid. Although we see some patients develop pancreatic fistulas, our rate for clinically significant pancreatic fistulas is lower in these incidentally discovered lesions (8%), than it is in our total resection cohort (14%). Still, those that have comorbidities are being followed, and we will certainly report back, because this subset of patients is a valuable asset to determine the nature and progression of this process and they may dictate how we treat our future patients with either observation or resection.

Lygia Stewart, M.D. (San Francisco, CA): I know that you are using EUS. Have you used any of the markers like CEA in your analysis in deciding whether to operate?

Dr. Sachs: Absolutely, absolutely. CEA and amylase are both levels at which we look. We do not place much value on aspirate CA 19-9 levels. Interestingly, of the patients who received EUS, those with elevated CEA levels have always been mucinous on final pathology, and so it is a very, very beneficial test for us at our center. Cytology was less specific, actually, although when diagnosis of malignancy on cytology was found, that always correlated with invasive disease. Furthermore, the finding of cytologic atypia was always associated with a malignant precursor lesion.

Carlos Fernandez Del Castillo, M.D. (Boston, MA): Congratulations on a very nice presentation, and I concur with you that we are all living an epidemic of incidentally discovered cystic lesions of the pancreas. What I am really struck with, and I think this paper is provocative and a little bit different than what we are seeing, is the number of solid incidentally discovered lesions. At Mass General we just finished looking at 4 years, 401 cystic lesions; 71% of them are incidental findings. That is 280 cystic lesions. In your experience, you said that half of the incidentally discovered lesions were solid. There is absolutely no way that there are 280, or even a fraction of those, solid. We do frequently see neuroendocrine tumors as an incidental finding, but I was

very surprised that you had 16% of adenocarcinomas in your series. So could you tell us how were those solid lesions identified, because this is very different from the experience of other centers.

Dr. Sachs: Very, very good question, and certainly in the literature, we were surprised to find a paucity of understanding of these solid incidental lesions, which is the impetus for our paper. As you mentioned, to date, most of the attention for this problem has focused on cystic diseases of the pancreas. Interestingly, I think that the presentations, as I illustrated earlier, were equally distributed for solid and cystic lesions. The specific exams acquired for solid lesions did not differ from the cystic ones. I don't know why we are seeing more and more of these as solid lesions asymptomatically, but we certainly are. You would think that a solid lesion within the pancreas would cause symptoms prior to these patients coming in, but as we showed not all of these are malignant or even invasive.

But as for the adenocarcinoma patients, the real issue that we bring up here is that the asymptomatic rise in liver function tests really *does* correlate with adenocarcinoma, and so it must be used proficiently by clinicians throughout medicine.

Dr. Fernandez Del Castillo: I would be careful, though, to call that asymptomatic, because if your bilirubin is elevated, even if the patient does not have clinical jaundice, unless the patient had the studies done as part of a routine physical, he or she really has some symptoms. So it may not be the right thing to put those patients in that category.

Dr. Sachs: That is true, that is true. Hyperbilirubinemia was encountered in very few of those patients with elevated liver function tests, but they did not manifest clinically as jaundice. We actually had two patients in our symptomatic cohort who presented to their primary care physicians with elevated liver function tests prior to presenting to us with symptoms. We elected to classify them as symptomatic, and therefore they were excluded from the cohort presented today. In those two cases, their liver function test elevation was chalked up to medications that they were taking. Had they been recognized earlier, they might have been operated on earlier as well.

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Validation of an English Version of the Padova Quality of Life Instrument to Assess Quality of Life Following Ileal Pouch Anal Anastomosis

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Abstract
Objective Ileal pouch anal anastomosis (IPAA) is the procedure of choice for most patients requiring surgery for ulcerative colitis and familial adenomatous polyposis because of its perceived improvement in health-related quality of life (HRQL). The aims of this cross-sectional study were to validate an English version of the Padova Inflammatory Bowel Disease Quality of Life questionnaire (PIBDQL) in patients undergoing IPAA and to investigate the pre- and postoperative predictors of long-term HRQL.
Materials and Methods In May 2005, the English version of the PIBDQL, Short Inflammatory Bowel Disease Questionnaire, and the SF-36 were mailed to 1,379 patients who underwent IPAA at the Mount Sinai Hospital between 1982 and 2004. The test–retest reliability, internal consistency, construct validity, and discriminative ability of the English version of the PIBDQL were assessed.
Results Nine hundred fifty-five patients (69%) (475 female, 480 male; mean, age 43 years) returned the questionnaires. The mean PIBDQL score was 21.1 (3.4), suggesting good quality of life. Test–retest reliability [intraclass correlation coefficient (ICC)=0.784] and internal consistency (Cronbach's α=0.83) were good. Construct validity and discriminative ability of the English version of PIBDQL were adequate. Multivariate analysis revealed that women ($p<0.01$) and Crohn's disease patients ($p<0.01$) had significantly worse PIBDQL scores.
Conclusions The English version PIBDQL is a reliable and valid disease-specific instrument for assessing quality of life in patients with IPAA. In this series, female gender and CD were significant predictors of worse HRQL.

Keywords Restorative proctocolectomy · Quality of life · Questionnaires · Ulcerative colitis · Indeterminate colitis · Familial adenomatous polyposis

Introduction

Ileal pouch-anal anastomosis (IPAA) is the procedure of choice for most patients requiring surgery for ulcerative

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colitis (UC) and selected patients with familial adenomatous polyposis (FAP).[1–3] Due to refinements in technique and increased surgical experience, the complication rate has decreased considerably,[4] and long-term outcome appears to be good.[1,2,5–8] Patients embraced IPAA almost immediately because it eliminated the need for a permanent stoma. As well, several studies using generic instruments such as the Short Form 36 (SF-36) and the Cleveland Global Quality of Life score (CGQL) have documented excellent HRQL compared to UC patients and the normal population.[9–14] However, the limitation of these instruments is that they lack discriminative ability.[15,16] As shown by Ko et al.,[17] there is a correlation between bowel function and HRQL, and generic instruments may fail to detect smaller differences in outcome.[16] The Inflammatory Bowel Disease Questionnaire (IBDQ) or its shortened version (SIBDQ), have been used to measure HRQL after IPAA.[18,19] However, this instrument was developed for use in trials assessing medical therapies in patients with inflammatory bowel disease and is not specific to patients with IPAA.

The Padova Inflammatory Bowel Disease Quality of Life instrument (PIBDQL) was developed in 1995 to assess HRQL in patients with inflammatory bowel disease.[20] This questionnaire has been shown to be reliable in healthy controls and in UC and IPAA patients.[21,22] It consists of items in four domains: intestinal symptoms, systemic symptoms, emotional function, and social function. In previous studies this instrument was shown to be sensitive to changes in the quality of life in Italian patients following IPAA.[21–23]

The aims of the present study were to validate an English version of the PIBDQL questionnaire in patients with UC, Crohn's disease (CD), indeterminate colitis (IC) and FAP who had IPAA; secondly, to assess its test-retest reliability: and thirdly, to investigate the effects of various pre and post operative factors on HRQL.

Materials and Methods

Thirteen hundred seventy-nine patients who had the IPAA at the Mount Sinai Hospital between 1982 and 2004 were mailed a package containing the English version of the PIBDQL, the SIBDQ, and the SF-36[24] in May 2005 as well as an explanatory letter and a self-addressed return envelope. A reminder card was mailed to all patients who had not returned the questionnaires 1 month after the first mailing. As well, 2 weeks following return of the fist 100 questionnaires, a second PIBDQL was sent to these patients to assess the test–retest reliability of the instrument. The study was approved by the Research Ethics Committee of the Mount Sinai Hospital.

Instruments

The PIBDQL instrument was developed at the University of Padova, Italy to assess quality of life in patients with IBD[20] and has been used predominantly in patients with UC having IPAA[21–23] and patients with CD undergoing surgery.[25] The instrument consists of 29 items, which explore intestinal symptoms (eight questions; score range, 0–24), systemic symptoms (seven questions; score range, 0–21), emotional function (nine questions; score range, 0–27), and social function (five questions; score range, 0–15). Possible scores for each item range from 0 to 3 and correspond to never or hardly ever, sometimes, often, and always or nearly always. The total score can range from 0 to 87 with a higher score indicating a worse HRQL. The translation–back-translation technique was used to translate the PIBDQL into English from Italian. The instrument has previously been shown to be valid if self-administered.

The SIBDQ is a disease-specific health-related quality of life questionnaire developed by Irvine and colleagues at McMaster University and is a shortened version of the IBDQ.[26] It consists of four domains including intestinal symptoms (three questions), systemic symptoms (two questions), emotional function (three questions), and social function (three questions). Each item is scored on a scale of 1 to 7 (1, worst; 7, best) so the total score may range from 7 to 70,[27] with higher scores indicating better quality of life.

The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) is a generic HRQL instrument. There are seven domains including physical functioning, physical health, bodily pain, general health, vitality, social functioning, emotional status, and mental health.[28] Scores may range from 0 to 100 for each domain with a higher score indicating a better health status. The SF-36 has been used extensively to assess the HRQL in the normal population and in various disease states. As well, it has been used previously to assess HRQL in IPAA patients.[8,12,13]

Data Analysis

Preoperative, surgical, and outcome data on all patients having a IPAA at the Mount Sinai Hospital are entered prospectively into the Mount Sinai Hospital IBD Database using Microsoft Access software. Questionnaire data obtained during this study were also entered into the database. The statistical analysis was performed using both Microsoft Excel and SAS 8.0 software (SAS Institute Inc., Cary, NC, USA). Data are presented as mean and SD. Differences were tested using two-tailed Student's t test for continuous data and Yates chi-square test for proportions.

Test–retest reliability was assessed using the ICC. The internal consistency of the English version of the PIBDQL

was investigated with the Cronbach's α.[29] A Cronbach's α of >0.8 indicates excellent internal consistency.

Construct validity was assessed by measuring the amount of correlation between the domain scores of the PIBDQL with the corresponding domains of the SF-36 and SIBDQ using the Spearman correlation coefficient.

To determine which variables are associated with HRQL in patients who had a IPAA, the following 12 variables were analyzed: gender, age at diagnosis (for inflammatory bowel disease patients), age at the first operation, current age, diagnosis (ulcerative colitis, Crohn's disease, indeterminate colitis, or famililial polyposis), duration of disease, time in months since last operation (IPAA or closure of ileostomy for those patients having a defunctioning ileostomy), pouch type (J or S), IPAA type (stapled or handsewn), postoperative complications, postoperative anastomotic leak, and previous combined abdominal and perineal reconstructive procedure. Univariate analysis of variance method (ANOVA) was performed for each putatitive predictor of PIBDQL, and multiple linear regression was then performed modeling PIBDQL on all predictors that were significant in the univariate analysis. Statistically significant predictors from the multiple regression model were then analyzed with Tukey Honestly Significant Difference (HSD) post hoc test to identify differences between levels of multi-category predictors. A level of $p<0.05$ was considered significant for all analyses.

Sample Size Calculation

Setting α (the probability of a type I error) at 0.05 (two-tailed), β (the probability of a type II error) at 0.10, and the smallest detectable r (expected Pearson correlation coefficient, effect size) at 0.20, a sample size of 259 patients was calculated to be adequate for assessing construct validity.

Setting α at 0.05 (two-tailed), β at 0.20, the smallest detectable R^2 (the proportion of variation in the HRQL outcome explained by this model) at 0.02 with the consequent effect size at 0.0204 and a maximum number of predictors at 10, the subsequent sample size was calculated to be 802 patients to be adequate for multiple regression analysis to assess the significant predictors of long-term HRQL.

Results

Patients Characteristics

Nine hundred fifty-five (69%) of the 1,379 patients returned the questionnaires. The characteristics of the respondents

Table 1 Characteristics of Respondents and Non-respondents

	Respondents	Non-respondents	*P* value
N	955 (69%)	419 (31%)	
Male/female			
Female	475 (49.7%)	153 (36.5%)	<0.01
Male	480 (50.3%)	266 (63.5%)	
Diagnosis			
UC	875 (91.6%)	359 (85.7%)	<0.01
FAP	34 (3.6%)	38 (9.1%)	
IC	23 (2.4%)	10 (2.4%)	
CD	18 (1.9%)	12 (2.9%)	
Mean age (years)	45 (12)	42 (11)	<0.01
Mean follow-up (months)	109 (70)	98 (70)	<0.01
Mean age at diagnosis (years)	29 (11)	26 (10)	<0.01
Mean age at first operation (years)	36 (11)	32 (11)	<0.01
Pouch type			
J	826 (89.6%)	361 (86.1%)	0.982
S	129 (10.4%)	57 (13.9%)	
Unknown	0	1 (0.2%)	
IAA			
Stapled	806 (84.4%)	349 (83.3%)	0.663
Hand Sewn	149 (15.6%)	70 (16.7%)	
Number of operations			
1 Stage	219 (22.9%)	92 (21.9%)	0.818
2 Stages	541 (56.6%)	243 (57.9%)	
3 Stages	174 (18.2%)	72 (17.2%)	
IAA leak	89 (9.3%)	43 (10.2%)	0.601

Table 2 Test–Retest Reliability of the PIBDQL

	Intestinal symptoms	Systemic symptoms	Emotional function	Social function	Overall
Time 1	8.2 (3.4)	6.6 (5.0)	3.8 (4.9)	2.4 (2.6)	10.8 (12.3)
Time 2	8.0 (3.9)	6.0 (5.3)	4.8 (5.2)	2.6 (3.6)	12.3 (15.9)
ICC	0.788	0.733	0.701	0.785	0.784

ICC intraclass correlation coefficient comparing results at time 1 and time 2

and those who did not return the questionnaires were similar as shown in Table 1. The majority of patients had surgery for ulcerative colitis. The proportion of male and female patients in the cohort was similar. Over 80% of patients had a J pouch constructed and a stapled ileoanal anastomosis. Over 50% experienced at least one complication. Nine percent of patients experienced an ileoanal anastomotic leak.

Validation of the English Version of PIBDQL

Of the 955 patients who returned the questionnaires, only 862 (90.3%) patients provided complete data for PIBDQL questions. The mean total PIBDQL score was 21.1 (13.4), indicating a fairly good quality of life. The mean domain scores were 7.8 (4.1) for intestinal symptoms, 6.1 (4.5) for systemic symptoms, 5.0 (4.8) for emotional function, and 2.3 (2.8) for social function.

Seventy-eight of the 100 patients who were sent a second questionnaire package to evaluate test–retest reliability returned it with complete data on PIBDQL at a mean time of 20 (5) days following completion of the first assessment. Test–retest reliability was excellent for the instrument overall as well as for each of the four domains as shown in Table 2. To determine internal consistency of the English PIBDQL, Cronbach's α was calculated on the 862 questionnaires where there were complete data. Cronbach's α was 0.83 demonstrating good internal consistency.

Construct validity of the English PIBDQ was analyzed with Spearman correlation test because of the distribution of the PIBDQ scores. The English PIBDQ was correlated with the generic SF-36 and the disease-specific SIBDQ. The English PIBDQ single item and overall scores correlated well with all SF-36 and SIBDQ domains ($p<0.0001$) as shown in Tables 3 and 4.

Factors Influencing Quality of Life

Twelve variables that might potentially affect quality of life were assessed: gender, age at diagnosis (for inflammatory bowel disease patients), age at the first operation, current age, diagnosis (ulcerative colitis, Crohn's disease, indeterminate colitis, or famililial polyposis), duration of disease, time in months since last operation (IPAA or closure of ileostomy for those patients having a defunctioning ileostomy), pouch type (J or S), IPAA type (stapled or handsewn), postoperative complications, postoperative anastomotic leak, and previous combined abdominal and perineal reconstructive procedure. As shown in Table 5, only gender, diagnosis, length of follow-up, pouch type, IAA type, and previous pouch reconstruction seemed to predict quality of life of patients in univariate comparisons. These predictors were then included in a generalized linear model. On multivariate regression analysis, female patients were found to have worse HRQL than male patients on the PIBDQL. There were five categories in the diagnosis variable (UC, CD, ID, FAP, other). The Tukey HSD post hoc test confirmed that the PIBDQL scores for CD patients were significantly higher (and so worse) than those for UC patients and those for FAP patients. PIBDQ score also showed a trend toward a significant linear relationship with whether a patient had had pouch reconstruction or not ($p<0.06$). ANOVA and *t* test showed that patients who had their pouch reconstructed scored significantly worse.

Table 3 Assessment of Construct Validity of the PIBDQL (Versus SF-36)

	Physical function	Role physical	Bodily pain	General health	Vitality	Social function	Role emotional	Mental health	Overall SF-36 score
Intestinal symptom	−0.329	−0.319	−0.409	−0.426	−0.398	−0.345	−0.279	−0.322	−0.456
Systemic symptom	−0.508	−0.539	−0.553	−0.678	−0.736	−0.556	−0.445	−0.561	−0.739
Emotional function	−0.440	−0.501	−0.457	−0.610	−0.625	−0.598	−0.511	−0.670	−0.701
Social function	−0.494	−0.540	−0.422	−0.499	−0.472	−0.502	−0.391	−0.396	−0.588
Total PIBDQL	−0.521	−0.563	−0.554	−0.676	−0.686	−0.605	−0.490	−0.598	−0.759

Correlation coefficients are negative because of the opposite orientation of the instruments. $p<0.001$ for all correlations

Table 4 Assessment of Construct Validity of the PIBDQL (Versus SIBDQ)

	Intestinal symptom	Systemic symptom	Emotional function	Social function	SIBDQ
Intestinal symptoms	−0.694	−0.403	−0.479	−0.480	−0.613
Systemic symptoms	−0.562	−0.766	−0.669	−0.545	−0.767
Emotional function	−0.554	−0.542	−0.747	−0.575	−0.730
Social function	−0.512	−0.409	−0.525	−0.692	−0.614
Total PIBDQL	−0.687	−0.663	−0.739	−0.664	−0.828

Correlation coefficients are negative because of the opposite orientation of the instruments. $p<0.001$ for all correlations

Discussion

The complete excision of the diseased bowel with the virtual elimination of the risk of cancer and the preservation of the natural route of defecation make IPAA the procedure of choice for the elective treatment of most patients requiring surgery for UC.[30,31] As well, IPAA is an option for patients with familial polyposis and indeterminate colitis.[11,24] Surgical outcomes are good in most patients.[31] As well, functional results and quality of life are also important outcome measures.[5,16]

Table 5 Factors Affecting PIDQL Scores

Predictors	Mean total PIBDQ (SD)	ANOVA *p* level	Multiple regression *p* level
Gender		0.002	0.007
Female	22.5 (13.9)		
Male	19.7 (12.7)		
Follow up[a]		0.015	
FU <12 months	18.6 (12.9)	*0.368*	0.189
FU 12-59	22.8 (13.3)		0.072
FU 60-119	21.8 (13.9)	*0.848*	0.116
FU >120	19.5 (12.9)	*0.017*	0.288
Diagnosis[b]		0.020	
UC	20.8 (13.0)		0.002
IC	24.7 (15.1)	*0.680*	0.801
CD	30.9 (23.0)	*0.016*	0.001
FAP	19.9 (13.1)	*0.997*	0.023
Pouch configuration		0.049	0.740
J	21.4 (13.3)		
S	18.8 (13.9)		
IPAA Type:		0.018	0.205
Handsewn	21.6 (14.3)		
Stapled	18.6 (13.1)		
Pouch Reconstruction		0.017	0.058
Yes	26.4 (17.9)		
No	21.0 (13.1)		

[a] *p* value obtained with Tukey HSD test of the comparison of PIBDQL score of patients with 12–59 months of follow-up versus that of other patients' groups are reported in the table in italics

[b] *p* value obtained with Tukey HSD test of the comparison of PIBDQL score of UC patients versus that of other patients' groups are reported in the table in italics

This study confirmed the reliability and validity of the PIBDQL to assess quality of life in patients having IPAA. The test–retest reliability of the English PIBDQL was assessed by comparing results obtained on two different occasions approximately 20 days apart. All but three patients who were assessed in this part of the study had had a pouch for more than 1 year so it is likely that their results are stable.[1,26] The test–retest reliability verified the homogeneity of the English PIBDQL scores, as the four domains and the overall score showed no statistically significant difference. Similarly, this study showed that the instrument has high internal consistency.[34] As well, the internal consistency was comparable to that reported for the Cleveland Global Quality of Life score.[1]

Construct validity was analyzed through the correlation of the English PIBDQL with the generic SF-36 and with the disease-specific SIBDQ. As expected, the English PIBDQL scores correlated moderately well with all SF-36 and SIBDQ domains. As one would expect, the correlations between the intestinal symptoms scores and the single item scores of the SF-36 were lower. Thus, it can be deduced that this questionnaire performs better in patients having IPAA. It measures what it is meant to measure but in a slightly different way from the previously validated instruments.

The discriminative ability of the PIBDQL was demonstrated analyzing the predictors of HRQL. Gender and diagnosis were found to affect PIBDQL scores. Previous studies have not shown that women have worse quality of life following IPAA. In this series, female patients experienced the same rate of postoperative complications and IAA leaks, and they reported the same stool frequency as male patients but they were significantly younger, and more women had had a pouch reconstruction. This may account for the observed difference. Furthermore, a recent study from the Academic Medical Centre of Amsterdam pointed out that body image and cosmesis are more important to female patients who undergo IPAA.[35]

As measured by the English PIBDQL, CD patients had a significantly worse long-term HRQL compared to UC or FAP patients. Patients with Crohn's disease are more likely to require excision of their pouch,[24] but it appears that those who still have their pouch also have a worse quality of life.

Patients who had had a pouch reconstruction had significantly worse PIBDQL scores on univariate analysis and a trend toward significance on multivariate analysis. Intestinal symptoms and social function were the domains that were poorer in this group of patients. These patients tend to have poorer functional results likely due to stretching of and injury to the anal sphincter at reconstructive surgery.[36] Poorer functional results tend to impact negatively on quality of life, so these results are not unexpected. That the results were not significant on multivariate analysis is likely due to the relatively small number of patients who had had reconstructive surgery in this series.

This study showed that the English version of the PIBDQL is useful in determining predictors of poor HRQL outcome after IPAA. In the Italian version, this questionnaire was also shown to be valid in assessing HRQL of patients after IPAA. In fact, studies performed with generic instruments such as CGQL or SF-36 have claimed that the HRQL is equal in patients with IPAA compared to healthy controls.[1,13] However, CGQL failed to differentiate IPAA patients from healthy controls and patients with mild UC or in remission from moderate UC. Studies using SF-36 showed a difference between IPAA and UC patients only because patients were all affected by severe UC.[13,23] Thus, it seems that generic instruments may lack discriminative ability, and comparisons between patient groups using a non-disease specific instrument should be interpreted with caution.

In conclusion, this study demonstrated that quality of life is good in most patients following IPAA. Furthermore, the English version of the PIBDQL questionnaire was shown to have good test–retest reliability, internal consistency, and construct validity. Thus, this instrument can be used to assess quality of life in this cohort of patients.

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Intestinal Afferent Nerve Sensitivity is Increased During the Initial Development of Postoperative Ileus in Mice

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Abstract
Introduction Neuronal reflex inhibition of gastrointestinal motility is a key mechanism in the development of postoperative ileus (POI). The aim of our study was to determine whether intestinal afferent nerve fibers are sensitized during the first hours after surgery contributing to this mechanism.
Methods Under enflurane anesthesia, C57BL/6 mice underwent laparotomy followed by sham treatment or standardized small bowel manipulation to induce POI. After 1, 3, or 9 h, extracellular multi-unit mesenteric afferent nerve recordings were performed in vitro from 2 cm segments of jejunum (subgroups $n=6$) superfused with Kreb's buffer (32°C, gassed with O_2/CO_2 mixture). Segments were cannulated to monitor luminal pressure and intestinal motility. Afferent impulses as response to bradykinin (0.5 μM) and to mechanical ramp distension of the intestinal lumen from 0 to 80 cmH_2O were recorded.
Results At 1 h, amplitudes of intestinal contractions were 0.8±0.2 cmH_2O after induction of POI and 5.0±0.8 cmH_2O in sham controls (mean±SEM; $p<0.01$). A similar difference was observed for segments harvested at 3 and 9 h. Afferent firing to serosal bradykinin was increased at 1, 3, and 9 h in POI segments compared to sham controls ($p<0.05$ at 1 h, $p<0.01$ at 3 and 9 h). During distension with high pressures, afferent firing rate was increased at 1 and 3 h in segments after induction of POI compared to sham controls. Nine hours postoperatively, contracted and dilated segments were observed during POI that were investigated separately. While afferent firing in dilated segments was increased to 176±16 imp s^{-1} at 80 cmH_2O luminal distension ($p<0.01$), it was 46±5 imp s^{-1} in contracted segments ($p<0.001$) compared to 77±4 imp s^{-1} in sham controls.
Conclusions Afferent firing to bradykinin and high threshold distension is augmented in the early phase of POI. As these stimuli are known to sensitize predominantly spinal afferents, this mechanism may contribute to reflex inhibition of intestinal motility during POI.

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Keywords Afferent nerve fibers · Bradykinin · Intestinal motility · Mechanosensitivity · Reflex inhibition

Introduction

After abdominal surgery, postoperative ileus (POI) occurs frequently to some extent and normally resolves spontaneously within 2 to 3 days. While this "physiologic" ileus rarely delays patients' recovery after surgery, it may be followed by more severe "paralytic" ileus that may persist for a longer period of time.[1]

The consequences of prolonged POI are multifold. Patients suffer from discomfort and pain secondary to abdominal distension and are at increased risk for pulmonary complications.[2] Furthermore, paralytic ileus may render oral food intake impossible with the consequence of prolonged parenteral nutrition. Overall, prolonged POI increases hospital stay and treatment costs substantially.[1,3]

Neuronal, inflammatory and pharmacological mechanisms have been described to contribute to POI, and it is known that these different mechanisms interact with each other to some extent. The relative importance of each factor, however, is still under debate.[4] Neuronal mechanisms are likely to prevail during the first hours of POI as nociceptive inhibitory spinal reflexes may rapidly inhibit intestinal motility.[5,6] These mechanisms were previously investigated by indirect methods,[7–10] while direct recordings from afferent nerves were not performed in the past.

Therefore, our aim was to study intestinal afferent nerve sensitivity during the early phase of POI by electrophysiological recordings from mesenteric afferent nerves as they may represent a part of the afferent limb of neuronal reflex inhibition of intestinal motility. We hypothesized that the afferent nerve response to the pain mediator bradykinin and to painful, i.e., high-threshold luminal distension, is increased in the early postoperative period.

Methods

Animals

All experiments were performed with male mice (C57 black 20–30 g). They were maintained on a 12 h light/dark cycle and fed a standard laboratory diet prior to the experiment. The study was approved by the local animal research committee.

Surgical Procedures

After the animal was deeply anesthetized by enflurane inhalation, a midline laparotomy was performed. Then, the animal's small bowel was surgically manipulated in a standardized fashion as described previously.[8] In brief, the small bowel was exteriorized to the left on a moist gauze and was entirely manipulated between two moist cotton applicators for 15 min. After manipulation, the laparotomy was closed with a double-layer running suture. Sham-operated animals serving as controls underwent laparotomy without small-bowel manipulation. All animals recovered quickly from surgery and began to eat and drink within 2 h. Although not quantified in detail, no obvious difference in feeding and drinking behavior was observed among the two experimental groups. One, 3, and 9 h postoperatively, animals were quickly anesthetized with enflurane and killed by exsanguination. The rationale for including early time points in the experimental protocol was the consideration that at this stage, inflammatory mechanisms for inhibition of intestinal motility are unlikely to have already come into play, while neuronal mechanisms were assumed to be activated immediately.

Afferent Nerve and Motility Recordings

Immediately after the animals' death, two segments of proximal jejunum with a length of 2 cm were excised with the mesentery attached. Those segments that were not immediately used for the experiment were stored in ice-cold Kreb's solution gassed with a O_2/CO_2 mixture (95%/5%) for a maximum of 1–2 h. No difference was observed between experimental data from segments processed immediately and stored on ice. The second segment was used for recordings only if no adequate afferent nerve signal was obtained from the first segment. If a recording from the first segment was possible, the second segment was discarded. Thus, only one recording per animal was performed. For this purpose, the segment was placed in a perfusion chamber and superfused with Kreb's buffer equilibrated with a O_2/CO_2 mixture (composition of Kreb's (mM): Na^+ 143.5, K^+ 5.9, Cl^- 126, Ca^{2+} 2.5, Mg^{2+} 1.2, H_2PO_4 1.2, SO_4 1.2, HCO_3^- 25, glucose 10, and sodium butyrate 1; pH 7, superfusion rate 7 ml min^{-1}, temperature 32°C). The mesenteric arcade was introduced into a separate recording chamber through an aperture that was sealed with vaseline before the chamber was filled with colorless heavy liquid paraffin prewarmed to 32°C to insulate the recording electrodes. The gut lumen was cannulated at both ends and perfused with normal saline from the proximal end (10 ml h^{-1}), while the distal cannula remained open to the atmosphere during the experiment. The intraluminal pressure was recorded continuously through a separate channel in the proximal cannula with a pressure transducer (Neurolog pressure amplifier NL 108, Digitimer Ltd., Welwyn Garden City, UK). This pressure was typically 1–3 cmH_2O at baseline on top of which phasic contractile events occurred that were evaluated as described below.

After the gut segment had been placed in the chamber, a single paravascular nerve bundle was dissected out from a mesenteric arcade. It was then attached to one of a pair of platinum recording electrodes, with a strip of connective tissue wrapped around the other to serve as a reference. The electrodes were connected to a Cambridge Electronic Design (CED) single-channel 1902 preamplifier/filter (CED, Cambridge, UK), and the signal was amplified 10,000 times and filtered with a bandwidth of 100 Hz to 1 kHz. Signals from the pressure transducer recording

the intraluminal intestinal pressure were relayed to another CED single-channel 1902 preamplifier/filter. The output from the 1902, together with the signals from the pressure transducers, were passed into a power Micro 1401 interface system (CED), captured, and viewed online by Spike 2 software (version 4.01; CED) on a personal computer.

Protocol for Afferent Nerve Recordings

Once a stable recording had been established for 20 min, the afferent response to luminal ramp distension from 0 to 80 cmH_2O was investigated. For this aim, the outflow cannula in the intestinal lumen was clamped, while perfusion into the lumen with Kreb's buffer was continued at a rate of 10 ml h^{-1} until 80 cmH_2O was reached. Thereafter, the outflow was reopened for a minimum of 15 min to allow afferent nerve discharge to stabilize again on baseline levels before the effect of serosal bradykinin application was investigated. For this purpose, the perfusion was stopped and bradykinin added directly into the organ bath establishing a bradykinin concentration of 0.5 μM for 2 min before the superfusion with Kreb's was continued to wash out the bradykinin. The dose of bradykinin was chosen based on previous dose–response experiments that identified 0.5 μM as a moderate, submaximal dose (data not shown).

Drugs

Enflurane was obtained from Abbott, Wiesbaden, Germany and Bradykinin from Sigma-Aldrich Chemicals, St. Louis, MO, USA.

Data Analysis

Baseline discharge frequency ($impsec^{-1}$) was calculated by averaging afferent nerve discharge per second for 60 s immediately prior to administration of the test stimuli. The response to bradykinin is expressed as the mean increase in the number of afferent impulses above baseline over a period of 60 s. Afferent nerve discharge to luminal ramp distension was determined separately as mean (±SEM) increase of afferent impulses over baseline during luminal pressure rises from 0 to 10, 10 to 20, 20 to 30, 30 to 40, 40 to 50, 50 to 60, 60 to 70, and 70 to 80 cmH_2O. Intestinal motility was quantified at baseline by determining the amplitudes of the phasic changes in intraluminal pressure over a period of 200 s. This evaluation was started after an equilibration period of 20 min. Data are presented as mean±SEM. Afferent discharge to bradykinin data was compared by one-way analysis of variance (ANOVA), while discharge to intraluminal ramp distension was analyzed by two-way ANOVA and post hoc Holm–Sidak test. A probability of $p<0.05$ was considered statistically significant. n refers to the number of segments.

Results

Motility and Macroscopic Aspect

Segments of small intestine from animals after bowel manipulation at 1 and 3 h were flaccid, while specimen from sham controls at the same time points showed continuous phasic increases in intraluminal pressure. In the 9-h postoperative ileus group, the mentioned motility pattern was unchanged, i.e., without phasic contractions, but the investigated small intestine showed dilated as well as contracted segments (see images in Fig. 1). Segment did not change their condition over time and remained either dilated or contracted during the entire observation period (i.e., throughout tissue preparation and afferent nerve

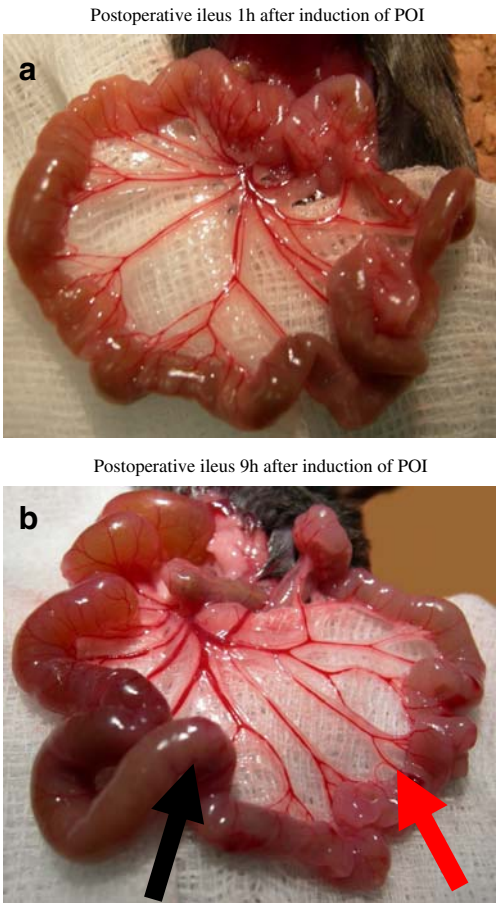

Figure 1 Representative photographs showing the small intestine 1 h (**a**) and 9 h (**b**) after induction of postoperative ileus by intestinal manipulation. At the latter time point, contracted (*red arrow*) and dilated (*black arrow*) segments were found in the small intestine which remained unchanged during the entire observation period.

recordings). Representative recordings are given in Fig. 2a and data are summarized in Fig. 2b.

Afferent Discharge at Baseline

Baseline afferent nerve discharge in the different subgroups is given in Table 1. Baseline discharge was not different 1 h after surgery ($p=0.18$). Discharge was evaluated separately for contracted and dilated segments 9 h after surgery as this phenomenon was observed at this time point only. Increased afferent nerve discharge was observed during POI 3 h ($p<0.01$) and 9 h after surgery compared to sham controls, regardless whether segments were dilated or contracted (both $p<0.05$, all $n=6$).

Bradykinin

The afferent nerve response to serosal bradykinin (0.5 μM) was followed by a robust increase in afferent discharge to 15±1 imp s^{-1} after 1 h, 38±4 imp s^{-1} after 3 h, and 35±2 imp s^{-1} in distended and 33±2 imp s^{-1} in contracted ileus segments after 9 h compared to 12±1 imp s^{-1} after 1 h, 14±1 imp s^{-1} after 3 h, and 15±1 imp s^{-1} after 9 h in sham controls ($p<0.05$ at 1 h, $p<0.01$ at 3 and 9 h; in the latter for both contracted and dilated segments). The intestinal motor response to serosal bradykinin was characterized by an initial decrease followed by an increase in intestinal intraluminal pressure independent of the afferent nerve response (Fig. 3).

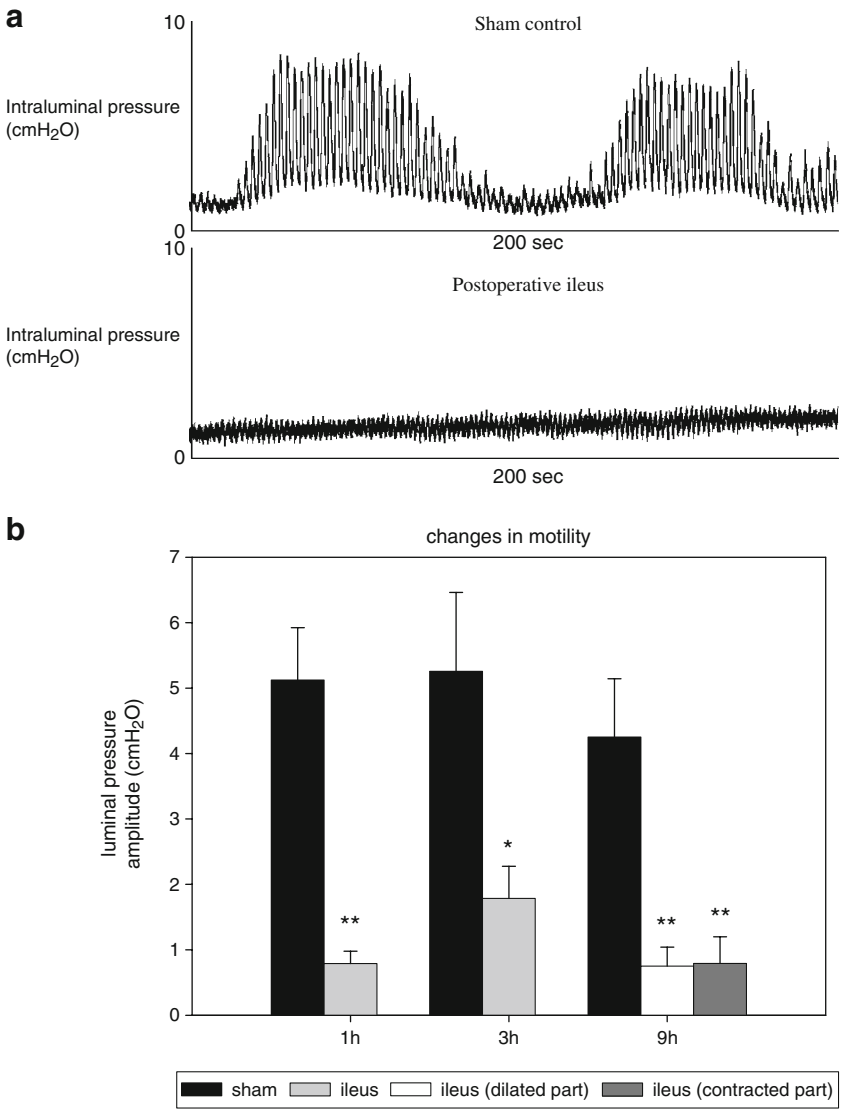

Figure 2 **a** Representative intraluminal pressure recordings from a segment of a sham-operated control animal (*upper trace*) and an animal 1 h after intestinal manipulation to induce postoperative ileus (*lower trace*). Note the normal phase III motility in the small intestinal segment of a control animal, while intestinal motility was virtually absent during postoperative ileus. **b** Summarized motility data as mean± SEM. Peak amplitudes were evaluated in order to quantify intestinal motor events. At the 9 h time point, contracted and dilated segments were investigated and analyzed separately. The inhibition of intestinal motility, i.e., postoperative ileus, was present at all time points compared to sham controls (*$p<0.05$, **$p<0.01$; each $n=6$).

Table 1 Baseline Afferent Nerve Discharge in Different Subgroups (imp s^{-1})

	1 h	3 h	9 h
Sham-operated	6.5±0.9	4.9±0.9	5.7±0.5
Postoperative ileus	8.5±1.0	13.7±2.6*	Dilated: 8.3±0.6* contracted: 9.1±1.4*

Discharge at baseline was evaluated separately for contracted and dilated segments during postoperative ileus at 9 h. Baseline discharge was not different 1 h after surgery but increased in the postoperative ileus subgroups at 3 and 9 h when compared to the corresponding sham-operated groups (group size n=6)
*p<0.05 versus sham controls

Luminal Ramp Distension of the Intestinal Segment

At all time points, a pressure-dependent increase in afferent nerve discharge was observed during intraluminal ramp distension in POI segments and in segments from sham-operated controls. Afferent firing was increased 1 h after surgery in segments from POI animals at an intraluminal distension pressure of 50–60 cmH_2O or higher and at 30–40 cmH_2O or more in animals with POI 3 h after surgery (Fig. 4a, b). Nine hours after intestinal manipulation for induction of POI, contracted and dilated segments were evaluated separately. In contracted POI segments, afferent discharge was reduced below 50–60 cmH_2O distension pressure, reaching 46±5 imp s^{-1} at 80 cmH_2O compared to 77±4 imp s^{-1} in sham controls (p<0.001; n=6 each). Afferent firing was increased in dilated POI segments at 40–50 cmH_2O and higher distension pressures with a maximum of 176±16 imp s^{-1} at 80 cmH_2O (p<0.01 compared to sham controls; Fig. 4).

Discussion

Small intestinal manipulation caused a profound decrease in motility representing a typical feature of postoperative ileus. Baseline afferent nerve discharge was not different 1 h after induction of POI but increased 3 and 9 h post-operatively compared to sham controls. The response to bradykinin was increased during POI at all time points. Afferent nerve discharge to low-threshold distention was never affected by POI, while high-threshold distension triggered peak afferent firing that was increased at 1 and 3 h in the POI groups. At the 9-h time point, some segments of the small intestine were dilated, while others were contracted in POI animals. These different contractile conditions did not affect the response to bradykinin, while the afferent nerve response to high threshold distension was increased in dilated parts of the gut and reduced in contracted segments.

This study confirmed that POI is characterized by inhibition of intestinal motility which is known to entail impaired transport of intestinal contents.[4] The pathophysiology of POI is complex as different mechanisms and an abundance of mediators seem to contribute to its development after surgery.[1–4] Two major phases may be distinguished, although this differentiation is far from being well established. The early acute phase is probably secondary to neuronal reflex inhibition of intestinal motility and not related to inflammatory events,[5,6] whereas the later and more sustained phase is associated with leucocyte recruitment into the intestinal muscularis and upregulation of proinflammatory cytokine production.[4,6,11] During this later phase, several mechanisms are obviously involved which results in the complex picture of POI with multiple interactions between immune cells, neurotransmitters, and neuronal elements.[12] At this late stage, modulation and treatment of POI becomes problematic as so many factors are involved. Therefore, the focus of the present study was on the early neuronal reflex mechanism that has been known for decades.[5,7,13] These early mechanisms are particularly of interest, as they might determine the final severity of POI, and alteration of these mechanisms could affect characteristics of POI in the later phase. The key question that we aimed to address was which are the afferent stimuli that potentially bring on the efferent inhibition of intestinal motility early after surgery.

Interestingly, we found that during the early phase of POI, the afferent nerve response to stimuli affecting predominantly spinal afferents, i.e., bradykinin[14] and high-threshold distension[15], was increased, while no differences were seen for low-threshold distension which predominantly involves vagal afferents.[15] Bradykinin is a pain mediator that sensitizes splanchnic afferents projecting to the spinal cord.[16] Spinal primary afferent neurons synapse with sympathetic neurons,[17] and sympathetic neuronal activation leads to an inhibition of gastrointestinal motility.[6] This phenonemon has already been described decades ago[5]; however, the new aspect of this study is that the afferent sensitization was quantified by direct electrophysiological recordings. But which mechanism is responsible for this increased afferent sensitization? One possibility is the involvement of circulating catecholamines at this early stage after surgery. These hormones have the potential to inhibit intestinal motility,[18–20] alter afferent sensitivity in somatic pain models,[21] and indirectly sensitize vagal afferents, e.g., in the lungs.[22,23] However at this time, there are no data supporting the sensitization of autonomous afferent nerve fibers by circulating catecholamines. Another possible explanation is that intestinal manipulation triggers mast cell degranulation[24] with the subsequent release of mediators such as prostanoids[25] that sensitize intestinal afferents to

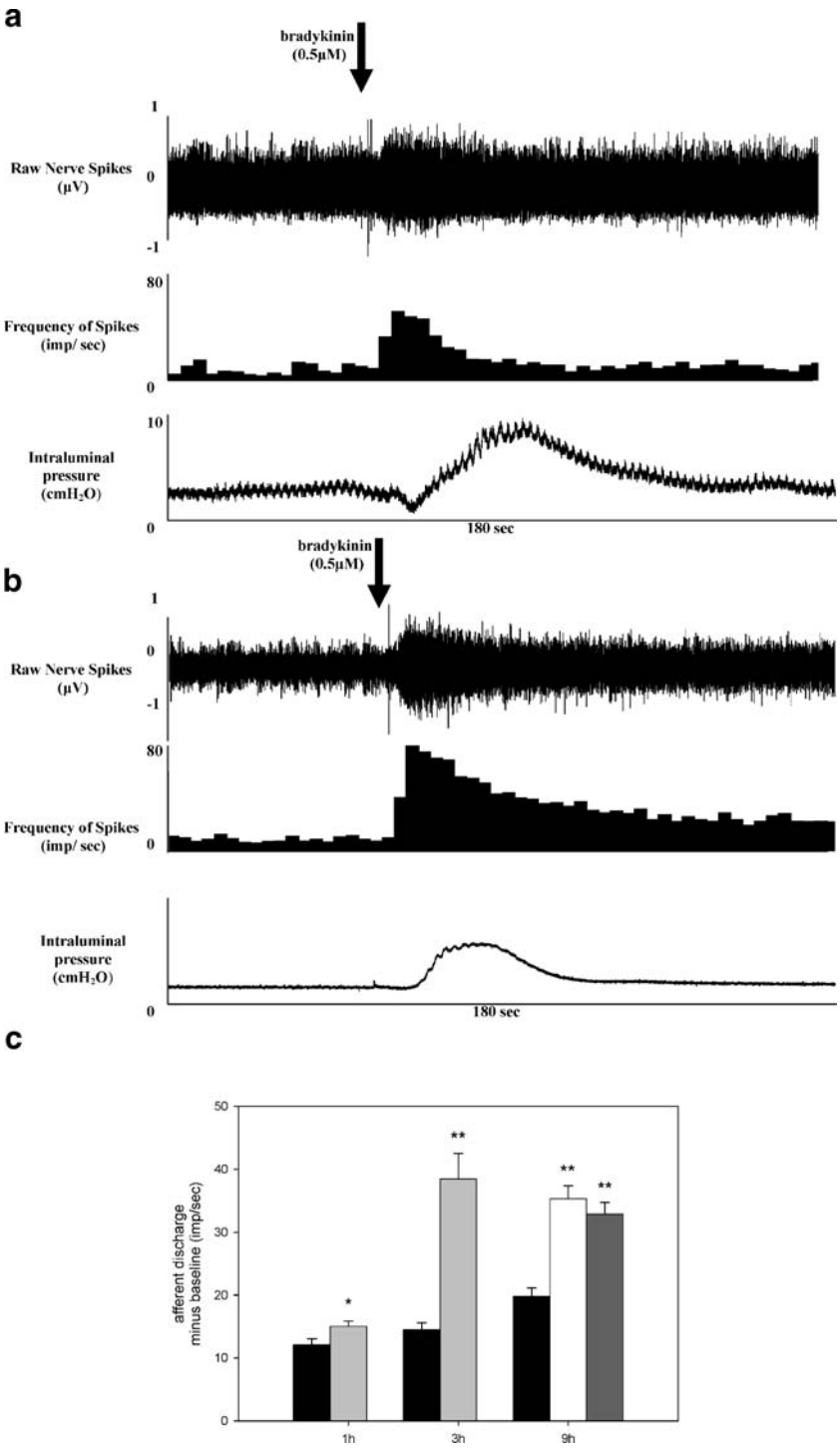

Figure 3 **a**, **b** Representative afferent nerve and motility recordings in a segment of small intestine from a 3 h sham control animals (**a**) and from an animal 3 h after induction of postoperative ileus. *Upper traces* show the raw nerve signal, *middle traces* the sequential rate histograms of afferent nerve discharge per second and the *lower traces* display intraluminal pressure which was recorded to assess intestinal motility. Following serosal bradykinin (0.5 μM) in the organ bath, a robust increase in afferent firing was observed that was accompanied by a rise in intraluminal pressure. **c** Afferent firing was increased 1, 3, and 9 h after induction of postoperative ileus compared to sham-operated controls (*black bars* sham controls, *light grey* postoperative ileus, *dark grey* postoperative ileus/contracted part, *white* dilated segment). The difference was present at the 9 h time point regardless of whether recordings were made from a contracted or dilated segment (data are mean± SEM; each group $n=6$, *$p<0.05$, **$p<0.01$).

bradykinin and mechanical distension.[26] This mechanism may have caused the increased afferent sensitivity to high threshold distension and bradykinin during the early hours after surgery shown in our study.

One of the most intriguing findings was that at the 9-h time point, segmental dilatation of the small intestine occurred that—to our knowledge—has not been described previously. POI is typically characterized by dilated and flaccid intestine,[8,11,27] but in these previous studies, the early phase of POI was not investigated. One possible explanation is that at the 9-h time point, a transition from an early neuronal period of POI with contracted intestine is

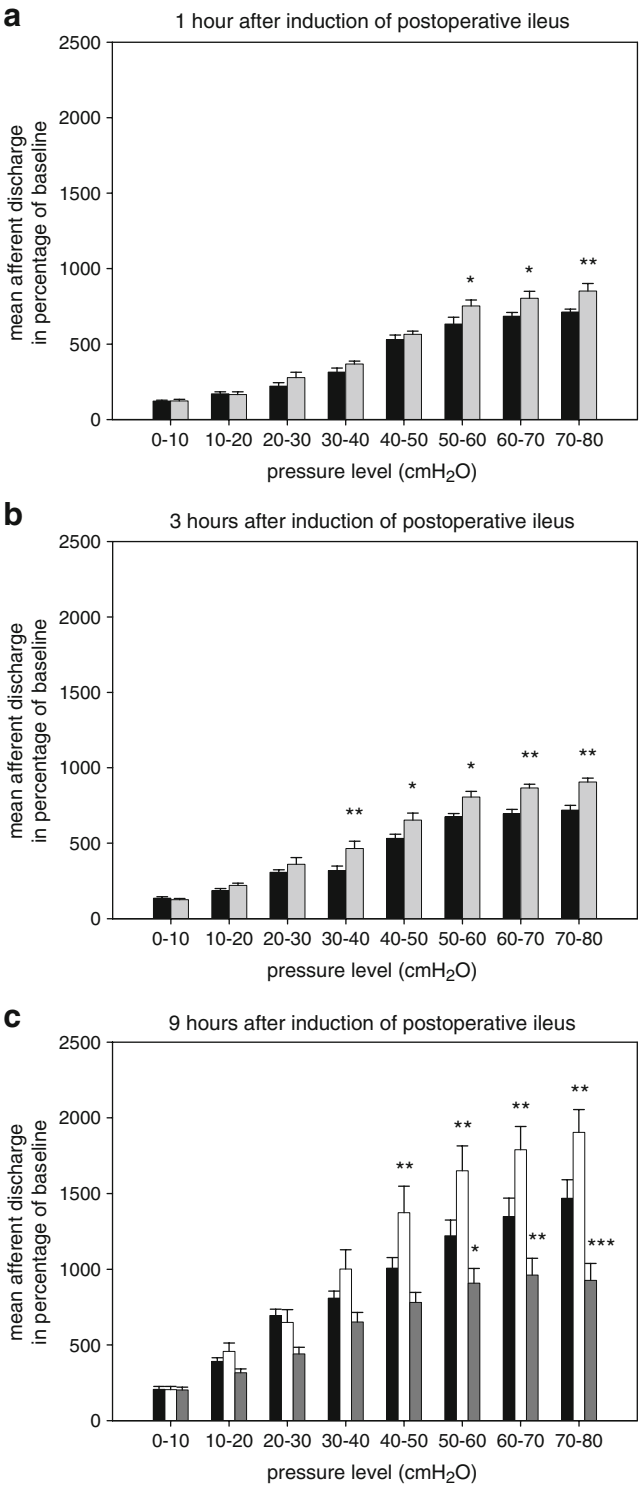

Figure 4 Graphs display afferent nerve discharge per second during mechanical stimulation of the intestinal segment by continuous intraluminal ramp distension from 0 to 80 cmH_2O. *$p<0.05$; **$p<0.01$; ***$p<0.001$ compared to sham-operated controls. Responses were normalized to baseline afferent nerve discharge. **a**, **b** Afferent nerve responses to distension 1 and 3 h after induction of postoperative ileus by mechanical manipulation. *Black bars* sham controls; *light grey* postoperative ileus. Note that afferent firing is increased at high threshold luminal distension during postoperative ileus. Each group $n=6$. **c** Afferent nerve discharge to intraluminal distension of the intestinal segment compared to sham-operated controls 9 h after induction of postoperative ileus. Note that at this time point some segments in the small intestine were dilated, while others appeared contracted. They were, therefore, studied separately. *Black bars* sham controls, *white* postoperative ileus/dilated segment, *dark grey* postoperative ileus/contracted segment. Comparisons versus sham controls. Each subgroup $n=6$.

followed by the later period that is known to entail an inflammatory response triggered by immune cells infiltrating the gut wall,[8,11] release of inflammatory mediatory, and intestinal dilation. This interpretation would be consistent with the clinical experience that it takes some time before patients develop a distended abdomen after surgery. Furthermore, we showed in a previous clinical study with barostat recordings that the intestine seems to be contracted during the first hours after surgery and that the distended bowel is a feature of later stages of POI.[28]

Spontaneous afferent nerve discharge and sensitivity to bradykinin was increased in segments from POI animals independent of whether recordings were made from contracted or dilated segments. At 9 h after surgery, afferent nerve discharge was increased at high thresholds in dilated segments, while it was reduced in contracted segments when compared to controls. There are several possible explanations for this observation, which was persistent during the entire observation period. First, neuronal reflex inhibition is followed by a local inflammatory response during the development of POI,[8,29] and considering that at 24 h the intestine was similiarly dilated in our previous study,[27] it appears possible that in the dilated parts a local inflammatory response already developed in the intestinal muscularis, while the contracted part did not yet show this pattern 9 h after surgery. Based on this assumption, the increased afferent nerve discharge in the dilated parts would then be secondary to inflammatory mediators such as prostanoids that have permissive effects on the afferent nerve response to bradykinin and high-threshold distension.[24–26] This interpretation, however, needs to be further substantiated by histological studies in the future. Second, pain perception following intestinal distension correlates well with strain on the intestinal wall.[30] Thus, considering that pain perception is a function of afferent discharge frequency at the intestinal nerve, afferent discharge would depend on wall strain. When we apply LaPlace's law to our experimental setup, wall strain is lower at a given pressure with a small diameter compared to bigger diameters of the intestinal segment. Thus, wall strain is higher in a dilated segment at a peak pressure of 80 cmH_2O compared to a contracted segment. This would explain the increased discharge frequency in dilated segments compared to

contracted segments on the basis of biomechanical alterations in the gut wall. Nevertheless, interpretations remain speculative, so that the phenomenon of different contractile states of the intestine 9 h after surgery warrants further investigation.

It is of note that afferent sensitivity during POI 1, 3, and 9 h after surgery is different when compared to a later stage of POI after 24 h. Contrary to the observations in this study, afferent mechano-sensitivity to low-threshold distension which is known to be mediated by vagal afferents is increased 24 h after surgery.[15] Furthermore, vagal nuclei in the brain stem are activated 24 h after surgery.[27] This vagal sensitization at 24 h is likely to be secondary to inflammatory mediators such as histamine and serotonin (5-HT) that have the potential to sensitize intestinal vagal afferents[31] and are probably released during the inflammatory response which occurs at that stage of POI.[8,11] In summary, the present study supports the concept that spinal afferents are involved during the initiation of POI (i.e., ≤9 h), while previous work provided evidence that vagal afferents come into play at a later stage when the immune response in the intestinal wall is established.[6,9,16]

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ORIGINAL ARTICLE

Does the Use of Nizatidine, as a Pro-kinetic Agent, Improve Gastric Emptying in Patients Post-oesophagectomy?

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Abstract
Purpose Delayed gastric emptying following oesophagectomy is common and can often lead to weight loss, malnutrition and a poor quality of life. Animal models have shown that nizatidine, a histamine H2-receptor antagonist, has pro-kinetic properties and can accelerate gastric emptying. Patients post-oesophagectomy require long-term acid suppression medication; if nizatidine can improve gastric emptying, it can be adopted for its dual pharmacological actions.
Methodology Twenty consecutive patients were prospectively enrolled in this trial following oesophagectomy. All patients were more than 6 months post-surgery and had no evidence of recurrent cancer. A baseline nuclear medicine scan following a radiolabelled meal was conducted and then repeated after 1 week of nizatidine (150 mg bd) treatment. Quality of life and eating comfort data were collected.
Results Oesophagectomy causes a significant delay in gastric emptying. Early satiety (80%) and reflux (65%) were the most common post-operative complaints. The percentage of food remaining in the stomach at 60 min post-meal was significantly more than normal values in both the pre- and post-nizatidine studies. There is no advantage in using nizatidine as a pro-kinetic agent.
Conclusions Impaired gastric emptying post-surgery causes a change in eating habits. Patients in this study did not lose a significant amount of weight despite all indicating worse eating comfort. Patients required more regular meals or snacks throughout the day and avoid foods that are difficult to swallow. It is likely that gastric motility only plays a small role in the emptying process and gravity combined with appropriate drainage procedures (pyloroplasty/pyloromyotomy) at the time of surgery are more important.

Keywords Pro-kinetic · Oesophagectomy · Clinical trial · Gastric emptying · Nizatidine

Introduction

Oesophageal cancer is a difficult disease to cure and surgical resection remains the mainstay of treatment.

All authors are in agreement as to the content of this manuscript.

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Unfortunately, there are a range of early and late complications that can occur. Finley et al.[1] looked specifically at complications following oesophagectomy for malignancy and found that impaired gastric emptying was a significant risk factor for pneumonia. Gastric reflux, dumping syndrome and diarrhoea were also common symptoms. Early satiety and alimentary discomfort[2] may lead to long-term weight loss, malnutrition and a poor quality of life for the patient.

The role of the stomach as an oesophageal substitute has long been regarded as an inert tube, with emptying occurring via gravity.[3,4] More recent research by Collard et al.[5] has shown that it progressively recovers motor activity over 3 years of follow-up. Erythromycin, a macrolide antibiotic, has been extensively studied and shown to improve gastric motility and emptying.[6–10] Erythromycin appears to act as a motilin receptor agonist allowing improved motility even within the denervated stomach.[11] Early post-operative erythromycin gives similar results to what would be expected from the denervated stomach after 3 years of spontaneous recovery.[9] It appears that pro-kinetic agents have an important role to play in the management of symptoms associated with impaired gastric emptying post oesophagectomy. Concerns over bacterial resistance associated with long-term erythromycin use combined with known adverse effects such as hepatic dysfunction, cardiac arrhythmias and hearing loss have led to alternative pro-kinetic agents being sought.

Nizatidine is a histamine H2-receptor antagonist that is widely used to treat gastric and duodenal ulcers as well as gastro-oesophageal reflux disease (GORD). It has been shown in animal models to possess pro-kinetic properties and to accelerate gastric emptying.[12–14] The only current study looking at the role of nizatidine to improve gastric emptying is in patients with functional dyspepsia[15] not post-oesophagectomy. The pro-kinetic activity of nizatidine is due to its non-competitive inhibition of acetylcholinesterase[13] and its action has been shown in some studies to be abolished by atropine[16] indicating involvement of the cholinergic pathway.

The majority of patients post-oesophagectomy require long term acid suppression medication with proton pump inhibitors often used. Nizatidine is a well-tolerated histamine H2-receptor antagonist used to suppress gastric acid secretion. If it can be shown to improve gastric emptying in humans, it may be adopted for its dual pharmacological action. Moreover, it has minimal side effects and is usually better tolerated than erythromycin.

The aim of this study was to determine if nizatidine used for 7 days improves gastric emptying in patients post-oesophagectomy. We expected the entire study population to have delayed gastric emptying.

Methods

We designed a prospective clinical trial looking at gastric emptying post-oesophagectomy. The study was conducted at Cabrini Hospital Malvern, a community-based private hospital and involved surgeons who specialise in upper gastrointestinal surgery. In total, 20 patients were recruited between January 2005 and April 2006.

Patients were recruited for this trial after presenting to the surgeons' rooms and fulfilling the inclusion criteria. All patients had to be 18 years of age or greater, have supplied written informed consent and were six or more months post-oesophagectomy. Exclusion criteria included patients with a known allergy to nizatidine, those who were unable to give informed consent, pregnant or potentially pregnant females and patients who were still undergoing treatment for oesophageal cancer. Participants were also excluded if their baseline gastric emptying study was normal.

After obtaining informed consent, a baseline nuclear medicine gastric emptying scan was organised. Two patients prescribed pro-kinetic agents (one on cisapride and one on metoclopramide), two prescribed nizatidine and two prescribed ranitidine were instructed to cease these 1 week prior to the scan. All patients who were taking proton pump inhibitors were advised to continue (13 in total). On the day prior to their gastric emptying scan, only fluids were allowed from midday and fasting from midnight was required. A nuclear medicine gastric emptying scan was then conducted with results expressed as lag time, half emptying time and percentage of meal remaining in the stomach at 60 min.

A solid meal of scrambled eggs contained the radioactive label Tc99m, calcium phytate. The radiation dose had been calculated to approximately 0.5 mSv and approval obtained from the Department of Human Services, Radiation Safety Program. Gastric emptying studies were conducted in the supine position to assess active gastric emptying rather than just the effect of gravity. The same radiologist was used to interpret the results of all the radionuclide studies.

The normal ranges for gastric emptying parameters are as follows:

Lag time (latency) for solids=15–20 min
Half emptying time (T 0.5) for solids=90±12 min
Normal emptying (% cleared at 60 min)>35% for solids

Patients with abnormal gastric emptying studies were instructed to remain off any pro-kinetic agents and also asked to cease proton pump inhibitors at this stage. They were then commenced on nizatidine 150 mg bd for 1 week, and a repeat nuclear medicine scan was organised for the end of this treatment period. All patients were given the

same instructions for food intake as had pertained prior to the first scan. The reason for treating patients for 7 days with nizatidine is that it was believed long enough to show an effect but short enough to allow 100% follow-up and compliance.

Baseline variables were collected for all patients: age, sex, weight, medications, co-morbidities, type of operation performed, date of surgery and pathology. The primary outcome measure was the percentage of a radiolabelled meal remaining in the stomach after 60 min. Information on quality of life and eating comfort was also collected.

A questionnaire was given to all patients to determine secondary outcome measures relating to their eating habits a subjective measure of their digestive functional outcomes post-surgery. These included eating comfort (assessed on a visual analogue scale with descriptors at, 0—unacceptable and 10—as good as prior to surgery), weight change, meals per day and snacks between meals and if the patient suffers from dysphagia, early satiety, vomiting or reflux. These questions relating to functional outcomes were collected prior to commencing the study and used as statistical co-variates to determine their effect on the primary outcome measures.

Sample Size

The gastric emptying scans in this study reported the percentage of food remaining in the stomach after 60 min. Each patient has an individual percentage suggesting a continuous variable. Normal patients have 30% of their food remaining within the stomach after 1 h while patients post-oesophagectomy commonly have up to 85% remaining. The percentage emptied at 60 min pre- and post-treatment was compared using a paired *t* test. It was calculated that we could show a difference of 1 standard deviation (approximately 25%) by having 16 patients in total, with each patient acting as their own control. To account for any dropouts, we aimed to recruit 20 patients.

Statistical Analysis

Information was collected and entered into an Excel worksheet which was then analysed with the advice and assistance of a statistician from the Cabrini Research Institute. The variables examined included the 'lag time', 'half emptying time' and 'percentage of food remaining in the stomach at 60 min' as assessed on radionuclide scans. 'Lag time' refers to the time taken for food to start emptying from the stomach and 'half emptying time' is the time taken for the stomach to have emptied 50% of the meal. Cox proportional hazard modelling was used to assess differences between the pre- and post-treatment groups. Likelihood ratios were then incorporated to assess the effect other variables had on these results. The upper limit for lag time was censored at 60 min and for half emptying time was 1,700min (greater than the largest calculated result).

Results

All patients recruited for this study had abnormal gastric emptying studies and therefore continued with the trial intervention as per the protocol. Patient demographics, post-operative weight and pathology results are displayed in Tables 1 and 2.

The primary outcome measures of time to first emptying ('lag time'), half emptying time and percentage of meal remaining at 60 min are summarised in Tables 3 and 4. The mean percentage of gastric contents remaining after 60 min were compared using a paired *t* test and showed no significant difference pre- and post-treatment (t test=1.05 on 19 degrees of freedom; p=0.3065).

Analysis of lag time using Cox proportional hazards modelling showed no significant difference (Hazards ratio= 0.99, 95% confidence interval (CI)=0.55–1.78; p=0.976). Incorporating secondary outcome measures to the model showed that lag time decreased with an increasing number of years post-surgery (p=0.046). This result is not significant if one outlying patient who was 10 years post-surgery is excluded. Analysis of results for patients within 3 years of surgery at the time of investigation shows no statistical significance (p=0.572). Weight gain was significantly higher in patients with shorter lag times (likelihood ratio test; p=0.001). A total of three patients were more than 3 years post-surgery which has been shown by Collard et al.[2] as the time it takes for the progressive return of motor

Table 1 Patient Demographics

	Mean	SD	Range
Age at time of investigation (years)	65.4	10.5	45–85
Weight at time of investigation	61.2	9.8	38–78
Male	64.9	7.5	52–78
Female	50.0	7.1	38–55
Weight change since surgery	-1.7	5.7	−15–5
Post-operative weight	62.8	10.9	45–85
Male	66.6	9.8	48–85
Female	51.6	4.1	45–55
Years since surgery	2.1	2.3	0.5–10.2
Age at surgery (years)	63.4	3.0	43–80
Meals per day	3.4	0.75	2–5
Eating comfort score	5.1	2.0	1–9

SD standard deviation

Table 2 Demographic and Clinical Characteristics of the 20 Patients

	Number	Percent
Male	15	75
Female	5	25
Pathology		
Adenocarcinoma	15	75
SCC	1	5
Barrett's with high grade dysplasia	3	15
Foreign body granulomatous reaction	1	5
Lymph node involvement	9	45
Dysphagia	8	40
Early satiety	16	80
Post-prandial vomiting	6	30
Reflux	13	65

activity. All these patients had abnormal gastric emptying studies and were acting as their own control and hence remained in the study analysis.

Cox regression analysis of half-emptying time also showed no difference (hazards ratio=1.60, 95% CI 0.87–2.94; p=0.130). Similar to lag time, patients with larger weight gain had lower half-emptying times (likelihood ratio test; p<0.0005).

There were no significant differences in the time to start emptying, the half-emptying time or percentage of a solid meal remaining after 60 min for studies conducted pre- and post-treatment with nizatidine. Adjustment for the other measured covariates did not alter this result. Interestingly, we did show that patients who gained weight post-surgery were more likely to have shorter lag times and patients who reported reflux symptoms were more likely to achieve half-emptying sooner than patients without reflux.

Discussion

Impaired gastric emptying is a recognised complication following oesophagectomy and multiple studies have shown that it has an adverse effect on quality of life.[1,2,17] When patients in this trial ingested a radiolabelled meal approximately 80% remained in the stomach after 60 min. In a healthy population, it is expected that at least 35% of a solid meal would have emptied in this time. Early satiety (80%) and reflux (65%) were the most common residual symptoms following oesophagectomy in our study population. Burt et al.[7] showed that early satiety after gastro-oesophagectomy is caused by delayed gastric emptying and not the decreased size of the gastric reservoir. The surgeons in this study use the whole stomach or a wide gastric tube (stomach minus cardia) as an oesophageal substitute. There is literature to support the argument that delayed gastric emptying is associated with this approach[18] and a gastric tube should be adopted.[19] There is also a belief that using the whole stomach may lead to better functional outcomes.[20] Obviously, this discussion has not been resolved and a more recent publication by Tabira et al.[21] concluded that the width of the gastric tube had no impact on tissue blood flow, leakage rates or nutritional status. The aim of our study was to look at the role of nizatidine to stimulate gastric emptying and we believe it is important therefore that all patients had a similar procedure.

A large randomised study by Fok and colleagues,[22] compared pyloroplasty versus no drainage procedure in patients post-oesophagectomy and showed that pyloroplasty significantly improved gastric emptying. Our study protocol therefore included pyloroplasty or pyloromyotomy for all study patients. There have also been studies looking at the role of balloon dilatation[23] and botulinum toxin[24] injection of the pylorus to improve gastric emptying post-oesophagectomy with promising results. Neither of these methods was adopted in this study. Despite these drainage procedures, it has been shown that pro-kinetic agents such as erythromycin have a more significant effect on improving gastric emptying.[8] As our investigation was conducted in the supine position to examine an increase in gastric motility, the importance of drainage procedures in gastric emptying associated with erect posture cannot be determined.

Data on quality of life was collected throughout the study and confirmed previous reports of ongoing alimenta-

Table 3 Primary Outcome Measure (Lag Time and Half-Emptying Time)

	Median (min)	Interquartile range (min)
Lag time		
Pre-treatment	17	8
Post-treatment	14	6
Half-emptying time		
Pre-treatment	199	76
Post-treatment	205	110

Failure criteria was when no emptying occurred within 60 min. Failure time for half-emptying was set at 1,700 min (larger than the largest observation)

Table 4 Primary Outcome Measures (Percentage Remaining at 60 min)

	Mean % (SD)	Minimum and maximum % range
Percentage remaining at 60 min		
Pre-treatment	83.6 (24.6)	17–100
Post-treatment	76.8 (28.3)	0–100

Failure criteria was when no emptying occurred within 60 min. Failure time for half-emptying was set at 1,700 min (larger than the largest observation)

ry discomfort following oesophagectomy.[2] Despite this discomfort, it did not equate to a loss of weight for 70% of the patients indicating there is no general decline in nutritional status. A sensation of early fullness was the most common residual symptom but most patients compensated for this by eating smaller more regular meals and snacking between them. Using a ten-point eating comfort score, we were able to show that 11 patients (55%) experienced only mild discomfort or better (a score of 5 or higher). Our functional outcome scores for dysphagia and reflux correlate well with figures published from the Mayo clinic by Headrick et al.[25] Fewer of our patient population had weight loss and more experienced weight gain than the Headrick et al. series (Table 5).

Nizatidine is a competitive antagonist for histamine at the H2 receptor. After oral administration, it has 95% bio-availability and a serum half-life of up to 2 h. Elimination occurs via a combination of hepatic metabolism (22%) and renal clearance (65%).[26] Multiple studies have reported that nizatidine has gastric pro-kinetic activity.[12,13,27] Ueki et al.[13] detected dose dependent pro-kinetic activity with nizatidine in both dogs and rats, using surgically implanted electrical transducers. Kaneko et al.[12] also showed that nizatidine, but not cimetidine or famotidine, dose dependently accelerated gastric emptying of a barium containing solid meal in rats. The lack of improvement in gastric emptying with cimetidine and famotidine was considered important because of previous reports that alkalization in the duodenum accelerates gastric motility.[28]

It is believed that nizatidine's pro-kinetic action is the result of its non-competitive inhibition of acetylcholinesterase. It has been shown in the laboratory that acetylcholinesterase from human erythrocytes is inhibited by nizatidine,[13] and tissue stimulation tests of guinea pig gastric smooth muscle also exhibited a nizatidine-induced contractile response.[16] The pro-kinetic effects of nizatidine occur at doses comparable to those required to suppress gastric acid.[27]

A systematic review by Zarling[14] examined the pro-kinetic activity of nizatidine and its implications for gastro-oesophageal reflux disease. Patients with GORD frequently require a combination of acid suppression and pro-kinetic support similar to our current study population. It was postulated that nizatidine appears to be well suited to fulfil both requirements, but further human studies on its pro-kinetic properties in humans was required.

Table 5 Comparison of Functional Outcome Scores

	Cabrini (n=20)	Mayo[a] (n=48)
Decreased weight	6 (30%)	31 (65%)
Increased weight	7 (35%)	7 (14%)
No weight change	7 (35%)	10 (20%)
Dysphagia	8 (40%)	18 (37%)
Reflux	13 (65%)	36 (68%)

[a] Headrick et al.[25]

The results of our study showed that nizatidine had no effect on improving the gastric emptying of a solid meal in patients post-oesophagectomy when used for a period of 7 days. Significant findings included that patients who gained weight since surgery were more likely to have shorter lag times and patients with reflux achieved an earlier half emptying time than patients without. The clinical significance of these findings is uncertain; a shorter lag time may encourage greater food intake and therefore weight gain. Six patients had lag times that extended beyond the 60-min duration of at least one of their two radionuclide scans, none of these patients gained weight post-surgery and four lost weight.

A possible explanation for the lack of an observed effect with nizatidine as a pro-kinetic agent relates to its mechanism of action. Total truncal vagotomy causes disruption to the parasympathetic neuronal control of the stomach. Acetylcholine (Ach) is the neurotransmitter involved in vagal stimulation of the stomach increasing gastric motility and secretory function; using a drug which improves the availability of Ach by inhibiting the enzyme acetylcholinesterase will have reduced effect when the pathway has been divided. Investigation of nizatidine as a pro-kinetic agent in patients who have not had vagotomy, such as those with GORD, may therefore still show a benefit. A recent study by Koskenpato et al.[15] concluded that nizatidine prolonged gastric emptying of solids in patients with functional dyspepsia. Koskenpato et al. investigated the use of nizatidine over a 2-month period whereas we looked at its effect over 7 days. The optimal length of treatment and any long-term effects are still not clear.

Impaired gastric emptying is common post-oesophagectomy but does not cause significant nutritional impairment. The radionuclide scan in our study was conducted in the supine position causing similar delays in gastric emptying as those seen by Morton et al.[3] It appears that surgical drainage procedures such as pyloroplasty or pyloromyotomy and even balloon dilatation or botulinum toxin injection, maintaining an upright posture and eating regular meals to accommodate the less distensible stomach are methods that can be adopted for improving gastric output.

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ORIGINAL ARTICLE

Major Airway Injury During Esophagectomy: Experience at a Tertiary Care Center

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Abstract
Background Tracheal laceration is a rare but life-threatening complication of esophagectomy. It is seen both with transhiatal and transthoracic esophagectomy.
Methods Three hundred eighty-two esophagectomies were performed from 1998 to 2008. The medical records of five patients with laceration of trachea during esophagectomy managed at a tertiary care center were reviewed retrospectively.
Results There were three males and two females with age range 18–62 years. The overall incidence of tracheal laceration was 1.31%. Four lacerations (1.30%) occurred during transhiatal and one (1.35%) during transthoracic resection of esophagus. Tracheal laceration was detected intraoperatively in all. Laceration was long (>3 cm) in three patients and short (<2 cm) in two. Patients with long laceration required direct suturing, while those with short laceration could be managed with gastric reinforcement. No patient required additional thoracotomy to access the lesion. Two patients had pneumonia, one had recurrent nerve palsy, while another developed anastomotic disruption. No patient died.
Conclusion Laceration of trachea is a potentially morbid complication of esophagectomy. Management should be individualized based on the extent and type of laceration. The surgical strategy depends upon the index procedure. The present series describes successful management of patients with tracheal injury associated with esophagectomy.

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Keywords Airway · Tracheal · Injury · Esophagectomy · Transhiatal · Transthoracic · Repair

Introduction

Tracheal laceration is a dreaded and potentially fatal complication of esophagectomy. Its incidence is reported to be 0.6% to 1.8% during esophagectomy.[1–4] Owing to the close proximity, the membranous trachea is always at risk while performing esophagectomy.[1–4] The risk further increases with the presence of tumor and inflammation in the region of trachea.[5] Tracheal laceration is associated with

loss of airway compliance and the respiratory insufficiency.[6–8] This can lead to a life-threatening hypoxia. The condition mandates immediate attention to ventilate the patient and subsequent management of laceration.[4–8] Various methods of tracheal repair have been described.[4,5,9–12] We herein describe our experience of managing tracheal injuries in patients undergoing esophagectomy over a period of one decade.

Patients and Methods

The records of five patients with major airway injury during esophagectomy over a period of 10 years (from August 1998 to August 2008) were reviewed at Postgraduate Institute of Medical Education and Research, Chandigarh, a tertiary care center in North India. During this period, 382 esophagectomies were performed—308 (80.6%) transhiatal (THE) and 74 (19.4%) transthoracic (TTE). The demographic parameters, operative management, and peri- and postoperative courses were studied.

Demographic Data

There were three males and two females with median age of 52 years (range 18–62). Three patients underwent surgery for benign disease and two for malignancy. Two patients with malignancy had received neoadjuvant chemotherapy (5FU and cisplatin, two cycles) prior to surgery. The location of the tumor was upper third in one and lower third in another. None of them had bronchial invasion on fiberoptic bronchoscopic examination. The indication of esophageal resection in the remaining three were achalasia cardia with sigmoid esophagus in one, giant leiomyoma of the upper esophagus in another, and corrosive injury to the esophagus in the third. The last patient had previously undergone esophageal exclusion and diversion following endoscopic perforation of the esophagus. The patient with giant leiomyoma had tracheal compression on imaging studies, but there was no invasion of broncoscopic examination (Table 1).

Operative Details

Injury Circumstances

Four patients had transhiatal esophagectomy, while one with giant leiomyoma underwent transthoracic esophagectomy. The overall incidence of tracheal injury during esophagectomy was 1.31–1.30% during THE and 1.35% during TTE.

During mediastinal dissection, there were dense adhesions between the membranous trachea and the esophagus in three patients. In an attempt to separate trachea from esophagus, inadvertent tracheal injury occurred. In two patients, one with lower third tumor and another with achalasia, injury occurred in an attempt to strip the esophagus away from trachea.

The diagnosis of airwary injury was made intraoperatively in all the patients. The injury was detected by sudden loss of airway resistance and leakage of large amount of air in an attempt to ventilate the patient.

Immediate Management

In four patients undergoing transhiatal procedure, the endotracheal tube was advanced into the right bronchus, and the patients could be ventilated. This maneuver was guided by the surgeon's finger in the upper mediastinum. The dissection of the esophagus was completed, and gastric tube was made. Once the specimen was retrieved, the tracheal rent was assessed.

In one patient with transthoracic esophagectomy (right posterolateral), the laceration was directly visualized, and ventilation was maintained through the double lumen tube.

Table 1 Clinical Profile of Patients

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5
Age/sex	45/M	52/M	55/F	62/M	18/F
Diagnosis	Carcinoma esophagus	Carcinoma esophagus	Giant leiomyoma	Achalasia cardia	Corrosive stricture
Procedure	THE	THE	TTE	THE	THE
Level of tear	Mediastinal trachea	Mediastinal trachea	Mediastinal trachea and right bronchus	Mediastinal trachea and right bronchus	Cervical trachea
Length of tear	1.5 cm	2 cm	4.5 cm	5 cm	3.5 cm
Repair	GR	GR	DR	DR	DR
Complications	Anastomotic leak, pneumonia	Nil	Nil	RLN palsy, pneumonia	Nil
ICU stay	1 day	1 day	6 days	3 days	2 days
Hospital stay	32 days	12 days	16 days	19 days	16 days
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered

TTE transthoracic esophagectomy, *THE* transhiatal esophagectomy, *GR* gastric reinforcement, *DR* direct repair, *RLN* recurrent laryngeal nerve

Injury Assessment and Repair

All the patients had vertical laceration of the membranous trachea. The length of laceration ranged from 1.5 to 5 cm. In patients with long laceration (cases 3, 4, and 5), the tear confined to mediastinal trachea was seen to extend into the right bronchus in two and was confined to cervical trachea in one. In two patients with small laceration (cases 1 and 2), the rupture was confined to the mediastinal trachea only.

Two patients with small laceration (<2 cm) could be managed by gastric tube reinforcement of the membranous trachea. The gastric tube was advanced through the esophageal bed in such a way so as to snugly fit into the upper mediastinum and remain in close proximity to trachea.

Three patients with long laceration (>3 cm) required suturing of the trachea. Direct suturing of trachea (interrupted, polypropylene suture 4-0) with pleural reinforcement was undertaken in one patient undergoing transthoracic procedure.

In one patient undergoing transhiatal esophagectomy and laceration confined to cervical trachea, suturing (interrupted, polypropylene suture 4-0) could be easily performed under direct vision through the neck wound. In another patient with laceration extending to the mediastinal trachea and right bronchus, the repair was performed through the neck wound. The surgeon positioned himself on the head end of the patient wearing a headlight. Retractors were placed so as to retract trachea anteriorly and sternomastoid muscle laterally. This widened the retro-tracheal space, and the rent could be easily visualized in its entirety. The repair was performed using interrupted, nonabsorbable suture (polypropylene 4-0).

After the repair, the endotracheal tube was withdrawn so as to ensure that there was no inadvertent suturing of the endotracheal tube.

Subsequent to tracheal repair, the gastric tube was advanced into the neck, and cervical esophago-gastric anastomosis was performed. Bilateral intercostal tubes were placed prior to completing the procedure.

Postoperative Management

Two patients with gastric tube reinforcement of trachea were extubated in the immediate postoperative period. Three patients with suturing of tracheal laceration were ventilated in the postoperative period for a period of 24–72 h. Deep breathing exercises were encouraged. Aggressive chest physiotherapy and coughing were avoided in all the patients.

Complications and Outcome

Three patients made an uneventful recovery. Two patients had evidence of broncopneumonia requiring prolonged hospitalization. One patient had anastomotic leak, while another had recurrent laryngeal nerve palsy. The median ICU stay was 2 days (range 1–6 days), and the median hospital stay was 16 days (range 12–32 days). There was no mortality.

Discussion

Major airway injury is an uncommon occurrence with a reported incidence of 0.6% to 1.8%.[1–4] It is encountered both during transhiatal and transthoracic esophagectomy.[1–4] THE has been implicated to cause airway injury due to blunt dissection.[1,4] Orringer et al.[1] in their series of two thousand THE have reported an incidence of less than 1%. The exact incidence following TTE is not known as this complication is less frequently addressed. The probable reason may be that the intraoperative management in such a situation does not mandate additional procedure to access trachea. In a study by 383 patients, the incidence of major airway injury following THE was 1.8% and that following TTE was 0.8%. The difference was not statistically significant. The present series describes four out of five cases during THE due to the fact that this is the preferred method of esophageal resection at our institution; however, the incidence was almost similar with both procedures.

The laceration can arise as a result of direct injury to trachea, particularly in those patients with dense periesophageal adhesions or tracheal compression secondary to tumor located in its vicinity.[5,9] However, Hulscher et al.[4] have failed to demonstrate any correlation of tracheal injury with TNM stage and location of the tumor. Blind stripping of the esophagus during THE has also been implicated in the causation of tracheal tear.[1,4] The occurrence of inadvertent tracheal injury during esophagectomy has also been reported with double lumen endotracheal tube placement.[10] In the present series, all injuries were secondary to surgical manipulations—direct injury in three and blind stripping in two. Three patients had difficult mediastinal dissection. However, in one patient, tracheal injury occurred despite thoracotomy, probably related to the large size and tracheal compression by the tumor.

The injury is usually detected on table by inability to ventilate the patient and leak of large volume of air into the mediastinum in an attempt to ventilate.[6–8] The situation is life threatening and demands immediate attention. Delayed detection of the injury and consequent tension pneumothorax has also been described.[13] In the present series, all the injuries were detected on table. The inability of ventilation can be overcome by advancing the endotracheal tube beyond the tear. Care should be taken so as not to extend the tear further. We used surgeons' fingers as a guide to advance the endotracheal

tube. The use of high-frequency jet ventilation has also been described in such a situation.[7]

The treatment entails repair of the trachea. Conversion to a thoracotomy and direct visualization and suturing of the rent is an acceptable method of repair.[4,5] Harney et al.[10] described the used laparoscopic instruments to repair the trachea and prevented another thorcotomy/sternotomy. Millikan and Pytvnia[14] described the use of synthetic material to patch the defect. The graft material later needed surgical removal in view of infection.[16] Thus, this modality is not an attractive option of management. In the presence of empyema, distant autologous fascia reinforced with gelatin resorcin-formaldehyde/glutaraldehyde glue has been used.[15] The use of the stomach to patch the rent has been described.[9,16,17] The stomach tube abuts the tracheal rent and acts like a patch. This isolates the tear from the rest of the environment. Adequate lung expansion and postoperative breathing without positive pressure ventilation are the key factors in this method of management. Failure to achieve lung expansion even with negative suction mandates surgical exploration and repair. Conservative treatment of tracheal laceration by advancing the endotracheal tube beyond tear and maintaining positive pressure ventilation has been reported.[12] The present series describes direct tracheal repair in three patients (one with TTE, two with THE) and gastric tube reinforcement in two. Grenstein et al.[11] has described transcervical repair of lower trachea using free pericardial flap. The present series also describes this technique in one case. However, this technique of repair was associated with recurrent laryngeal nerve injury. We have tried to classify the extent of injury and base the management accordingly. No patient in the present series required additional access procedure for tracheal repair.

Tracheal injury is associated with significant increase in the pulmonary morbidity secondary to single lung ventilation and aspiration of blood.[4,5] In the present series, two patients with pulmonary complications required prolonged hospitalization.

Careful patient selection and addition of an elective thoracotomy can avert this injury during transhiatal resection. In a retrospective study of 70 patients undergoing THE, eight had inflammatory tracheoesophageal adhesions, and no patient developed major airway injury. Modification of the surgical technique like inversion esophagectomy and conversion to a transthoracic procedure could avoid major airway or adjacent visceral injury.[18]

Concluding, tracheal injury is a dreadful complication of esophagectomy. The condition mandates immediate recognition and repair. Therapeutic strategies should be based on the extent and location of the laceration. The use of cervical approach to repair lower trachea can avert thoracotomy.

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ORIGINAL ARTICLE

Dendritic Cell-Associated Immune Inflammation of Cardiac Mucosa: A Possible Factor in the Formation of Barrett's Esophagus

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Abstract
Background The development of Barrett's esophagus is poorly understood, but it has been suggested that cardiac mucosa is a precursor of intestinal type metaplasia and that inflammation of cardiac mucosa may play a role in the formation of Barrett's esophagus. The present study was undertaken to examine the presence and distribution of immune-inflammatory cells in cardiac mucosa, specifically focusing on dendritic cells because of their importance as regulators of immune reactions.
Material and Methods Endoscopic biopsy specimens were obtained from 12 patients with cardiac mucosa without Barrett's esophagus or adenocarcinoma and from 21 patients with Barrett's esophagus without dysplasia (intestinal metaplasia). According to histology, in nine of the 21 specimens with Barrett's esophagus, areas of mucosa composed of cardiac type epithelium-lined glands were present as well. Immunohistochemical staining and electron microscopy were used to examine immune-inflammatory cells in paraffin-embedded sections.
Results Immune-inflammatory cells, including T cells, B cells, dendritic cells, macrophages, and mast cells, were present in the connective tissue matrix that surrounded cardiac type epithelium-lined glands in all patients with cardiac mucosa. Clustering of dendritic cells with each other and with lymphocytes and the intrusion of dendritic cells between glandular mucus cells were observed. In the Barrett's esophagus specimens that contained cardiac type glands, computerized CD83 expression quantitation revealed that there were more dendritic cells in cardiac mucosa than in intestinal metaplasia.
Conclusion Immune-inflammatory infiltrates containing dendritic cells are consistently present in cardiac mucosa. The finding of a larger number of dendritic cells in areas of cardiac mucosa in Barrett's esophagus biopsies suggests that the immune inflammation of cardiac mucosa might play a role in modifying the local tissue environment to promote the development of specialized intestinal type metaplasia.

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Keywords Cardiac Mucosa · Barrett's esophagus · Intestinal metaplasia · Dendritic cells · Inflammation

Introduction

Cardiac mucosa is a type of mucosa that is lined by simple mucinous columnar epithelium with no parietal cells or chief cells, and this distinguishes cardiac mucosa from gastric oxyntic mucosa.[1–3] In the past, it was believed that up to 2 cm of cardiac mucosa was normally present in the most proximal section of the stomach where it separates the parietal and chief cell-containing gastric oxyntic mucosa from the esophageal mucosa lined by squamous-stratified epithelium (squamous mucosa).[1–4] This prevailing view was challenged by studies suggesting that cardiac mucosa, rather than being a normally occurring mucosa, might be an acquired, metaplastic epithelium that develops in response to exposure of esophageal squamous epithelium to gastric acid.[2] According to this hypothesis, at the normal gastro-esophageal junction, squamous mucosa transitions directly with oxyntic mucosa of the gastric fundus with no interposed segment of cardiac mucosa.[2] An examination of the gastroesophageal junction in a large number of autopsies of subjects, the medical records of whom had no mention of gastroesophageal reflux disease, has revealed that, in most children and adults younger than 20 years of age, the squamous mucosa of the distal esophagus transitioned directly with the oxyntic mucosa of the gastric fundus with no interposed segment of cardiac type simple columnar epithelium.[5] Further observations suggested that the development of cardiac mucosa is induced by exposing squamous epithelium to refluxed gastric acid.[2,6–8] This introduced the possibility that the formation of cardiac mucosa may be the first step in the development of Barrett's esophagus,[1,2,5,6] although controversy regarding the nature and etiology of cardiac mucosa remains. Unfortunately, limitations as to the accurate location of endoscopic biopsies[1,3,6] and the rapid autolysis of the mucosa of the gastroesophageal junction in autopsy specimens[1,5] have made it difficult to resolve this controversy.

It is thought that the primary importance of cardiac mucosa is that it represents the only mucosal type that can progress to specialized intestinal type metaplasia.[1,2] Once intestinalized, the esophagus seems to acquire an increased ability to withstand damage by refluxed gastric juice, compared with cardiac mucosa.[1,2] However, the development of specialized intestinal type of metaplasia (Barrett's esophagus) can also be a detrimental change because specialized intestinal type epithelium is capable of further progression to epithelial dysplasia and adenocarcinoma.[1–8] Available evidence suggests that cardiac mucosa itself is benign and that it is only with the development of intestinal type metaplasia the mucosa becomes premalignant.[1,2]

It is established that premalignant conditions develop in the presence of chronic inflammation and that immune mechanisms are critically involved in the development of cancer in these precancerous tissues.[9–11] A variety of inflammatory and immune cells populate the Barrett's esophagus mucosa, including T and B lymphocytes, mast cells, and macrophages.[12–14] We recently reported that antigen-presenting dendritic cells are present in Barrett's esophagus with a significant increase in their spatial density in adenocarcinoma compared to benign Barrett's esophagus.[14] Dendritic cells are powerful initiators and regulators of immune reactions[15–19] and thus may have a role in the pathogenesis of Barrett's esophagus and adenocarcinoma.[14]

In contrast to Barrett's esophagus, cardiac mucosa has received only very limited attention, possibly because it is not associated with an increased risk of cancer.[1,2] Nevertheless, it has been noted that inflammatory cells are so routinely present in cardiac mucosa biopsies that an alternative term for cardiac mucosa is "carditis."[1,3] The inflammation is not related to either *Helicobacter pylori* infection or other gastric mucosal pathology.[2] This prominent inflammatory infiltrate led to the suggestion that it may play a role in the formation of Barrett's esophagus, but there have been no detailed studies in this area.[2,4] We undertook this study to examine the immune-inflammatory cells, especially the presence, distribution, and cell interactions of dendritic cells, in cardiac mucosa.

Material and Methods

Tissue Specimens and Routine Histology

Endoscopic biopsy specimens selected for the present study were obtained from 12 patients without Barrett's esophagus or adenocarcinoma and from 21 patients with Barrett's esophagus without dysplasia. The specimens were taken from the tubular esophagus above the proximal extent of the gastric rugal folds from varying areas of the columnar-lined segment. The length of the columnar-lined esophagus varied from approximately 1 cm to approximately 4 cm. Tissue specimens were defined as Barrett's esophagus when specialized intestinal type columnar epithelium containing true goblet cells (specialized intestinal metaplasia) was present in any length of the columnar-lined esophagus. Cardiac mucosa was diagnosed by the presence of columnar epithelium consisting of mucous cells without any specialized cells such as parietal, chief, or goblet cells. Histological examination demonstrated that amongst 21 biopsy specimens with Barrett's esophagus, cardiac type glands were also present in nine specimens, while no

gastric (oxyntic) type epithelium was detected in any specimen. Only intestinal metaplasia was present in the other 12 specimens. Tissue specimens were processed by standard formalin fixation and paraffin embedding.

Material was collected in accordance with the principles outlined in the Declaration of Helsinki and informed, written consent was obtained from each patient. The study was approved by the Institutional Review Board of St. Vincent's Hospital, Sydney and the University of New South Wales, Sydney.

Single and Double Immunostaining Procedures and Quantitative Analysis

Dendritic cells were identified using anti-CD83 (Immunotech; cat. no. IM-2069; 1:50 dilution) and anti-DC-SIGN (Santa Cruz; cat. no. sc-65892; 1:50 dilution). CD83, an inducible glycoprotein belonging to the immunoglobulin superfamily, is important in T cell immunity mediated by dendritic cells.[20–24] CD83 is the most specific dendritic cell marker expressed by maturing and mature dendritic cells.[21–24] DC-SIGN is dendritic cell-specific intercellular molecule-3 (ICAM-3)-grabbing nonintegrin.[25,26] T cells were identified using anti-CD3 (Dako; cat. no. A0452; 1:100 dilution); B cells were identified with anti-CD20 (Beckman-Coulter; cat. no. 1925; 1:50 dilution); macrophages were identified with anti-CD68 (Dako; cat. no. M0876; 1:50 dilution); mast cells were identified with antimast cell tryptase (Abcam; cat. no. ab 2378; 1:50 dilution).

For single immunostaining, after elimination of endogenous peroxidase activity by 3% H_2O_2, sections were preincubated with normal nonimmune serum and then tested by avidin–biotin complex (ABC) using a standard ABC immunoperoxidase method. Briefly, after washing in Tris-phosphate buffered saline (TPBS), pH 7.6, the sections were incubated with a biotin-labeled secondary antibody, followed by a treatment with ABC (ELITE ABC, VECTOR PK61000). After washing in TPBS, brown staining was produced by 5 min treatment with 3,3′-diaminobenzidine (DAB). All the incubations were completed at room temperature. Archival lymph node sections were used for positive controls. For negative controls, the first antibodies were omitted or the sections were treated with an immunoglobulin fraction of nonimmune serum as a substitute for the primary antibody. None of the negative control sections showed positive immune staining. Counterstaining was performed with Mayer's hematoxylin.

A computerized quantitative analysis of CD83 expression was carried out at ×400 magnification using the Image-Pro Plus image analysis program (Media Cybernetics, Bethesda, MD, USA). CD83 expression was measured in each section in at least seven randomly selected microscopic fields containing both $CD83^+$ cells and epithelial glands. Statistical comparison of expression, measured in pixels per standard microscopic field (0.04 mm^2), was performed by *t* test using Prism® 5 (GraphPad Software, San Diego, CA, USA).

Double immunostaining with CD83/CD3 and CD83/CD20 was used to analyze the possible colocalization of dendritic cells with lymphocytes, using previously reported methods.[14,27] In brief, after visualization of CD83 with the ABC substrate kit, sections were washed with 0.1 M glycine–hydrochloric acid buffer, pH 2.2, and then incubated with anti-CD3 or anti-CD20 antibody. After rinsing in TPBS, the sections were incubated with biotinylated secondary antibody and then with alkaline phosphatase-conjugated streptavidin (Dako) or with ABC (Dako). A combination of the peroxidase–antiperoxidase (PAP) and alkaline phosphatase–antialkaline phosphatase (APAAP) techniques with antigen visualization with DAB or Fast Red was also used. Controls were the same as for single immunostaining. Counterstaining was performed with Mayer's hematoxylin.

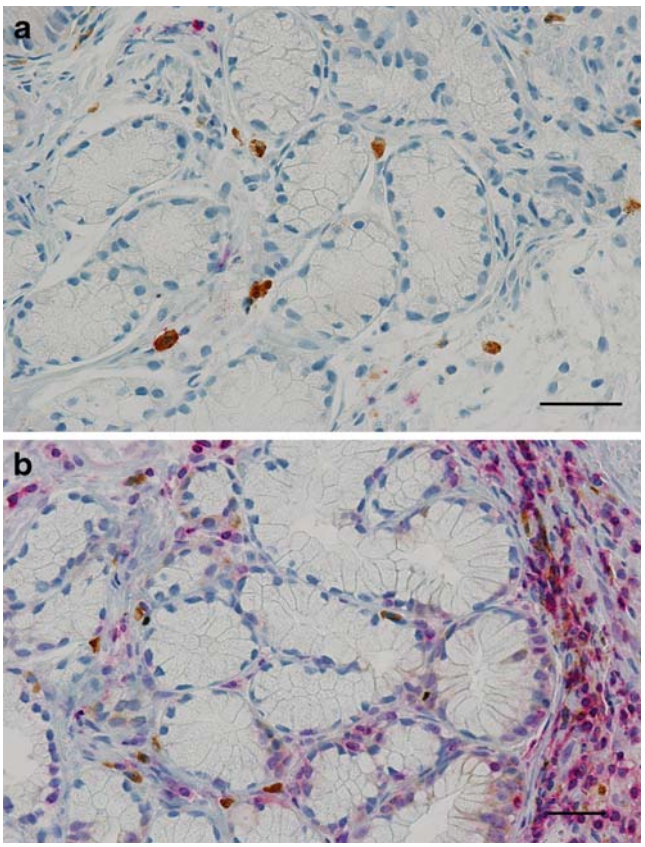

Figure 1 Dendritic cells and T cells in cardiac mucosa in esophageal biopsy specimens showing different degrees of inflammation (**a**, **b**). In **a** and **b**, CD83 antigen was visualized using ABC immunoperoxidase reaction (*brown* reaction product) while $CD3^+$ cells were visualized using a Fast Red substrate kit (*rose* reaction product). Counterstaining with Mayer's hematoxylin. Bars=50 μm (a, **b**).

Electron Microscopy

Fresh endoscopic biopsy specimens were fixed in 2.5% glutaraldehyde in 0.1 M sodium cacodylate buffer (pH 7.4), routinely processed and embedded in Spurr resin. Ultrathin sections were stained with uranyl acetate and lead citrate and examined with the aid of a Morgagni 268D electron microscope. The electron microscopic identification of dendritic cells was carried out according to their distinctive ultrastructural features which include the tubulovesicular system and atypical granules as previously used.[14,28]

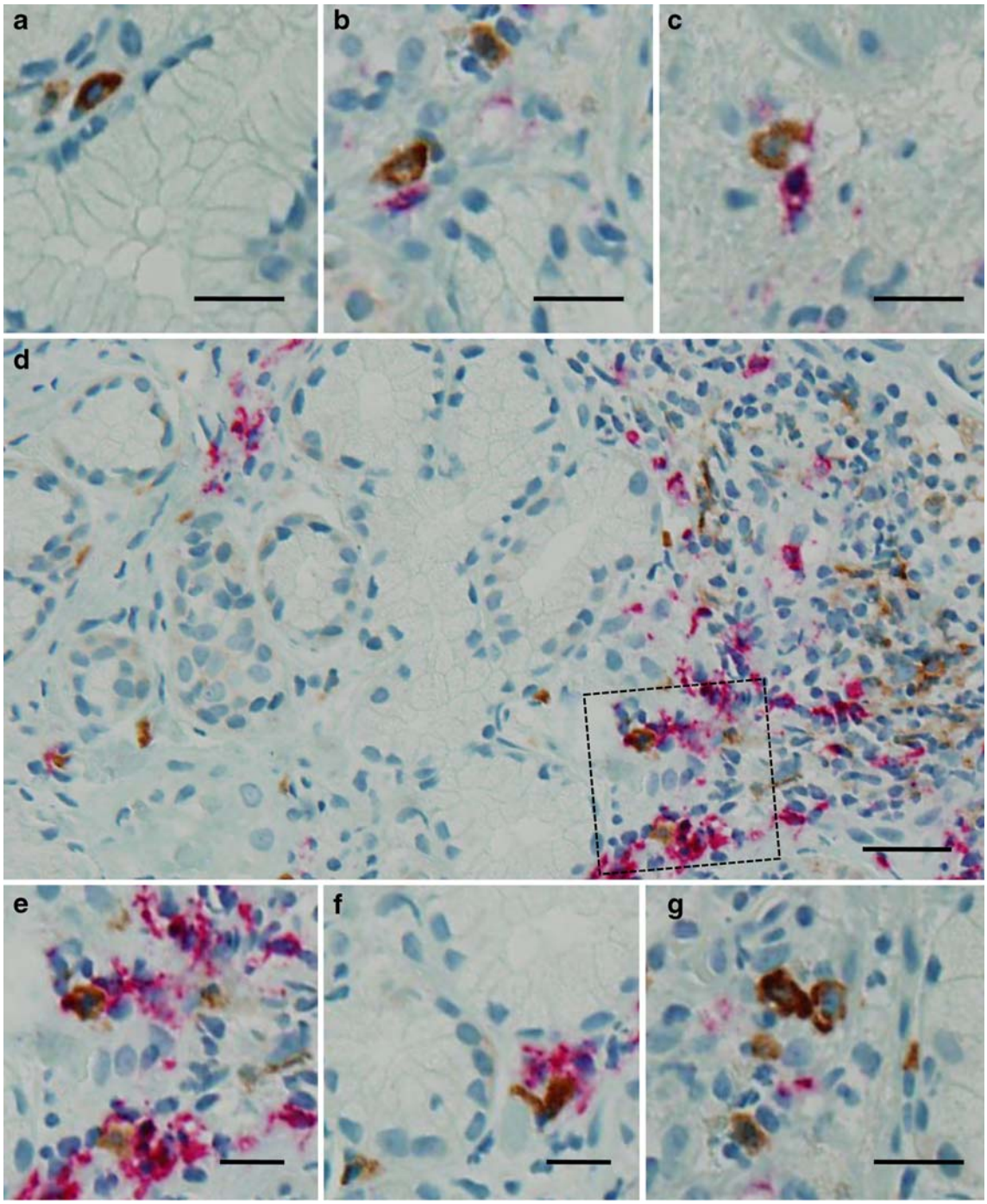

Figure 2 Direct contacts between dendritic cells and lymphocytes in cardiac mucosa (**a**–**g**). CD83 antigen was visualized using ABC immunoperoxidase reaction (*brown* reaction product) (**a**–**g**) while $CD3^+$ T cells (**b**, **c**) and $CD20^+$ B cells (**d**–**g**) were visualized using a Fast Red substrate kit (*rose* reaction product). Counterstaining with Mayer's hematoxylin. **e** is a detail of **d**. **g** Dendritic cells contacting each other. Bars=25 μm (**a**–**c**, **e**–**g**) and 50 μm (**d**).

Results

Tissue specimens in which metaplastic intestinal type columnar epithelium was not present contained only cardiac type columnar epithelium consisting of mucous cells. No parietal or chief cells were detected in any of these specimens, and thus, these tissue specimens were identified as cardiac mucosa. According to routine hematoxylin and eosin histology, all 12 cardiac mucosa specimens contained inflammatory cells in the connective matrix surrounding the glands. Immunohistochemistry revealed that immune-inflammatory infiltrates consisted of T cells ($CD3^+$), B cells ($CD20^+$), macrophages ($CD68^+$), and mast cells (mast cell $tryptase^+$).

The use of dendritic cell-specific markers, including CD83 and DC-SIGN, demonstrated the presence of dendritic cells in all tissue specimens where they represented a minor cell population (Fig. 1a,b). The degrees of immune inflammation varied markedly between the specimens. Figure 1a,b shows representative images of double-immunostained cardiac mucosa specimens in which a difference in the intensity of immune inflammation is readily identifiable. Despite that the intensity of immune inflammation varied markedly in all specimens examined, individually located dendritic cells (Fig. 2a) as well as dendritic cells contacting T cells were observed in the connective matrix of the cardiac mucosa (Fig. 2b,c). In all specimens, dendritic cells clustering with B cells (Fig. 2d–f)

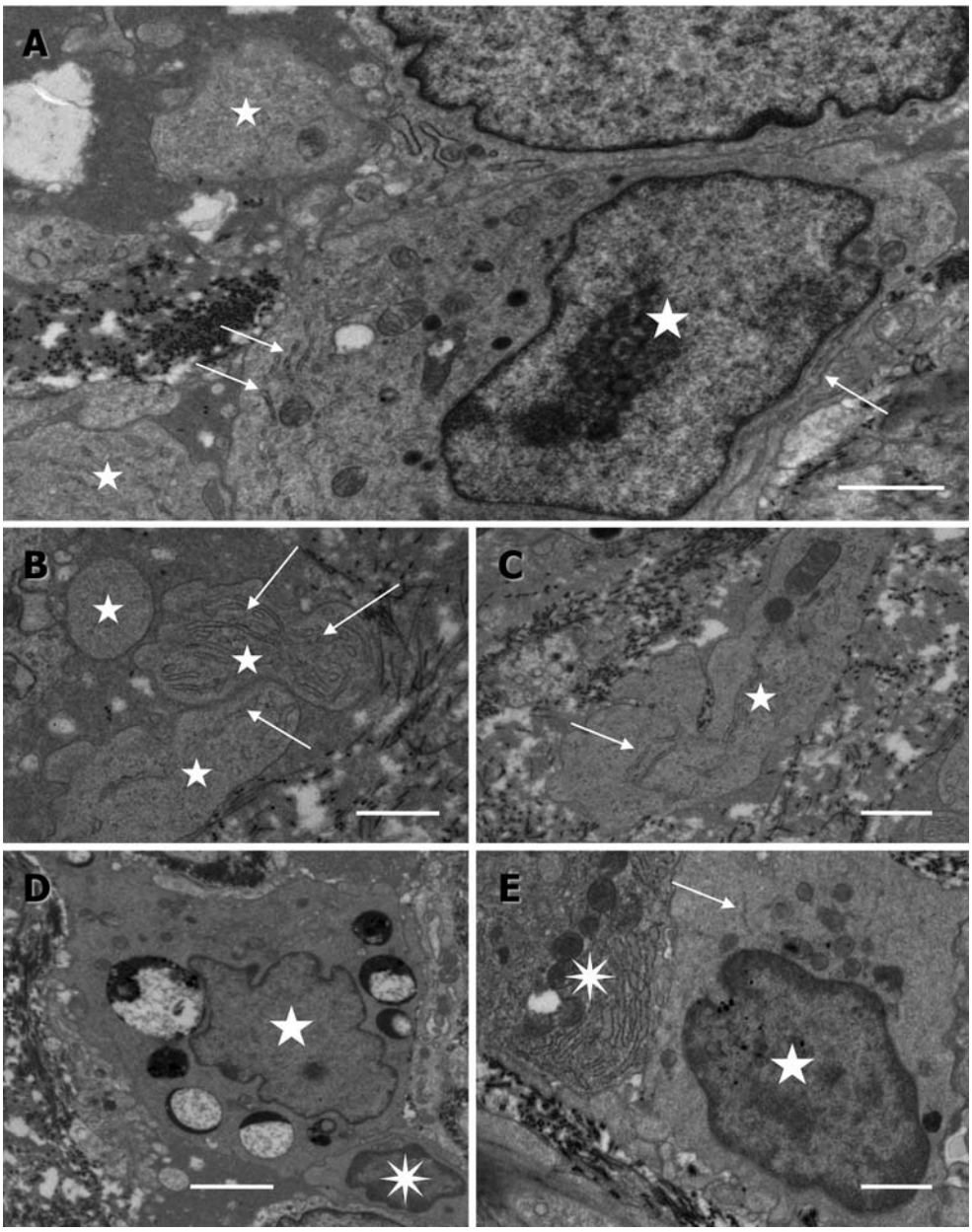

Figure 3 Electron micrographs showing dendritic cells and their direct contacts with lymphocytes in cardiac mucosa (**a**–**e**). In **a**, **d**, and **e**, dendritic cells are marked by *large stars* while dendritic cell processes are marked by *smaller stars* (**a**–**d**). *Arrows* in **a**–**d** show the tubulovesicular system which is markedly hypertrophied in the cellular processes (**b**, **c**). **d** A close apposition between a dendritic cell and a lymphocyte-like cell (*asterisk*). **e** A contact between a dendritic cell and a plasma cell (*asterisk*). In **d**, note hypertrophy of atypical granules in the dendritic cell. Bars=2 μm (**a**), 1 μm (**b**, **c**), 5 μm (**d**), and 3 μm (**e**).

as well as dendritic cells contacting each other (Fig. 2g) were also observed.

Immunohistochemical findings were confirmed by the identification of dendritic cells and their direct contacts with lymphocytes in the cardiac mucosa by electron microscopy (Fig. 3a–e). Cells with the unique ultrastructural features of the dendritic cell family, including the tubulovesicular system and atypical granules,[16,28,29] were seen in ultrathin sections (Fig. 3a–e). Through cell processes or by direct apposition of cell bodies, dendritic cells formed contacts with lymphocytes (Fig. 3d,e). Cisterns of the tubulovesicular system were usually hypertrophied in dendritic cell processes (Fig. 3a–c) while the hypertrophy of atypical granules occurred predominantly in the perinuclear cytoplasm of dendritic cells (Fig. 3d).

In cardiac mucosa, dendritic cells were found not only in the connective tissue matrix but also along the basal membrane of epithelial cells as well as, in some glands, between mucous cells (Fig. 4a–e). The intensity of the expression of CD83 notably varied between dendritic cells located along the glandular basal membrane (Fig. 4a–e). In the glands, which contained dendritic cells incorporated between mucous cells, the focal accumulations of T cells were also observed (Fig. 4a–e). In these foci, the clustering of dendritic cells with T cells occurred along the basal membrane (Fig. 4a–e).

Apart from being located in the connective matrix or being associated with the glands, dendritic cells were regularly observed around and within capillaries and microvessels, forming a network in cardiac mucosa. In this location, dendritic cells typically displayed high levels of CD83 expression.

The present study aimed to not only examine the features and patterns of distribution of dendritic cells in cardiac mucosa but also to compare the spatial density of dendritic cells located in the tissue matrix containing cardiac type epithelium-lined glands with the spatial density of dendritic cells located in the tissue matrix containing specialized

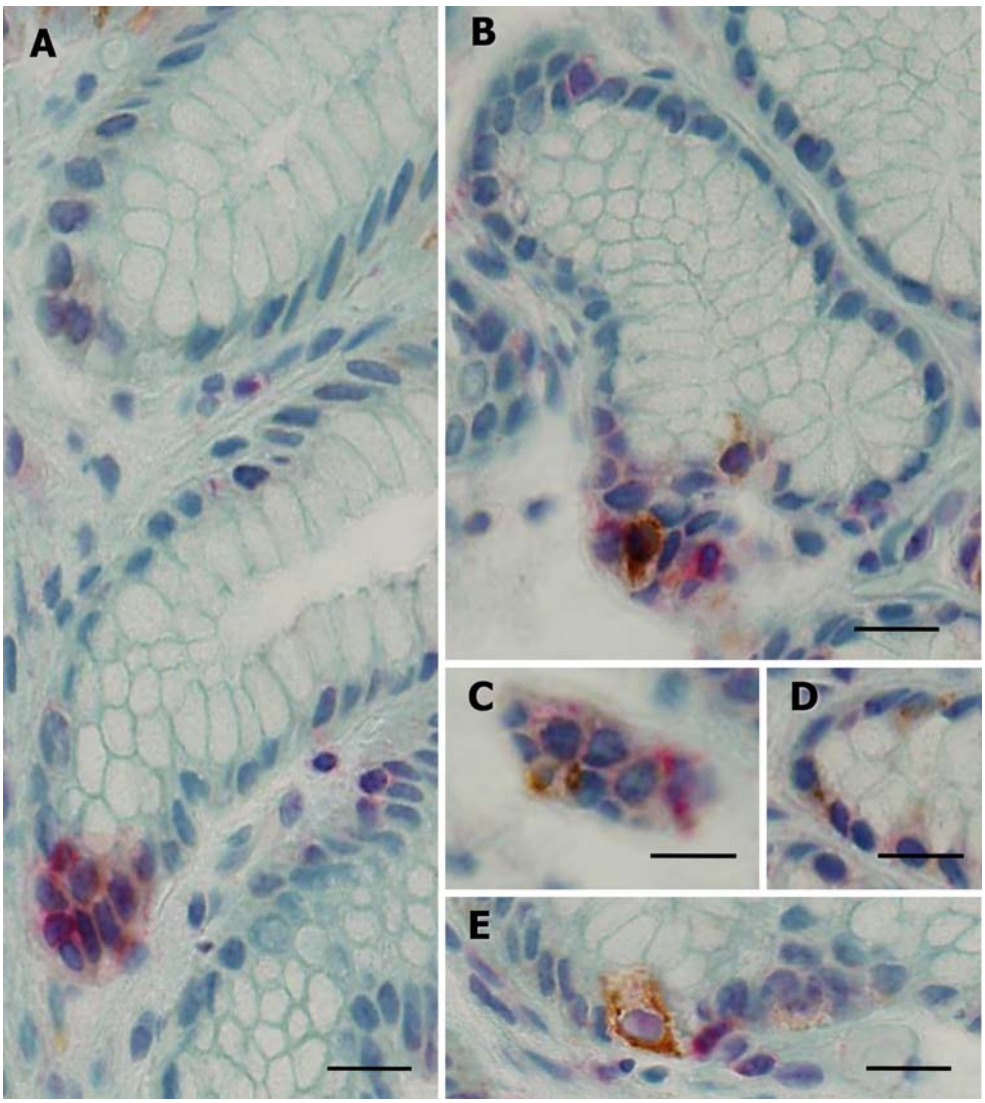

Figure 4 Intrusion of dendritic cells and T cells between mucous cells in cardiac mucosa (**a**–**e**). Note contacts between dendritic cells and T cells along the affected basal membrane, underlying mucous cells (**a**–**e**). Note also various intensities of the expression of CD83 antigen by dendritic cells located along the basal membrane of the glandular epithelial cells (**a**–**e**). In **a**–**e**, CD83 antigen was visualized using ABC immunoperoxidase reaction (*brown* reaction product) while $CD3^+$ cells were visualized using a Fast Red substrate kit (*rose* reaction product). Counterstaining with Mayer's hematoxylin. Bars=25 μm (**a**–**e**).

intestinal type epithelium-lined glands in tissue specimens of Barrett's esophagus which contained areas with cardiac mucosa. A semiquantitative analysis indicated that, in these specimens, the numbers of dendritic cells in the connective tissue matrix surrounding cardiac type epithelium-lined glands were greater than the numbers of dendritic cells in the connective tissue matrix that surrounded intestinal type epithelium-lined glands. This was verified by a computerized quantitative analysis of CD83 expression, which found an approximately twofold higher expression of CD83 in cardiac mucosa tissue matrix, compared with that in the Barrett's esophagus connective tissue matrix (959±254 vs 616± 172 pixels per standard field; Fig. 5a–c). The distribution patterns of dendritic cells around specialized intestinal type epithelium-lined glands in tissue specimens of Barrett's esophagus corresponded to those described by us earlier.[14]

Discussion

In agreement with previous notes,[2–4] this study showed that cardiac mucosa contains an immune-inflammatory cell infiltrate. Immune inflammation was present in all cardiac mucosa tissues examined in the present study, although the degree of inflammatory cell infiltration varied considerably between cardiac mucosa specimens. The immune-inflammatory infiltrates were consistently enriched by dendritic cells, which were present not only around glands in cardiac mucosa but also focally penetrated between glandular mucous cells, suggesting that the integrity of the epithelium in these foci was disrupted. Dendritic cells often formed contacts with both T cells and B cells in areas of the affected glandular basal membrane as well as in the connective tissue matrix adjacent to the glands. This could indicate that the activation of some lymphocytes might occur in situ within the mucosa, although the classic pathway for the migration of antigen-loaded dendritic cells through the vascular system to lymphoid organs cannot be excluded, especially as dendritic cells intensely expressing CD83 antigen were observed around and within capillaries and microvessels.

The intensity of the expression of CD83, a marker of dendritic cell maturation,[21–24] varied between the cells in cardiac mucosa, but dendritic cells that were in contact with lymphocytes typically displayed high levels of CD83 expression. Supporting the possibility that some dendritic cells were activated cells, electron microscopy revealed a marked hypertrophy of atypical granules and cisterns of the tubulovesicular system, both of which are known to represent structures involved in antigen-presenting functions of dendritic cells.[16,17]

An intriguing and potentially important finding of this study was that focal aggregations of dendritic cells and dendritic cells contacting each other were identified in the tissue matrix of cardiac mucosa. Clustering of dendritic cells with each other is known to occur in a number of autoimmune diseases[16,17,30] and has not been described in any disease in which autoimmune mechanisms are not involved. We, therefore, speculate that the immune inflam-

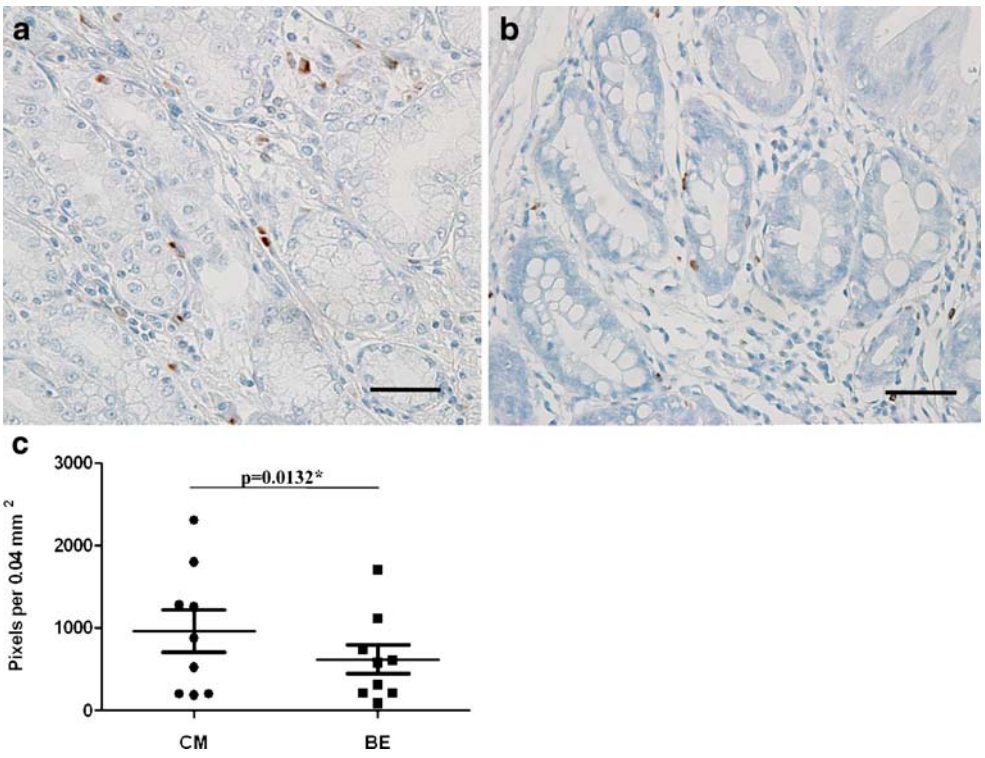

Figure 5 Dendritic cells in Barrett's esophagus tissue specimens containing both cardiac type epithelium (**a**, **c**) and specialized intestinal type epithelium (**b**, **c**). **a** and **b** Single ABC immunostaining of tissue slides showing the presence of dendritic cells (*brown*) in the lamina propria surrounding two different types of glands. Counterstaining with Mayer's hematoxylin. Bars= 100 μm (**a**, **b**). **c** Expression of CD83 antigen in cardiac mucosa (*CM*) and in specialized intestinal type mucosa of Barrett's esophagus (*BE*), evaluated as the number of pixels per standard field using a computerized quantitative analysis (see the "Material and Methods" section).

mation observed in cardiac mucosa might represent an ongoing autoimmune reaction or that autoimmune mechanisms are at least involved. The finding of dendritic cells penetrating into glands and closely apposed to glandular mucous cells also supports this possibility. Further studies are needed to evaluate the possible role of recruitment of autoimmune mechanisms in the formation of both cardiac type metaplasia and Barrett's esophagus.

Perhaps surprisingly, there were more dendritic cells in the connective tissue matrix surrounding cardiac type epithelium-lined glands compared to intestinal type epithelium-lined glands in the specimens which contained both cardiac mucosa and Barrett's intestinal metaplasia. This was confirmed by measuring the expression of CD83 antigen by dendritic cells, which was significantly higher in cardiac mucosa compared to intestinal metaplasia.

Overall, this study's findings suggest that the individual's immune response to ongoing exposure to noxious luminal contents may have a role in both the development of cardiac mucosa and its replacement by Barrett's esophagus. The importance of cardiac mucosa as the possible precursor lesion to Barrett's esophagus is indicated by studies showing similar protein expression profiles for both cardiac mucosa and Barrett's esophagus, including the expression of the small intestine marker proteins sucrase–isomaltase and crypt cell antigen, and DAS-1, a marker of specialized columnar mucosa.[31–34] Compelling evidence has also been provided by studies that found cardiac mucosa developing in the cervical remnant esophagus after esophagectomy, an in vivo human model for de novo reflux disease.[3,35] In one such study,[35] intestinal metaplasia developed in some patients with adenocarcinoma subsequently arising in one protein expression features. The specific cellular and molecular mechanistic events that induce change from cardiac mucosa to Barrett's esophagus are unknown[1–8,35–37] but the reduced inflammation in intestinalized mucosa compared to cardiac mucosa, shown in the present study, supports the teleological argument that intestinal metaplasia develops to protect the esophagus against the inflammation induced by injurious components of the refluxate.[2] The role of immune mechanisms, and possibly autoimmune mechanisms, in the neglected cardiac mucosa and in the formation of Barrett's esophagus requires further evaluation.

The present study is the first to report the presence of dendritic cells in cardiac mucosa. There is an ever-increasing body of data on the use of dendritic cells in immune therapeutic approaches against cancers and autoimmune diseases.[38–41] The finding of dendritic cells in cardiac type metaplasia might have a practical implication.

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ORIGINAL ARTICLE

Use of Positron Emission Tomography in Surgery Follow-Up of Esophageal Cancer

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Abstract
Introduction Although the prognosis of patients with esophageal cancer has been improved by extended dissection, the incidence of recurrence still remains high. In esophageal cancer, positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) already demonstrated to be useful for initial staging and monitoring response to therapy. This prospective study compared the ability of FDG-PET and conventional imaging to detect early recurrence of esophageal cancer after initial surgery in asymptomatic patients.
Materials and Methods Between October 2003 and September 2006, 41 patients with esophageal cancer were included in a prospective study after initial radical esophagectomy. FDG-PET, thoracoabdominal computed tomography (CT), abdominal ultrasonography, and endoscopy were performed every 6 months after initial treatment.
Results and Discussion Twenty-three patients had recurrent disease (56%), mostly within the first 6 months after surgery (70%). Despite two false-positive scans due to postoperative changes, FDG-PET was more accurate than CT (91% vs. 81%, $p=0.02$) for the detection of recurrence with a sensitivity of 100% (vs. 65%), a specificity of 85% (vs. 91%), and a negative predictive value of 100% on a patient-by-patient-based analysis. For the detection of locoregional recurrence, FDG-PET was more accurate than CT (96.2% vs. 88.9%). FDG-PET was also more accurate than CT for the detection of distant metastases (92.5% vs. 84.9%), especially when involving either bones (100%) or liver (98.1%). A lower sensitivity of FDG-PET (57%) for the early detection of small lung metastases did not affect patient management (accuracy=92.5%).
Conclusion FDG-PET appears to be very useful for the systematic follow-up of asymptomatic patients after esophagectomy with an initial scan performed 6 months after surgery.

Keywords Esophageal carcinoma · FDG-PET · Positron emission tomography · Follow-up · Recurrence

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Introduction

Esophageal cancer is an aggressive gastrointestinal disease and surgery remains the main potential curative treatment. According to the two randomized trials published on the subject, neoadjuvant treatment before surgery may improve local tumor control but it does not increase overall survival compared to chemoradiation alone.[1,2] The use of preoperative radiotherapy (RT) failed to improve outcome,[3] most likely because of a high rate of distant metastasis, whereas the use of preoperative chemotherapy in US trials had little impact on either local failure or distant dissemination of disease. A recent meta-analysis did report a significant benefit for preoperative chemoradiotherapy,[4] but neoadjuvant radiochemotherapy is still debated in advanced esophageal cancer.[5] Although the prognosis of patients has been improved by extended dissection,[6,7] the incidence of recurrence still remains high with a reported rate in the range of 36% to 64%.[8–11] More than half of all recurrences occur within 12 months after surgery.[11] The early diagnosis of recurrence in esophageal cancer can be of potential interest. Until now, once recurrence occurs, some patients will receive chemotherapy or radiation therapy,[12] while some will only go through palliative treatment because of their poor general condition. In few cases, salvage surgery may be considered, since some authors reported a better associated outcome.[13–15] Although the management of a recurrence greatly depends on the pattern of recurrence and the general status of the patient, a consensus treatment strategy has not yet been established. Concerning the patients with distant metastasis, a recent issue of the Cochrane database tends to show that there is no statistically proven impact of the use of chemotherapy.[16] New targets are actually the subject of intensive research in the field of esophageal neoplasms. We have previously published the potential impact of epidermal growth factor receptor (EGFR) status in the management of surgically resected patients.[17] The use of anti-EGFR targets could be a good way for prospective trials in this type of patients. At present, one of the prerequisites in order to improve patient management is the detection of recurrences as early as possible based on the usual follow-up procedure that includes endoscopy, ultrasonography, and thoracoabdominal computed tomography (CT) every 3–6 months. Endoscopic examination is appropriate only for the detection of local recurrence or metachronous cancer of the gastroplasty that could be cured by minimal surgery.[18] Since CT is a morphological-based investigation tool, it is now well-known to be suboptimal in the diagnosis of nodal involvement, since nodal size is not an accurate parameter for predicting involvement. It is also suboptimal for the differentiation between posttreatment fibrosis and recurrence. Functional imaging may provide a promising alternative. Positron emission tomography using ^{18}F-fluorodeoxyglucose (FDG-PET) permits the functional characterization of tissues by in vivo imaging glucose metabolism. In oncology, FDG-PET is successfully used for the assessment of tumor viability and the staging of many malignancies with increased glycolysis. In esophageal cancer, FDG-PET has been gaining acceptance for initial staging by improving the detection of unsuspected distant metastases.[19–21] Monitoring therapy response is the second major indication for FDG-PET in esophageal cancer.[22–25] Some authors have also suggested that FDG may have a predictive value of patient outcome in esophageal cancer,[26] as it has already been demonstrated for other types of malignancies including lung cancer, lymphoma, or head and neck cancer.[27–30]

FDG-PET has also been largely used for restaging symptomatic recurrent cancer. In esophageal cancer, Flamen et al. demonstrated that FDG-PET is highly sensitive for staging recurrent symptomatic patients.[31] In addition, Kato et al. reported in a retrospective study that PET has a better accuracy than CT in the follow-up of asymptomatic patients when PET is performed more than 1 year after surgery. It remains unknown whether repeated FDG-PET can be used earlier and systematically in the follow-up period, which would be of great interest in a disease such as esophageal cancer which is characterized by high potential of early recurrence.[32] Therefore, the main objective of our prospective study was to determine whether FDG-PET can provide more accurate information than CT in a routine follow-up procedure of patients with esophageal cancer early after surgery.

Materials and Methods

In this prospective study, we considered patients undergoing surgery in our institution whose follow-up was also performed in our institution in order to minimize variability in the procedures.

The required sample size for the comparison of PET and CT sensitivities was calculated with an α level of 0.05 and a type 2 error (β) of 0.1. Considering a hypothesized difference of 30%, the required sample size was 39 patients. So, 41 patients were included taking into account incomplete data (5%). The current study was carried out after an approval by the institutional ethical review committee.

Surgery and Initial Patient Management

Between October 2003 and September 2006, 41 consecutive patients with esophageal cancer were included in the present study after they underwent esophagectomy with curative intention. All procedures were performed by the

same surgical team. The vast majority of patients (90%) underwent a transthoracic esophagectomy (Ivor Lewis procedure). In one patient, an additional cervicotomy was performed in order to do the anastomosis in the neck after the reconstruction of the digestive tract using a gastric tube (Akiyama procedure). Three patients had a laparoscopic transhiatal esophagectomy. All surgical procedures were associated with traditional two-field lymphadenectomy (thoracic and abdominal). All suspect distant macroscopic lymph nodes visually depicted by the surgeon were removed for frozen histology. Tumor was present in margins in six patients (15%).

Nine patients received neoadjuvant chemoradiation before surgery because they had a locally advanced disease at presentation. Standard cisplatin and 5-fluorouracil-based chemotherapy regimens with concurrent radiation therapy were used. In addition, six patients received an adjuvant chemoradiation because of non-R0 resection.

Clinical Follow-Up

After initial treatment, each patient was monitored regularly every 4–6 months during the first 2 years and every year after the second year in case of no recurrence. Every follow-up evaluation included a complete clinical examination. Thoracoabdominal CT, abdominal ultrasonography, and endoscopy were performed every 6 months or more frequently depending on the clinical situation. FDG-PET examinations were added to this routine follow-up procedure, every 6 months during the first 2 years and every year after the second year. Comparative CT and PET scans were performed within 1 month from each other.

Positron Emission Tomography

All patients fasted for a minimum of 6 h before the PET examination. The blood glucose level was confirmed to be <9 mmol L^{-1} before injection of the ^{18}F-FDG. All FDG-PET examinations were performed using an Allegro dedicated PET scanner (Philips Medical Systems).[33] An emission whole-body scan was performed for each patient from thigh to head 60 min after the injection of a mean activity of 355 MBq of ^{18}F-FDG (5–6 MBq/kg). Emission scans were acquired for 3 min per bed position. Whole-body transmission scans using a ^{67}Cs source were also obtained for the purpose of performing attenuation correction. Emission data were corrected for scatter, random events, and dead time losses and images were reconstructed both with and without attenuation correction using a previously optimized 3D RAMLA reconstruction protocol.[34] Baseline PET images were reported by two experienced nuclear physicians unaware of the CT, endoscopic ultrasound findings, and histological results. Images were analyzed visually and semiquantitatively. Regional lymph node involvement and distant metastatic disease were assessed as present or absent. Lymph nodes and metastases were considered as FDG-positive if focal-prominent ^{18}F-FDG uptake compared to normal mediastinal activity was found at least in two consecutive transaxial slices. In identified lesions, the maximum standardized uptake values (SUVmax) corrected for the body weight of each patient were calculated performing region of interest analysis on the transaxial slice of the attenuation-corrected images in which the highest uptake was found.

Follow-up data concerning the 41 patients were prospectively collected in a database for further analysis. The current analysis was carried out after an approval by the institutional ethical review committee. Regional and distant recurrences were established by biopsy, if feasible, or by clinical follow-up and repeated examinations. Distant metastases could involve either distant organs or celiac lymph nodes for tumors of the lower thoracic esophagus or metastasis in cervical nodes for tumors of the upper thoracic esophagus according to the TNM system.[35]

Statistical Analysis

All semiquantitative data are presented as the mean±standard deviation (SD). In this study cohort, local recurrence was determined by endoscopic biopsy. The sensitivity, specificity, and accuracy of CT and PET were calculated using the standard definitions.[36] CT and PET performances were compared using a χ^2 Mac Nemar test for paired data and a statistically significant difference was defined as a p value ≤ 0.05.

Kaplan–Meier methods were used to estimate the survival distributions.[37] Survival was calculated from the date of initial diagnosis to the date of death or most recent follow-up in case of patients still alive.

Results

Patient characteristics are presented in Table 1. Thirty-eight were male (93%) and the mean age at the time of diagnosis was 60.7±9.4 years. Most of the tumors were squamous cell carcinoma (76%) and most of the patients had a well-differentiated or moderately differentiated tumor (90%). The majority of the tumors originated from the middle and lower esophagus (93%). In the population included in this study, 51% of the patients had an early stage disease (stage I or IIa), while 58% of the patients had a T3 primary lesion. Twenty patients (48%) had lymph node metastases (N1) at presentation.

At the time of the last follow-up, 31 patients were alive, 18 with no evidence of disease, and 13 with recurrence. The

Table 1 Patients Characteristics

Characteristics	All patients *N*=41 (%)
Gender	
Male	38 (93)
Female	3 (7)
Age at diagnosis	
Median	59
Range	43–83
Primary site	
Upper esophagus	3 (7)
Middle esophagus	20 (49)
Lower esophagus	18 (44)
Tumor cell type	
Squamous cell carcinoma	31 (76)
Adenocarcinoma	10 (24)
Histologic grade	
Well-differentiated	22 (54)
Moderately differentiated	15 (36)
Poorly differentiated	4 (10)
Treatment	
Surgery alone	25 (61)
Surgery+adjuvant CT±RT	7 (17)
Surgery+neoadjuvant CT+RT	9 (22)
Pathological stage	
I	6 (14)
IIa	15 (37)
IIb	5 (12)
III	15 (37)

RT radiotherapy, *CT* chemotherapy

recurrence rate was 56% and the mean time to recurrence was 8 months (5–39 months). With a mean follow-up of 46 months (30–55 months, median of 48 months), the median survival for all patients was 51 months. The 1- and 2-year survival rates were 80% and 65%, respectively, for patients with negative margins. The Kaplan–Meier curves on disease-free survival and overall survival are in presented in Figs. 1 and 2.

The mean time after surgery for the first PET scan was 6.3 months. It was positive for all six patients with involved margins. Two patients had regional nodal uptake and FDG-avid distant metastases (involving either the liver or vertebrae). Two patients had evidence of local recurrence and regional nodes on PET images; while for the two remaining patients, only local uptake evoking progressive residual disease was described. This first FDG-PET was considered as positive in 18 patients, demonstrating local recurrence in 13 cases and distant metastases in 12 cases. Seven of these patients had both local and distant lesions avid for FDG. In case of regional recurrence, 7 out of 18 patients had more than one abnormal foci corresponding to involved nodes. Confirmed distant metastases occurred in distant lymph nodes (five out of 12), bones (five out of 12), liver (three out of 12), lung (two out of 12), and adrenal

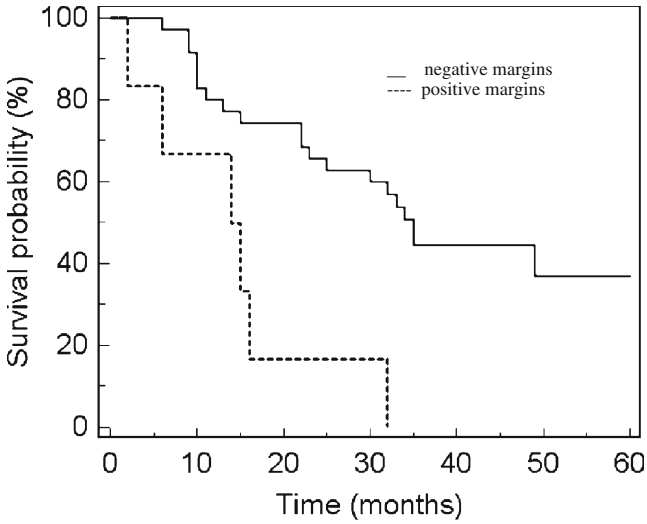

Figure 1 Kaplan–Meier analysis of the overall survival of esophageal cancer patients according to the margin status (negative of positive).

gland (one out of 12). Seven patients had more than one distant metastatic site.

A second FDG-PET scan was performed within a mean delay of 12 months after surgery (12±2 months). One year after surgery, only one more patient, in comparison to the results of the first PET examination, had a true-positive scan for recurrence corresponding to locoregional disease without distant metastasis. For the third systematic evaluation, FDG-PET was performed with a mean delay of 19 months after surgery (19±1.6 months). In four patients, FDG-PET was abnormal, demonstrating local recurrence in one patient and both local disease and distant metastases in three patients. Those late scans were all confirmed to be true-positive findings (using the assessment criteria described in the "Positron Emission Tomography" section).

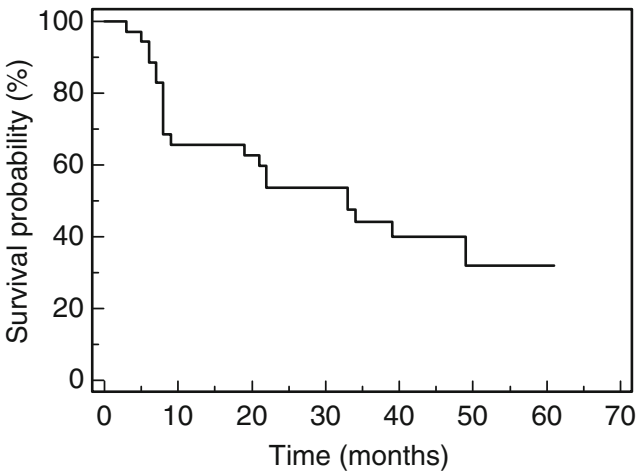

Figure 2 Kaplan–Meier analysis of the disease-free survival of esophageal patients with negative margins after initial surgery.

On a patient-by-patient analysis, sensitivity, specificity, and accuracy were, respectively, 65%, 91%, and 81% for CT and 100%, 85%, and 91% for FDG-PET (Table 2). The performance of the two modalities were statistically significantly different ($p=0.02$).

Local or regional recurrence was observed in 15 patients (seven with no distant metastases and eight with associated distant metastases). For the detection of locoregional recurrence, FDG-PET had a better accuracy than CT (96% vs. 89%, $p=0.05$) due to a higher sensitivity (93% vs. 60%) with similar specificity (97% vs. 100%; Table 2). There were two false-positive results on PET at 6 months, one in the gastroplasty and one in a perigastric node (abdominal). In both cases, abnormal uptake was moderate (SUVmax<3) and disappeared on the subsequent scans. False-positive results were confirmed based on a favorable outcome and no evidence of disease on the biopsy.

FDG-PET was globally more accurate than CT for the detection of distant metastases (92.5% vs. 84.9%, $p=0.002$; Table 2). Considering the different sites of recurrence, we found five false-negative PET results in the lung (two patients), liver (one patient), and in a celiac node (one patient). In all these cases, patients had substantial FDG-avid recurrence on other sites. Therefore, not detecting one small lesion (in the lung or liver) did not affect either the overall conclusion of the PET study or patient management.

For example, at 6 months, thoracoabdominal CT demonstrated small lung nodules in two patients confirmed to be lung metastases which were missed by the first FDG-PET scans corresponding to false-negative results in the lung. However, for both those patients, the lung nodules were associated to other metastatic foci correctly depicted by FDG-PET. Lung nodules became FDG-avid on the following PET examination as their size increased. On the other hand, PET allowed to discover distant metastases involving the lung, liver, or bones, which were not detected on CT in six patients (15%), leading to a change in the patient management.

No patient had a negative PET and a recurrence detected by another exploration. Therefore, considering a patient-by-patient analysis, we had no false-negative PET scan, corresponding to a 100% negative predictive value.

Of the 16 patients having a true-positive first PET examination, seven patients underwent additional chemotherapy and four patients underwent additional combined chemoradiotherapy. Because of poor medical condition, only a palliative regime was proposed to five patients with metastatic recurrence.

Discussion

To our knowledge, our study is the first report of a prospective repeated and systematic use of FDG-PET in the follow-up of asymptomatic esophageal cancer patients after surgery. Esophagectomy remains currently an option for the treatment of esophageal cancer. Several phase III trials have been conducted over the past 10 years to evaluate the potential interest of adding medical treatment prior to surgery. Recently, Tepper et al. have presented the final results of the CALGB 9781 study.[38] In this prospective phase III trial, 500 patients were targeted for enrolment and the primary endpoint was the overall survival. However, the final result of this trial cannot be conclusive due to poor recruitment rates (only 56 patients were finally included). Therefore, surgery alone remains today a valid option in the treatment of patients with squamous cell esophageal neoplasm. This explains the relative limited percentage among our patient population that underwent neoadjuvant chemoradiation.

After esophagectomy with or without additional medical treatment, the overall 3-year survival rate of our patients was 56%. This result is compatible with those of previous reports (40% to 56%).[39–41] In addition, in our series, 23 of the 41 patients (56%) developed recurrent disease. This

Table 2 Comparison of Sensitivity, Specificity, and Accuracy of FDG-PET and CT for the Detection of Recurrence in Esophageal Cancer

Site of recurrence	PET				CT			
	Sensitivity (%)	Specificity (%)	Accuracy (%)	NPV (%)	Sensitivity (%)	Specificity (%)	Accuracy (%)	NPV (%)
All[a]*	100	85.3	90.7	100	65	91.2	81.5	81.5
Locoregional**	93.3	97.4	96.2	97.4	60	100	88.9	86.7
Distant*	100	89.4	92.5	100	66.6	92.1	84.9	87.5
Liver	75	100	98.1	98	50	96	92.5	96
Lung	57	97.9	92.5	93.8	71.4	95.7	92.5	95.7
Bone	100	100	100	100	33.3	100	92.5	92.3
Distant lymph node	88.9	95.5	94.4	97.7	55.5	100	92.5	91.8

NPV negative predictive value
*$p=0.002$; **$p=0.05$
[a] Patient-by-patient analysis

result is also similar to the rate reported by Chen and colleagues.[40] Recurrence of esophageal cancer is known to appear early after surgery, almost within the first year, justifying an early follow-up. Indeed, in this study, we were able to demonstrate that most of the recurrences (70%) were diagnosed very early after operation (16 patients at 6 months and one at 12 months). All six patients with non-R0 resection belonged to this early relapsing group and none of them is still alive at the time of the last follow-up. An additional ten patients also relapsed within the first 6 months after surgery. Those patients might have had micrometastatic disease beyond the area of extensive procedures at the time of resection and were unlikely to be cured by surgery alone. In our study, recurrence was classified as locoregional and/or distant recurrence. Half of recurrences (47%) were both distal and locoregional, and only one third (28%) were considered as only locoregional relapse. FDG-PET was more sensitive than CT in detecting recurrence on a patient-by-patient-based analysis (100% vs. 65%). For locoregional recurrence, FDG-PET was more accurate than CT.

Since FDG is not a tumor-specific tracer and is known to accumulate also in activated inflammatory cells, FDG-PET may fail to differentiate postoperative changes from recurrent tumor. As such, it is recommended not to scan patients immediately after surgery, which is why we began to perform FDG-PET only 6 months after surgery. For similar reasons, Kato et al., studying FDG-PET for postsurgery follow-up, only report on examinations performed a year after initial surgery in a retrospective series of 55 patients.[30] In our study, the performance of early scans, at an average 6 months after surgery, were not significantly compromised by postoperative changes. Only two false-positives were found due to moderate increased uptake in the gastric tube and a perigastric node. These findings, most probably due to postoperative inflammatory changes, disappeared in the second PET examination.

With regards to distant metastases, FDG-PET was also more accurate than CT on a patient-by-patient-based analysis. Only small lung nodules less than 1 cm, confirmed to be lung metastases based on the follow-up in three patients, were missed using PET. Those lesions became significant on the following scan after their size increased. This could also explain the miss of a small hepatic lesion and a celiac node. This lack of sensitivity for the detection of small lesions is a well-known technical limitation of FDG-PET due to partial volume effects as a result of limited spatial resolution leading to potential miss of small structures with moderate uptake. However, this limitation did not influence our results, since those small lesions have been always associated with other metastatic sites, leading to an overall positive for recurrence PET examination. Nevertheless, in case of small pulmonary lesions on CT without any evidence of recurrence on FDG-PET images, further investigation such as biopsy could be suggested since localized treatment could be considered.

For the detection of distant metastases elsewhere than in the lungs, FDG-PET was also more accurate than CT in our study. This is in accordance with data already available concerning the use of PET for the initial staging of esophageal cancer that can be explained by a larger field of view considered when scanning PET, generally from head to thigh. We found only one false-positive result due to a moderate uptake in the celiomesenteric area 6 months after initial surgery leading to a similar specificity with CT for distant metastases.

Based on our PET results only, patient management has been modified in five patients with recurrences been treated using additional chemotherapy. However, this group of patients is currently too small in order to determine the impact on survival as a result of the observed changes in patient management based on PET. On the other hand, it is interesting to note that Raoul et al. demonstrated that early detection of recurrence is of great interest because more aggressive strategy can be considered leading to better outcome.[42] It is also by detecting recurrence earlier that patients will benefit from the inclusion in prospective trials using new therapeutic approaches as salvage surgery for single metastasis or new chemotherapy agents.[12–15] Consequently, a more accurate assessment of patient status will contribute to a better evaluation of such new therapeutic approaches. Based on our results, FDG-PET is more accurate than CT for this purpose as early as 6 months after surgery.

The major limitation of our study concerns the definition of the truth as commonly encountered in studies addressing the outcome of cancer patients. For obvious ethical and practical reasons, we could not biopsy all identified lesions. So, we designed our study as commonly done in such a case by establishing the truth based on different options: if a biopsy was feasible, then the truth was established by the pathologist; if the biopsy of a lesion was not feasible, the truth was established based on the follow-up. For example, a lesion was considered as a metastasis (true-positive) if it was found on repeated examinations and/or concordant on different modalities and if it was associated with an unfavorable outcome. Sensitivity, specificity, and accuracy values were calculated after the truth has been established as described. It is unsure whether we did depict all sites of recurrence by the different imaging modalities we have used. Most probably, it is not the case since it has been already demonstrated in a different and more favorable context of initial staging that none of the available imaging modalities has 100% sensitivity.[43] Therefore, the true incidence of recurrence is unknown and we can only try to estimate it by combining all available diagnostic tools as we did in this study.

This study has been performed using a dedicated PET scanner. Combined PET/CT devices are now widely available and increasingly used in clinical practice. Such facilities offer, in a single study, the best of each technology. Aside from the obvious gain of time, the gain of performance in the follow-up of asymptomatic patients after esophagectomy may be limited. Based on our results, the most likely benefit may concern a better definition of regional nodal involvement, since it is difficult to differentiate between one or many coalescent nodes based on PET images only. Combined PET/CT will, therefore, be useful in providing accurate anatomical information differentiating between nodal uptake and nodal station involvement with the potential impact of such distinction after initial surgery still to be determined.

Conclusion

Surgery remains a major option in the management of esophageal neoplasms. Early diagnosis of recurrence in asymptomatic patients could be a good way to improve the management of those patients. The present study is the first prospective study systematically using FDG-PET in the follow-up of surgically resected patients and it has shown that FDG-PET is accurate for the detection of early recurrence of esophageal cancer after initial surgery. Based on the presented results, FDG-PET could be included in the routine protocol for the evaluation of asymptomatic patients after surgery, as early as 6 months after the initial operative procedure. The use of FDG-PET in comparison with the use of endoscopy, CT scan, and/or echography remains to be demonstrated in terms of cost-effectiveness.

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ORIGINAL ARTICLE

Hiatal Hernia Recurrence: Surgical Complication or Disease? Electron Microscope Findings of the Diaphragmatic Pillars

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Abstract
Introduction Although laparoscopic Nissen fundoplication has been recognized as the standard of care for hiatal hernia (HH) repair, HH recurrence due to breakdown of the hiatoplasty have been reported as a common mechanism of failure after primary repair. Different surgical techniques for diaphragmatic pillars closure have been proposed, but the problem remains unsolved. The authors hypothesized that ultrastructural illness may be implicated in this recurrence. The aim of this study was to investigate the presence of changes at esophageal hiatal area in patients with and without HH.
Materials and Methods One hundred and thirty-two laparoscopic samples from phrenoesophageal membrane and diaphragmatic crura were collected from 33 patients with gastroesophageal reflux disease and HH (HH group) and 60 samples from 15 patients without HH enrolled as the control group (NHH group). All specimens were processed and analyzed by transmission electron microscopy.
Results Muscular and connective samples from the NHH group showed no ultrastructural alterations; similar results were found in phrenoesophageal ligament samples from the HH group. In contrast, 94% of the muscular samples obtained from the crura of the HH group have documented four main types of alterations. In 75% of HH patients, the pillar lesions were severe.
Conclusion Patients with hiatal hernia have ultrastructural abnormalities at the muscular tissue of the crura that are not present in patients with a normal gastroesophageal junction. There is no difference in the microscopic damage at the connective tissue of the phrenoesophageal membrane surrounding the esophagus of the two groups of patients. The outcome of antireflux surgery could depend not only on the adopted surgical technique but also on the underlying status of the diaphragmatic crura.

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Keywords Hiatal hernia · Recurrence · Cruroplasty · Electron microscopy, diaphragmatic pillars

Introduction

Although laparoscopic Nissen fundoplication has been recognized as an effective alternative therapy to lifelong antireflux medication and as the standard approach to hiatal hernia (HH) repair,[1,2] the herniation of the wrap into the chest or the accidental transposition of the gastric fundus alongside the fundoplication caused by the breakdown of hiatoplasty have been reported as a common mechanism of failure after primary repair[3] with an incidence rate up to 23% or 42% of the operated subjects.[4,5]

Table 1 Grading of the Electron Microscope Pillar Changes

Grade	Ultrastructural findings
I	Dilation of the intermyofibrillar spaces
II	Swelling of sarcotubular structures
III	Focal degeneration of myofibrils
IV	Extended disruption–degeneration of the muscle architecture

The esophageal hiatus is the only opening in the diaphragm which is liable to visceral herniation because its borders are formed of pliable skeletal muscle rather than tendinous fibers. Moreover, the esophagus does not completely fill the hiatus and the Laimer-Bertelli's phrenoesophageal membrane is responsible of its stabilization within the abdominal cavity. An enlarged esophageal hiatus is most usually closed by means of a simple direct cruroplasty. This, however, is susceptible of disruption, primarily for diaphragm being continuously stressed by vomiting, coughing, straining, sneezing, and laughing.[3] In an effort to reduce the incidence of this complication, some authors have advocated anchoring the wrap to the esophagus, the crura, or both, buttressing the hiatal defect with a prosthetic reinforcement,[6] adding an anterior gastropexy or fashioning an intrathoracic fundoplication thrust upon the hiatus.[3]

Irrespective of the surgical techniques adopted to prevent it, further causes responsible for hiatoplasty disruption have never been investigated. Based on the idea that in patients with hiatal hernia some alterations at the crura may be present, as recently reported in a preliminary study,[7] the authors aimed to investigate, in a larger group of patients with HH and in a control group without HH, the type, frequency, and severity of the main microscopic alterations found in the esophageal hiatus, in order to establish their possible role in the pathogenesis of hiatal hernia recurrence or wrap migration after antireflux surgery.

Material and Methods

After Ethical Committee approval and written informed consent were obtained, we enrolled 48 consecutive patients aged not over 50 years.

Of these 48 patients, 33 (15 men and 18 women; mean age, 35.4 years; range, 18–46 years) affected by simultaneous hiatal hernia and gastroesophageal reflux disease (GERD) composed the HH group; the remaining 14 patients with cholelithiasis and one patient reporting a symptomatic cyst of the spleen (seven men and eight women; mean age, 33.4 years; range, 23–44 years) were included as the control group (NHH group).

Preoperative contrast roentgenographic studies of the esophageal and gastric anatomy were performed for both HH and NHH groups. Hiatal hernia was measured by barium esophagram. Patients with paraesophageal (type 2), mixed (type 3), or giant hernias (>5 cm) were excluded from the study.

Additional exclusion criteria were: recurrent hiatal hernia, morbid obesity (i.e., body mass index (BMI)>40), patients taking anticoagulant drugs within 2 weeks of the intervention, collagen diseases (i.e., scleroderma, Ehler-Danlos and Marfan's syndromes), cardiac and/or pulmonary diseases (e.g., congestive and/or ischemic heart disease, emphysema), abdominal aortic aneurysm, metabolic and neuromuscular diseases, familiar increased creatine kinase, patients using statin drugs and smokers.

In the HH group, GERD was documented through 24-h esophageal pH monitoring[8] and esophagitis through upper gastrointestinal endoscopy, according to Los Angeles Classification System.[9]

The patients with hiatal hernia underwent laparoscopic Nissen-Rossetti fundoplication with our personally modified technique, which has been described in detail elsewhere;[10] the NHH completed the planned laparoscopic operation, with 14 cholecystectomies and one splenectomy performed.

Specimen Collection

All the patients underwent laparoscopic procedure by a single team with a large experience in esophageal surgery: with the trocars at the standardized position, the anterior hiatal dissection was accomplished.[10] Collection of biopsy specimens was the first step of the procedure after the 12-mmHg pneumoperitoneum was induced; the second step was the intraoperative measurement of the opening at the diaphragmatic hiatus by a sterile and flexible ruler.

Each patient underwent four biopsies: two at the phrenoesophageal ligament–Laimer-Bertelli membrane (connective tissue) and one on each diaphragmatic crus (muscular tissue) halfway from the anterior and posterior limit of each crus. All tissue samples were obtained by cold

Table 2 Baseline Demographic and Morphologic Data

Characteristics	NHH group (n=15)	HH group (n=33)	p value
Male gender (%)	46.6	45.4	N.S
Female gender (%)	53.3	54.5	N.S
Age, years (mean±SD)	33.4±5.1	35.4±4.3	N.S
Weight (kg)	73.9±7.3	72.8±7.8	N.S
Body mass index (BMI)	25.4±2.1	24.9±3.0	N.S
Hiatus diameter, cm (mean±SD)	1.8±0.3	3.9±0.5	<0.001

NHH patients without hiatal hernia and without GERD, *HH* patients with hiatal hernia and GERD

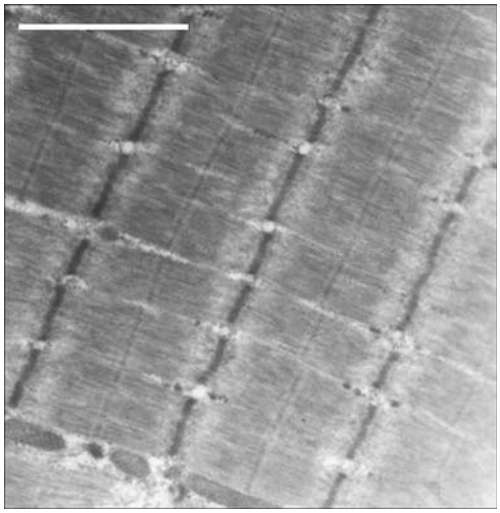

Figure 1 Normal ultrastructure of diaphragmatic crura. TEM. Original magnification ×4,100; scale bar 5 μm.

scissor excision, avoiding the use of monopolar or any other hemostatic energy.

The collected specimens were promptly fixed by immersion for 2 h at room temperature in a solution composed of 2.5% glutaraldehyde in 0.1 mol/l of Na-cacodylate buffer, pH 7.2 with an osmolarity of 410 mOsm. Post-fixation was performed for 1 h at 4°C in 1% osmium tetroxide (OsO_4) in 0.1 mol/l of Na-cacodylate buffer, pH 7.2. Samples then were dehydrated in graded series of ethanol (EtOH) from 40% up to absolute EtOH. This was next replaced with propylene oxide before epoxy–resin embedding. Ultrathin sections (400–500 nm) were cut with a diamond knife on a Reichert Joung Ultracut-E ultramicrotome (Heidelberg, Germany). They were stained with uranyl acetate and lead citrate then analyzed using a transmission electron microscope (EM-109, Zeiss, Jena, Germany). A single pathologist (S.S.) blinded to the preoperative diagnosis (HH vs NHH) completed the histologic assessment of the resected specimens. The grading of the identified ultrastructural muscular lesions ranged from a low severity degree (type 1) to a high severity degree (type 4), as detailed in Table 1.

Statistical Analysis

Statistical analysis was performed using SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL, USA). All data were

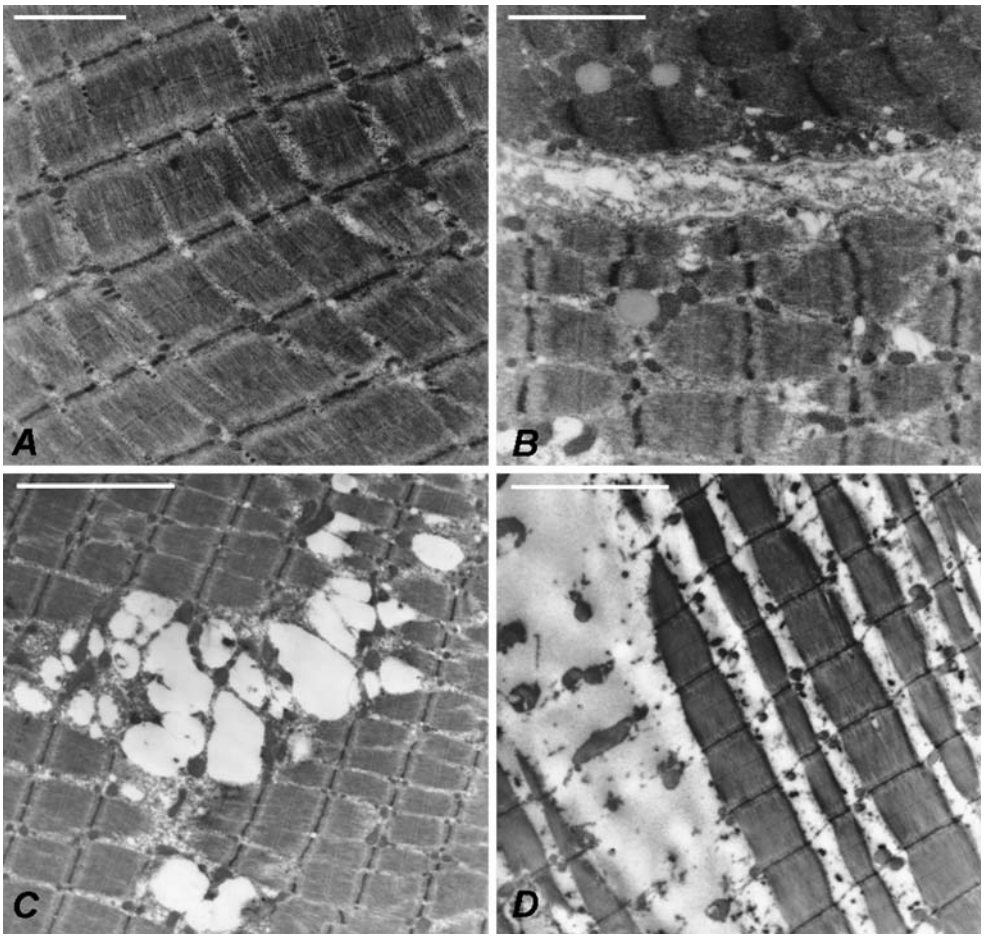

Figure 2 a Almost-normal myofibril–sarcomere organization with only slight dilation of the intermyofibrillary spaces. Original magnification ×5,800; *scale bar* 2.5 μm. **b** Some sarcotubular structures appear swollen. Note also the presence of scattered large lipid droplets between the myofibrils. Original magnification ×7,150; *scale bar* 2.5 μm. **c** Focal degeneration of myofibrils leading to disruption of several sarcomeres which appear as "empty" vacuolar spaces. Original magnification ×4,100; *scale bar* 5 μm. **d** Extended disruption–degeneration of the muscle architecture with myofibril degeneration and massive dilation of the intermyofibrillar spaces. Original magnification ×4,100; *scale bar* 5 μm.

expressed as mean±standard deviation (SD) unless otherwise indicated. Student's *t* test, the chi-square test, and Fischer's exact test were used as appropriate. The two-tailed significance level was 0.05.

Results

Patient characteristics are summarized in Table 2. No statistical difference was found among the two groups of patients with regard to gender, age, weight, and BMI parameters. Diaphragmatic hiatus diameter was statistically increased ($p<0.001$) in the HH group compared to NHH group. Preoperatively, eight patients (24,2%) were grade A; 21 patients (63.6%) were grade B; three patients (9.1%) were grade C, and one patient had a short Barrett esophagus. Esophageal stationary manometry showed lower esophageal sphincter hypotonia in 90.2% of the HH group. The mean interval between induction of anesthesia and collection of the four specimens was 18±2 min. No complications occurred during acquisition of the samples. The postoperative course was regular in all patients and mean postoperative hospital stay was 2.5±1.6 days.

Electron Microscope Analysis

One hundred and ninety-two specimens were analyzed: 132 from the HH group and 60 from the NHH group. In all patients, samples from the phrenoesophageal membrane documented no alterations that could be detected using transmission electron microscopy: there were no morphostructural or quantitative alterations of the collagen fibrillary component and no morphologic or quantitative modifications to the resident connective tissue cell elements.

Analysis of muscular specimens of the NHH group did not show any ultrastructural changes in both diaphragmatic pillars (Fig. 1).

Ultrastructural muscular lesions were present in a mix of combinations in 94% (31/33) of the patients affected by HH; they showed at least one or more than one of the main types of electron microscope alterations. These findings were present in each of two pillar samples (Fig. 2a–d).

The frequency of the different degrees of crura alterations (muscular tissue) in the HH group was summarized in Table 3. Types I, II, III, and IV muscular changes have been documented in 45%, 39%, 51%, and 75% of the cases, respectively. Overall, three patients had simultaneously all types of muscular changes; seven patients had three types (five type I, four type II, five type III, seven type IV); 16 patients had two types (seven type I, six type II, eight type III, 11 type IV) and five patients had a single type of muscular changes (one type III and four type IV).

Table 3 Incidence and Combination of the Four Types of Muscular Changes in 33 HH Patients

	Patient	Type I	Type II	Type III	Type IV
1	L.G.	1	0	1	0
2	F.M.	0	0	0	0
3	V.P.	1	0	1	1
4	D.C.	0	1	1	0
5	M.C.	0	1	0	1
6	A.M.	0	0	0	1
7	L.B.	1	1	1	1
8	S.T.	1	1	1	1
9	M.C.	0	1	1	0
10	P.L.	1	0	1	1
11	A.S.	0	0	0	1
12	V.N.	0	0	1	1
13	A.DG.	1	0	1	0
14	C.S.	1	1	1	1
15	T.S.	1	0	0	1
16	C.T.	0	1	0	1
17	S.A.	1	0	1	1
18	I.A.	0	0	0	1
19	F.S.	0	0	1	0
20	A.P.	0	0	0	0
21	C.O.	0	1	0	1
22	D.G.	0	1	1	1
23	M.A.	1	1	0	1
24	F.S.	0	0	1	1
25	P.MT.	0	0	1	1
26	C.M.	0	1	0	1
27	P.M.	1	0	0	1
28	L.E.	1	1	0	1
29	G.G.	0	1	1	1
30	P.C.	1	0	0	1
31	G.P.	0	0	0	1
32	S.C.	1	0	1	0
33	A.A.	1	0	0	1
	Total (*n*)	15	13	17	25
	Rate (%)	45	39	51	75

0 absence, *1* presence

Discussion

One of the most frequent cause of anatomic failure after laparoscopic fundoplication is the migration of the wrap into the chest, associated or not to the disruption of the wrap.[3] This is consistent with the observation that HH recurrence alone accounts for over 70% of the surgical indication after a failed primary repair.[11,12] Described possible mechanisms for postoperative intrathoracic migration of the wrap include inadequate mobilization transhiatal of the esophagus,[10,13] excessive tension on the sutures due to an excessively enlarged hiatus or inadvertent postoperative stressors, and inappropriate manual activities in the early postoperative period. Additional reported possible

causes of failure are a wrongly estimated amount of tissue included when the crura were approximated or exclusion of the subdiaphragmatic fascia from the bites.[3]

According to the physical model of Casaccia et al.,[14] a direct cruroplasty produces a conflict of strengths, which puts the hiatal repair under stress and accounts for laceration of crura and hernia recurrence. A sudden increase in abdominal pressure, induced by vomiting, coughing, constipation, or vigorous manual work, may push the wrap through the freshly reconstructed hiatus.[3] The stitch perpendicular to the muscular fibers transfers the pressure onto the crural tissue, which may disrupt if the amount of bite incorporated in the suture is insufficient.

The aforementioned data[7] and the absence, to our knowledge, of previous investigations led us to investigate whether, in addition to the surgical technique, an underlying ultrastructural changes may play a contributory role in crural disruption and hiatal hernia recurrence. We theorized that these changes of the diaphragm may affect the ultrastructure of its sarcolemmal–plasmic components as well as the extracellular matrix of the muscle. This hypothesis was sustained by the observation of high frequency relapses of hiatus hernia after traditional surgical intervention in spite of the lacking of an objective and/or instrumental evidence of any alteration affecting the muscle–connective components of the diaphragm in such type of patients. At the same time, it is interesting to note that the muscle dystrophy as well as a metabolic or inflammatory muscle disease seems not to be themselves a risk factor for a diaphragmatic hiatal hernia. Either these remarks led us, though unlikely, to find any muscle tissue changes at light microscope level of resolution and to focus our research at an ultrastructural level.

Data of this study clearly demonstrate that patients with hiatal hernia have ultrastructural abnormalities at the muscular tissue (62/66, 94%) of the crura that are not present in patients with a normal gastroesophageal junction. At contrast, there is no difference in the microscopic damage at the connective tissue of the phrenoesophageal membrane surrounding the esophagus of the two groups of patients.

We could deduce that the diaphragmatic crural alterations could influence the outcome of hiatal hernia repair as it occurs for inguinal, ventral, and/or incisional hernias. This concept is supported by the fact that the ultrastructural changes were found only in the muscular tissue, and by the fact that the incidence of severe muscular lesions, as types IV and III, was very high (75% and 51%, respectively; Table 3). It has to be noted that a causal–effect relationship for the HH group cannot be definitively excluded, being the microscopic alterations in these patient potentially due to the physical stretch of the crura caused by the stomach herniation; however, the patient exclusion criteria (type 2 and type 3 giant hernias) and the not excessively increased diameter of the hiatus (3.9±0.5 cm) make this hypothesis unlikely.

At the present time, it is not possible to establish the possible role of these morphostructural alterations on HH recurrence or to express any advice in favor or against of the use of prosthetic reinforcement[15] but we can assert that the outcome of antireflux surgery could depend not only on the adopted surgical technique but also on the underlying status of the diaphragmatic crura. A larger long-term follow-up clinical trial is warranted to definitively answer this question.

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ORIGINAL ARTICLE

Bariatric Surgery: A History of Empiricism, a Future in Science

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Abstract
Background The observation that obesity can be successfully treated by gastrointestinal surgery is a tribute to the innovative efforts by determined surgeons and the ever improving safety of general anesthesia. Yet as the body of knowledge and discovery on the root causes of human obesity accumulate, surgical approaches to treat morbid obesity are likely to change dramatically. While there is little doubt that dramatic weight loss can be achieved by surgically creating volume and absorption limitation to the reservoir and digestive functions of the gastrointestinal tract, human progress to more processed foods, less physical activity, and the pervasive public opinion that obesity is self-imposed are major obstacles to more widespread application of this approach.
Discussion Here we provide a mechanico-physiologic analysis of current operations, their rationale and limitations, as well as a glimpse of how future interventions might develop as a result of current knowledge in the field. The future of bariatric surgery is discussed in the context of these emerging technologies and in the context of the politics of obesity.

Keywords Obesity · Bariatric · Weight loss

The Politics of Obesity

Obesity is a disease of human progress resulting from excess calorie intake relative to energy expenditure. The degree to which obesity contributes to human disease is substantial, although its causality to specific diseases such as cancer and diabetes is debated.[1] Obesity-related illness is a major cause of healthcare expenditures and its rate of rise in the USA is alarming. The extent to which the current rise in obesity can be attributed to genetic, epigenetic, or environmental causes is not known. In addition, the relative contribution of each factor on the development of an overweight person to one who is morbidly obese is unknown. As most individuals are not morbidly obese, it seems intuitively obvious that human volition alone is in control of caloric intake and energy expenditure. Skepticism by the public at large as to whether morbid obesity can be shown to be a biologic destiny for individuals as a result of an environmental trigger(s) in a genetically susceptible host will persist unless convincing data to the contrary are generated. Proving such a hypothesis may be critically important in sustaining the financial support necessary to control obesity. For example, if the disorder is viewed to be self-imposed and self-correctable, then the unaffected or minimally affected public will be resistant to bear the cost of expanding research and treatment. Yet, when obesity becomes disabling and medically severe, the unaffected public bears the high cost of chronic treatment. Current measures to control the rate of rise in obesity have universally failed. How the general public and policy-makers view the current threat of obesity and its causes will likely affect how resources are allocated to its various treatment and prevention options. Drug therapy for obesity

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is potentially a highly profitable but risky approach as the number of patients that will take an effective drug is enormous. Experience from drug trials of efficacious weight loss agents demonstrates that the rate of weight regain once the agent is withdrawn approaches 100%. As such, these drugs will likely need to be administered on a continuous, long-term basis. If applied to the majority of the obese public, now defined as a body mass index (BMI) or >30 kg/m^2, the cost of drug therapy would be prohibitive for the nearly 100 million candidates. The long-term risks of extended use of these agents cannot be predicted. When indicated, bariatric surgery is the most cost-effective treatment for morbid obesity. Today, bariatric surgery is a tightly rationed health service and is often not available for the most at risk patients. The rationale provided by third party payers in this regard reflects situational ethics at best. The ethical issues that underlie the rationing of bariatric surgery have not been adequately studied and addressed.

The Politics of Bariatric Surgery

Approximately 150,000 surgical procedures for weight loss (bariatric surgery) are performed in the USA annually despite estimates that there are 15 million candidates for bariatric surgery assuming a BMI of greater than 40 kg/m^2 as the major indication for surgery. Today, bariatric surgery in the USA is a four billion dollar a year business. Most patients suffering from morbid obesity (BMI>40 kg/m^2) do not choose surgery to lose weight. Most physicians believe surgery should only be performed in the most severe cases of morbid obesity, and in general, physicians ascribe low value towards bariatric surgery regarding it as risky and avoidable if patients would follow proper diet and exercise.[2] Demographic analyses demonstrate that patients who most benefit from bariatric surgery, i.e., those with the highest BMI's and greatest number of associated medical co-morbidities, are the least likely to receive it.[3] Patients at lower socioeconomic status, who are disproportionately affected by morbid obesity, have limited access to centers offering bariatric surgery as they represent the highest risk and lowest rate of reimbursement. Patients with the lowest risk and highest rate of re-imbursement generally include the youngest, healthiest, and lowest range BMI patients. Patients willing to pay for bariatric surgery on an out of pocket basis can obtain bariatric surgery based on less stringent criteria than recommended by the National Institutes of Health (NIH) consensus panel.

The concept of pre-emptive bariatric surgery has been presented to include children, although there are major concerns with this approach. Although the NIH has drafted a consensus statement on the criteria on which to base candidacy for bariatric surgery, the statement was drafted in 1992 and does not specify the indications but rather the criteria upon which to base candidacy for bariatric surgery.[4] In the USA, bariatric surgery is becoming a highly outsourced surgical procedure. In India, bariatric surgery is a common procedure performed on non-national patients.[5] In the USA, several state-issued mandates have been passed to include bariatric surgery when medically indicated.[6] Governance of bariatric surgery in the USA has been initiated by the American Society of Metabolic and Bariatric Surgery and the American College of Surgeons. Each has developed a process by which surgeons and hospitals can be designated as centers of excellence in bariatric surgery. In many states, Medicare and Medicaid have mandated that patients can only have surgery in designated centers of excellence. Another mechanism of rationing involves mandating a 6–12-month trial of weight loss prior to surgery. It now has been documented that this practice has no effect on post-operative weight loss, complications, or patient success following bariatric surgery.[7] Since there is significant variance on the criteria that define the medical indications for bariatric surgery among payers, referring physicians, and surgeons, the opposing interests of these various stakeholders will likely contain growth in bariatric surgery relative to the rising incidence of obesity.

Surgical Procedures for Weight Reduction: Rationale, Limitations, and Analysis

Roux-en-Y Gastric Bypass

Rationale Roux-en-Y gastric bypass (RYGB) was developed as a hybrid operation following the realization that mechanically restricting the volume of the stomach alone was both surgically imprecise and ineffective at achieving sustained long-term weight loss. The RYGB procedure combines both mechanical restriction and a neurophysiologic satiety signal. RYGB has been performed for approximately 30 years with more than 500,000 operations performed in the USA to date. RYGB now accounts for approximately 85% of the weight loss operations performed in the USA.[8] More recent studies comparing the RYGB to a newer restrictive operation, the laparoscopic adjustable gastric band (LAGB), suggest that the RYGB results in an increase in the plasma concentration of the well-known satiety hormone peptide YY as well as GLP-1 compared to the LAGB, possibly accounting for its greater effect on weight loss and resolution of diabetes compared to mechanical restriction of the proximal stomach alone.[9] Although this latter observation is highly contested among LAGB proponents, rigorously performed prospective trials are not yet available. Currently, the RYGB is performed

laparoscopically and is constructed with a 30-ml proximal gastric pouch, a 0.8–1.5-cm gastrojejunal anastomosis, and a 100–150-cm roux limb (Fig. 1a). Studies examining pouch size, gastrojejunal anastomotic diameter, and roux limb length have failed to demonstrate dependence of long-term weight loss on any of these variables.[10] Lengthening the roux limb to encompass the proximal 80% of the small bowel (distal RYGB) and banding the proximal pouch have been proposed as mechanisms to improve weight loss in the super-obese (BMI>50 kg/m^2).[11,12] Results from these extended procedures have been reported as uncontrolled case series and their long-term efficacy is unknown. Long-

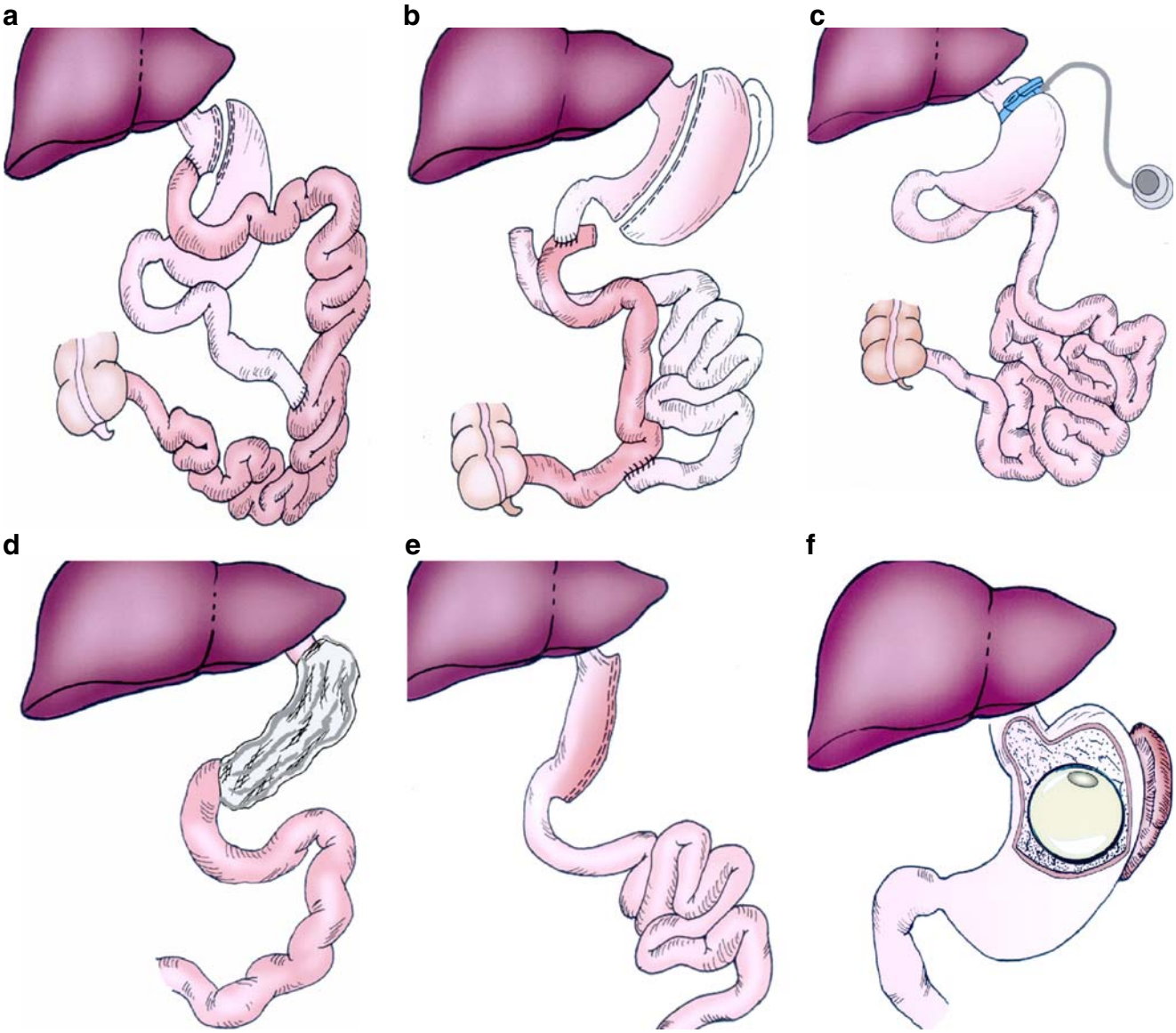

Figure 1 **a** Roux-en-Y gastric bypass. The stomach is stapled and transected to create a 20–30-ml proximal gastric pouch. The proximal small intestine 30–60 cm distal to the duodenum is transected and the distal end anastomosed to the proximal gastric pouch. The roux limb is created by re-anastomosing the proximal jejunal end 100–150 cm down on the newly created roux limb. **b** Duodenal switch. The duodenum is stapled and transected just distal to the pylorus. The ileum is stapled and transected 250 cm proximal to the ileo-cecal junction and the distal end anastomosed to the post-pyloric duodenum. In order to drain the pancreatico-biliary secretions, the proximal end is anastomosed to the ileum 100 cm proximal to the ileo-cecal junction, leaving only this length for the mixing of food and pancreatico-biliary digestive enzymes. The lateral divided stomach is removed. **c** Laparoscopic adjustable gastric banding. The prosthetic device is placed high on the proximal stomach so as to leave only a 15–25-ml reservoir of proximal stomach to serve as the mechanical fullness signal. The subcutaneously placed reservoir allows period adjustment to calibrate the outlet of the proximal gastric pouch to an acceptable fullness signal and weight loss. **d** Gastric wrap. The gastric wrap material is placed around the entire stomach from the most proximal stomach down to the antrum. The material is ribboned and sutured tightly around the stomach without excising any stomach tissue. **e** Sleeve gastrectomy. The stomach is stapled and transected along its vertical axis so as to excise 75% of the stomach. **f** Gastric balloon. Endoscopic placement of a free-floating balloon is accomplished by inflating the balloon after it is placed via an endoscope.

term outcomes analysis of the RYGB suggests that the procedure is durable in approximately 75% of patients, and there is significant resolution of major medical co-morbidities such as diabetes, sleep apnea, venous stasis disease, and hypertension.[13] Results are less favorable for the super-obese. Operative mortalities range between 0.5% and 1% and long-term risks include osteoporosis, vitamin deficiencies, and oxaluria.

Limitations A major limitation of the RYGB is its long-term failure rate. The degree to which the RYGB affects the physiology of satiety and hunger has not been fully characterized in the long term. As intestinal adaptation following surgery is a well-established phenomenon, the degree of intestinal adaptation that occurs following RYGB remains to be fully elucidated. For example, a brief review of the anatomy of the RYGB demonstrates that following this procedure, foodstuffs do not come into contact with either the antrum or the duodenum and as such, plasma levels of gastrin and cholecytokinin (CCK) would be predicted not to be produced in response to orally ingested food. Yet, studies performed at 6 months following RYGB demonstrate that meal-related gastrin and CCK levels are normal, suggesting a major re-learning of the neuroendocrine unit of the intestine to its new anatomy.[14] The science of measuring post-prandial plasma hormone levels is labor-intensive, requires multiple measurements to generate the "area under the curve" or integrated responses, and mandates strict environmental control. Furthermore, there is a paucity of studies that track the neurohormonal response following RYGB over long time periods in direct comparison to other bariatric procedures with properly matched controls. Therefore, the science underlying the perception that the RYGB, in the long term, is a more physiologic operation than mechanical restriction alone is lacking. Studies attempting to determine whether there are differences in the neurohormonal profile of patients with successful weight loss after bariatric surgery versus those who have failed are not available. Finally, while there have been numerous claims that RYGB resolves diabetes mellitus better than mechanically restrictive operations as a result of its more physiologic effect on intestinal hormones and the enteroinsular axis, whether this effect occurs independent of energy balance, food intake, changes in the intestinal microflora, or exercise has not been rigorously tested.[15]

Analysis RYGB is the most common operation performed in the USA for obesity, although its numbers appear to be decreasing. The mechanisms leading to its success or failure are incompletely understood. The neurophysiologic mechanisms that confer an advantage of the RYGB over purely mechanically restrictive operations may dissipate over time and more detailed studies are required to document the durability of the satiety response and its possible link to genetic polymorphisms for a given patient.[16] The current evidence justifying the superiority of the RYGB over restrictive operations such as the adjustable band will be challenged by its cost, complication rate, long-term vitamin deficiencies, and its real rate of long-term failure. There appears to be a growing tendency for patients facing major health problems and considering obesity surgery to choose less distorting and invasive procedures such as the LAGB.

Duodenal Switch

Rationale The observation that Western societies continue to consume highly processed foodstuffs that require little to no digestion for absorption has led some surgeons to believe that creating anatomic malabsorption will be the only durable approach to treat obesity by surgical means. The anatomy of the duodenal switch (DS) is created in a manner in which food passes directly from the stomach into the distal 40% of the small bowel and only admixes with pancreatico-biliary secretions in the distal 1/3 of the newly constructed alimentary conduit (Fig. 1b). There are several mechanico-physiologic mechanisms that might explain the reported superior weight loss and durability of the duodenal switch/pancreatico-biliary bypass compared to the RYGB.[17] While an obvious mechanism of action is its malabsorptive anatomic configuration, its mechanical restriction involves the entire stomach mucosa including the antrum and an intact pyloric valve. Proponents of the operation claim that the intact pyloric valve is important to create a natural satiety signal by delaying food emptying from the stomach, although there is no information to support this claim. The causes of the differences in outcome between the various DS procedures performed throughout the world cannot be properly evaluated as they vary on multiple levels of stomach volume and amount of intestine bypassed. There are no studies which have properly documented that the degree of functional intestine bypassed correlates to the observed weight loss, as the variables are many, and the studies poorly designed. A major confounding variable with the DS is the ability to absorb highly refined processed carbohydrates. While fat may be significantly malabsorbed by the various DS operations, many carbohydrates are not, and thus in many cases the results of malabsorptive operations may not appear very different from non-malabsorptive procedures when refined carbohydrate intake is not precisely accounted for.

A review of the anatomy of this operation demonstrates that in contradistinction to all other operations, the ileum is directly attached to the partially digested food exiting the

stomach. Since the highest concentration of the potent anorexigenic hormone peptide YY is in the ileum and colon, and its secretion is stimulated by undigested food, the potential for a robust PYY plasma level following a meal is potentially greatest with this operation.[18] Yet, fully integrated analyses of post-prandial PYY levels and their time dependence and durability following several years after the DS operation are not available. Therefore, the suggestion that this operation manipulates satiety on a neurophysiologic level superior to other operations has no scientific basis.

A completely unstudied aspect of the DS is its effect on the microbial ecology of the intestinal tract, an area that has recently received attention as having a major effect on mammalian energy metabolism.[19] Following the DS, patients experience a major change in the smell, consistency, and color of their stool.[20] Most patients complain of a major increase in the amount of flatus, which is often extremely foul smelling. Significant changes in the composition of the intestinal microflora have been documented following the DS/PBB procedures, although information is incomplete.[21] The putative role of the intestinal microflora as a major contributor to malabsorption and energy metabolism following the DS is largely based on the observation that antibiotic use dramatically changes the degree of malabsorption, diarrhea, and compositional changes in stool color, smell, and consistency in these patients.[20] A shift in the composition and phylotype of the intestinal microflora following the DS can now be assessed using recently published genome-wide analyses.[22] Such an approach might reveal a specific pattern of intestinal microbial phylotypes that develop as a result of the DS anatomy that are specifically associated with weight loss.

Limitations Less than 5% of patients in the USA undergo the DS as their primary choice of weight loss surgery. Most patients self-select for this operation and there is major resistance on the part of insurance companies to approve this procedure as most consider the DS to be experimental. Patients are aggressively marketed to this procedure and the notion of a larger stomach capacity, greater weight loss, and better durability are perceived to be major benefits. Despite compelling evidence of superior weight loss with this operation, the lack of controlled prospective data showing that a greater percentage of medical co-morbidities are resolved relative to other operations, and major concerns over long-term safety of this procedure, are likely to retard any increase in its use. Although the procedure can be performed laparosopically with the same morbidity and mortality as the laparoscopic RYGB, the operation suffers from its appearance as a major distortion in physiology and anatomy. Finally, the real concern over vitamin D absorption and its long-term effect on bone health and renal function is a major obstacle with this operation.

Analysis Despite the recognition that super-obesity (BMI> 55 kg/m^2) is a major life-threatening and disabling disorder often resistant to many of the currently performed operations, the advantages documented by the DS operation are overshadowed by concerns of long-term safety. The operation is often viewed by patients, physicians, and insurers as experimental and unsafe. Medicare and Medicaid, the major insurance carrier for the heaviest and largest population of patients who need bariatric surgery, now covers the DS. Proper application of the DS to super-obese patients has the greatest potential to provide significant and durable weight loss to the most medically needy of patients and the potential to avoid the often poor results seen in this group following the RYGB and laparoscopic adjustable gastric banding. As obesity rates climb in the USA, patient preferences for less invasive and distorting operations will increase as will failure rates for these lesser operations in the super-obese. Therefore, the DS is likely to remain an operation rarely chosen to treat morbid obesity.

Laparoscopic Adjustable Gastric Banding

Rationale The LAGB offers the ability to provide adjustable mechanical restriction to the proximal stomach with very low morbidity and with a negligible mortality rate (Fig. 1c).[23] Although the procedure appears to function purely by mechanical restriction of food intake, the fact that the device is placed high up on the stomach and envelops the anterior and posterior vagus nerves may induce satiety beyond its mechanical effect alone. There are no studies, however, that exist to explain the mechanisms of weight loss of the LAGB beyond its mechanical restriction effect. Simplicity of placement, low complications rates, and success rates in terms of percent excess body weight loss approaching that of the RYGB at 3 and 4 years justify its use.[24]

Limitations As there is virtually no neuroendocrine type mucosa within the proximal restricted stomach that remains above the LABG, foods that accumulate in this region are not likely to elicit the same satiety signal as other operations. Recent studies have confirmed this notion by showing that PYY levels and GLP-1 levels are not affected with the LAGB as with the RYGB[9] although whether these differences remain durable is unknown. Nonetheless, refinements in placement techniques with the LAGB and aggressive adjustment protocols have demonstrated that significant weight loss is achieved with this device that rivals the RYGB at years 3 and 4, a time when

neurophysiologic satiety signals inherent in the RYGB may become extinguished. If morbid obesity is viewed as a disorder of appetite regulation and energy expenditure, the LAGB has the potential to fail long on a long-term basis given that highly processed, liquid foods can readily pass through the restriction site. Finally, deterioration of the device itself cannot be predicted in the long term.

Analysis Refinement in the technique of placement of the LAGB, new generation bands, lower costs, and high patient acceptance has the potential to place this device as the first line treatment for morbid obesity refractory to medical treatment. Although many devices will fail, removal and replacement is viewed as a possible option, although the real costs and morbidity of band adjustment and replacement have not been assessed. The procedure will become a routine outpatient procedure and a growing number of patients will pay out of pocket for the device. A randomized trial lasting at least 5 years is needed to determine the real cost, morbidity, and efficacy differences between the RYGB and the LAGB. As patient preference, surgeon bias, and insurance approval drive operation choice, only with a truly randomized, fully funded, adequately powered, and comprehensively analyzed end-point study will we ever be able to determine whether cost and efficacy benefits of the LAGB are superior to the RYGB.

Intestinal Bypass Without Gastric Stapling

Rationale Assuming a neuroendocrine basis for diabetes resolution following RYGB, Rubino and colleagues have advanced the notion that the intestinal bypass portion of the RYGB alone can resolve type II DM via manipulation of the concentration and/or function of hormones such as GLP-1.[25] Significant animal work by this group has advanced this hypothesis and several non-morbidly obese subjects have undergone the procedure. Enthusiasm for curing diabetes using intestinal bypass has led to surgeons claiming they are metabolic surgeons in addition to bariatric surgeons.

Limitations The absence of a complete understanding of the mechanisms of action of this procedure, its durability, and the time dependency of intestinal adaptation will require extensive testing in patients before it can be accepted. For example, the ability of this procedure to activate a durable GLP-1 response superior to the newly available GLP-1 mimic drugs needs to be determined in order to claim victory of surgery over medicine for the type II diabetic who is not morbidly obese.

Analysis The experimental work to use intestinal bypass without gastric stapling to treat type II diabetes mellitus represents an important example by which examination of the scientific basis for diabetes resolution following RYGB might be translated to create a surgical treatment for DM. However, if applied to patients directly as a cure for type II diabetes without the specific intent to directly study its mechanisms of action, durability, and superiority over medical management, the procedure has the potential to be misapplied. If the procedure can be determined to be safe, durable, and capable of reducing the complications of type II DM in a cost-effective manner superior to medical management alone, then the procedure has the potential to be accepted. Significant barriers exist, however, to advance this treatment including referral bias, patient acceptance, and insurance approval.

The Gastric Wrap

Rationale The gastric wrap involves a complete wrapping of the stomach with a sheet-like material in order to restrict its volume (Fig. 1d). From a mechanico-physiological perspective, the gastric wrap is conceptually the most logical approach to create a satiety signal in the stomach via surgical means. Restricting intake due to limited capacity while at the same time exposing the entire stomach mucosa and underlying nervous plexus to food and mechanical force is the most likely mechanism to elicit a durable neurophysiologic and mechanical fullness signal by surgical means. The entire mucosa of the stomach including the highly dense mass of neuroendocrine cells in the antrum is exposed to ingested foodstuffs that must slowly pass through the restricted channel of the stomach. Comparison studies between the gastric wrap and the RYGB show the wrap to be a superior operation with weight loss at 5 years as a major endpoint.[26] Patient comfort and tolerance appears to be surprisingly high with this operation.[26] As there is no anastomosis, no stapling, and no intestinal reconstruction, patient acceptance may be greater as it is perceived to be less deforming and with the use of the proper material, completely reversible.

Limitations The gastric wrap has been abandoned due to major complications related to the materials used.[27] The use of the marlex mesh led to the development of erosion and bleeding as the material became imbedded in the stomach wall. Mesh erosion has led to total gastrectomy in several cases (Alverdy, personal communication). The use of Gortex as a wrapping material was proposed to improve this problem; however, only sporadic anecdotal reports have been available. Therefore, the single limitation to the gastric wrap appears to be the safety profile of the material used.

Analysis Devices analogous to the LAGB that restrict a more complete volume of the stomach with biologically

inert materials have the potential to exert a more natural feeling of satiety by manipulating the entire neuroendocrine/mechano-sensory unit of the stomach. Current measures of satiety involving plasma hormone profiling coupled with the use of functional magnetic resonance imaging (MRI) of the brain to assess the central nervous system readout of satiety are now available to allow for direct comparison of this approach to more traditional operations.[28]

Sleeve Gastrectomy

Rationale Sleeve gastrectomy is a restrictive operation lacking convincing scientific evidence that represents a novel physiologic mechanism to distinguish it from other restrictive operations. A recent prospective randomized double blind study between RYGB and sleeve gastrectomy in which the stomach volume was reduced dramatically to 40–60 ml of volume, compared to the standard of 200 ml, demonstrated greater suppression of the appetite hormone ghrelin with the sleeve gastrectomy compared to the RYGB, although the differences were small and the dataset involved only 12 patients (Fig. 1e).[29] The operation is technically simple, can be performed laparosopically, and is gaining popularity as a primary procedure for obesity.

Limitations The short-term results of sleeve gastrectomy suggest that it achieves significant weight loss, although the long-term durability of the operation remains in question.[30] Loss of parietal cell mass and its effect on vitamin absorption is unstudied. The scientific basis of satiety and weight loss underlying the sleeve gastrectomy is essentially unstudied, despite initial reports that it manipulates hormone profile distinct from other bariatric procedures. Long-term risks such as stricture, ulcer, esophagitis, GERD, etc. are unknown.

Analysis Traditionally, sleeve gastrectomy has been considered to be a temporizing operation to bridge high risk patients to more definitive weight loss procedures.[30] There is growing enthusiasm that it can function as a stand-alone therapy by continuing to push the limits of reducing the stomach volume to approach that of the traditional RYGB. An important ethical consideration with this technique is that its application it is not restricted in any way by a device, and therefore proponents of its use have declared freedom to operate without regulatory obstacles. As such, the public is at risk that the procedure will be claimed to be equivalent to standard operations, incompletely analyzed for its risks and efficacy compared to standard operations, and therefore misapplied.

Endoscopic Balloon Placement

Rationale Endoscopic placement of a space-occupying mass in the stomach, such as an inflatable balloon, increases satiety by creating a mechanical fullness signal to lower amounts of food (Fig. 1f).[31] Other self-expanding products have been proposed and include sponge-like materials and self-expanding and degrading hydrogels.[32] Several balloon products are on the market around the world and show that a device inflated to approximately 500 ml causes significant weight loss with an acceptable safety profile. Intragastric balloons could represent bridge therapy for patients needing more extensive surgical procedures who are not candidates based on BMI. The simplicity of the approach is attractive and the device could be used as a biofeedback tool in a multidisciplinary program for weight reduction. A more thoughtful approach to the shape and position of an intragastric balloon could potentially be demonstrated to elicit a more physiologic satiety signal compared to LAGB or pacing. Currently, there is no medical science that seeks to understand how gastric balloons induce weight loss beyond their mechanical limiting effects on gastric volume.

Limitations As currently designed, devices do not present a long-term solution to the chronic problem of obesity. Complications include obstruction, abdominal pain, need for repeat endoscopy, balloon rupture, and occasional need for emergency surgery. Medical liability for the balloon is potentially high. Its application in certain high risk population that otherwise do not qualify for more routine approaches may represent an orphan indication for these devices.

Analysis Carefully constructed gastric balloons and other space-occupying devices could be positioned to be highly beneficial in patients as an adjunct to a multidisciplinary approach to obesity. Plasma hormone profiling coupled with functional MRI of the brain to assess satiety could help define its mechanism of action. Public and physician acceptance of intragastric space-occupying devices has the potential to be high depending on issues surrounding safety and durability. Without measures of durability and without a critical assessment of the mechanism of action of these devices, the procedure has high misapplication potential.

Natural Orifice Transesophageal Endoscopic Surgery (NOTES) for Obesity

Rationale The ability to endoscopically restrict stomach volume and create a mechanical fullness signal would be

highly attractive to patients by offering a "surgical" option through a natural orifice without a skin incision.[33] Transoral endoscopic stomach reduction surgery could serve as a bridge procedure to other bariatric interventions or as an adjunct to multimodality therapy for obesity. The procedure has already been performed in a human trial.[33] Although results indicate that the procedure is safe and induces significant weight loss, the durability of the procedure remains in question.

Limitations Experience with surgical procedures that restrict the stomach volume demonstrates that the stomach needs to be maximally restricted in volume to produce significant and durable weight loss.[34] Furthermore, extrapolation of the experience of the laparoscopic adjustable band suggests that the ability to adjust the outlet of the restricted portion of the stomach is a key feature of a restrictive operation in order to account for changes in tissue edema, scarring, and expansion over time. Lack of this feature with both the sleeve gastrectomy and NOTES has the potential to result in long-term failure. As such, the results of complete endoscopic placation of the stomach with or without stomach excision are likely to parallel the results of sleeve gastrectomy which to date demonstrate that its long-term durability is unknown.

Analysis Industry and entrepreneurs will technically succeed in perfecting a transoral endoscopic stomach volume restricting procedure. Major obstacles in winning acceptance by patients and insurers will be its safety and efficacy profile relative to the laparoscopic adjustable gastric band or small volume sleeve gastrectomy. Lack of regulatory oversight with this approach as the technique does not require implantation of a device is a potential problem. The ethical issues surrounding this approach have not be developed and as such, misapplication of its use and indications is likely by surgeons or gastroenterologists who will use the argument that surgically induced weight loss, independent of its degree and durability, is beneficial to obese patients.

Ileal Transposition

Rationale Studies beginning over 30 years ago have demonstrated that interposition of a 10-cm segment of ileum into the proximal jejunal position causes weight loss in rats by a mechanism that appears to involve the release of satiety signals within the transplanted intestinal segment.[35] As the most abundant concentration of the satiety hormone PYY can be found in the ileum and proximal colon, recent studies suggest that the observed weight loss from ileal transposition is associated with increased plasma PYY and GLP-1 levels (Fig. 2).[36] Rats subjected to ileal interposition lose weight and diabetic rats are cured of their diabetes following this procedure. This surgical strategy seems highly attractive as satiety is induced in direct response to food intake via endogenous hormone release rather than via malabsorption or mechanical restriction.

Limitations Transposition of the ileum within the duodenal conduit remains a surgically challenging proposition with potentially significant morbidity as anastomotic leak represents a clear and present danger to the patient. The extent to which the transposed segment will adapt to its new position and thus lose its endocrine effect is unknown.

Analysis Although ileal interposition may represent a highly physiologic approach to appetite regulation in the obese, it is a major intestinal reconstruction and carries a high risk of anastomotic disruption. Both patient and referring physician are likely to view this approach as distorting, risky, and of uncertain outcome.

Endoscopic Submucosal Implantation of Satiety-Hormone-Producing Cells

Rationale Repopulating the foregut mucosa with epithelial cells that release an anorexigenic quantity of gut-derived satiety hormones in response to food has the potential to offer a physiologic approach to treating obesity. Reseeding of the foregut mucosa (stomach, duodenum, and proximal jejunum) with cultured cells programmed to release increased amounts of satiety hormones such as peptide YY or GLP-1 could be accomplished by injecting cultured

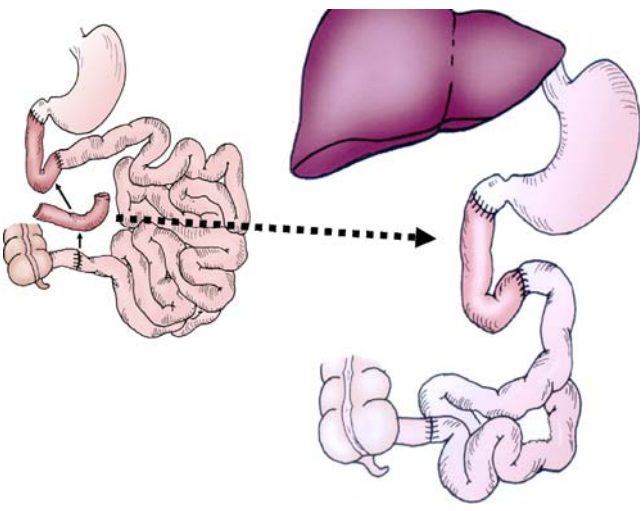

Figure 2 Ileal transposition. A segment of ileum harvested from the distal intestine is interposed in a proximal position between the first portion of the duodenum to allow partially digested food to stimulate the ileal mucosa to release satiety hormones such as PYY and GLP-1.

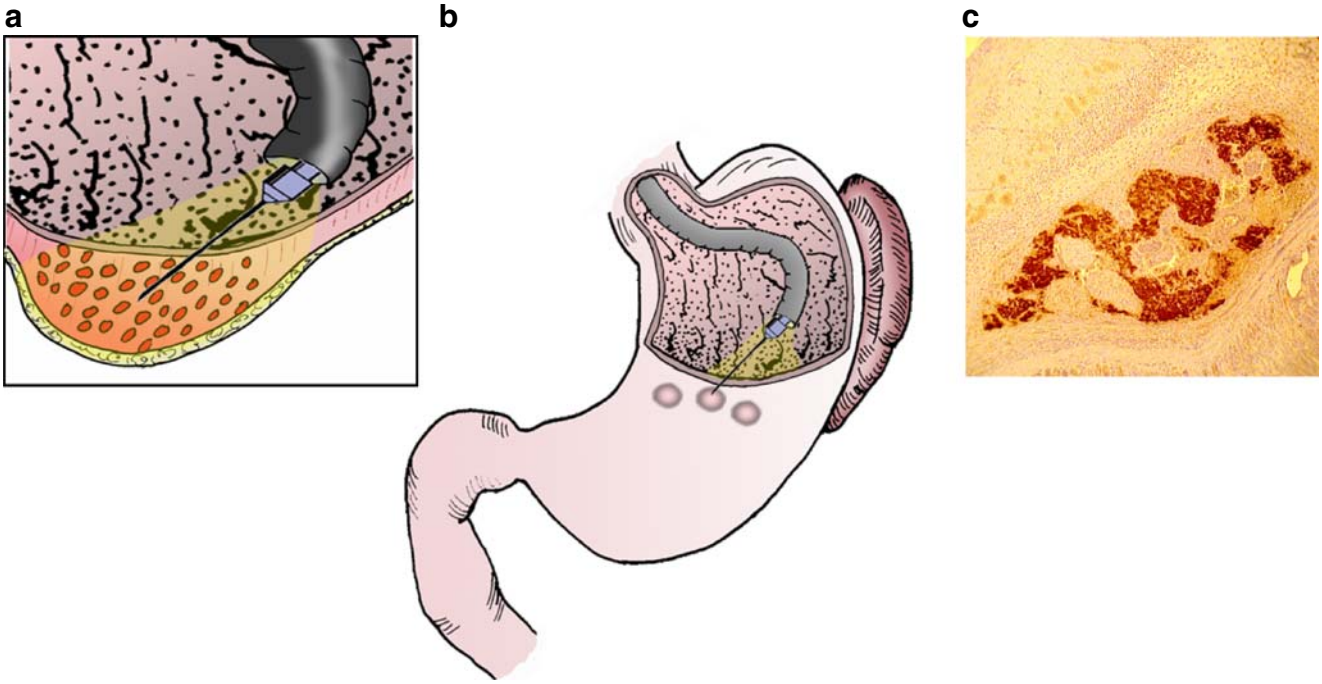

Figure 3 Endoscopic submucosal implantation of satiety-hormone-producing cells. **a**, **b** Injection of viable cells into the stomach submucosa (**a**) is accomplished via endoscopy (**b**). **c** Cells proliferate within the submucosa and secrete hormones which mediate satiety centrally as is depicted in the histology specimen of experimentally injected pancreatic islet into the rat stomach. Viability is demonstrated 7 days after implantation.

peptide-producing epithelial cells directly into the intestinal submucosa (Fig. 3a,b). Implanted cells could be fused with fluorescent probes that allow for their endoscopic detection and hence excision or replacement in the event that the response becomes excessive or diminished. We have proved the feasibility of this approach by implanting pancreatic islet cells into the stomach submucosa of rats and demonstrating that cells are viable 7 days after implantation (unpublished observations; see Fig. 3c). Once stem cell lines that differentiate to peptide YY or GLP-1 cells are developed, they could be easily implanted endoscopically.[37]

Limitations The costs, feasibility, and durability of this approach are unknown. Currently, there is no published work in this area.

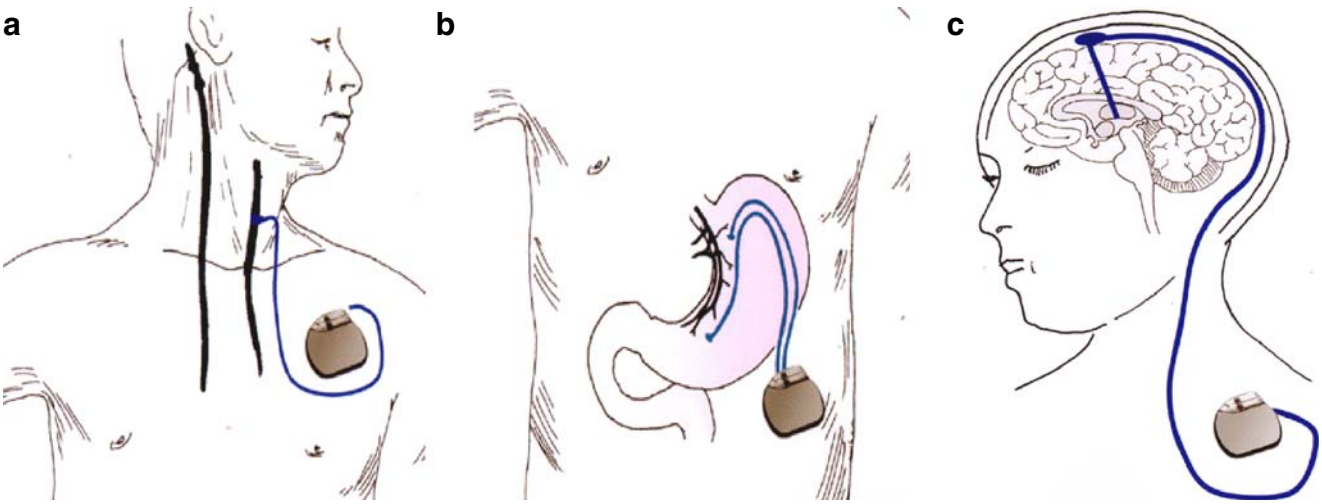

Figure 4 **a**, **b** Vagal nerve gastric pacing. Vagal nerves could be stimulated via the neck or around and within the stomach. **c** Deep brain stimulation. Electrodes could be stereotactically placed to attempt to direct target satiety centers within the hypothalamus.

Analysis As stem cell research moves forward, endoscopic mucosal cellular reprogramming to control obesity could be experimentally modeled. If feasible, this approach would represent a novel and highly physiological approach to regulate the satiety response to food.

Electric Impulse Stimulation of the Stomach and Vagal Nerves

Rationale Gastric pacing and vagal nerve stimulation have been shown to decrease weight by incompletely understood mechanisms that include release of anorexigenic hormones, reverse peristalsis of the stomach, delayed stomach emptying, and stomach contraction (Fig. 4a,b).[38] Each effect produces a variegated array of symptoms many of which are well tolerated by patients. Lead placement is non-invasive with a negligible operative morbidity and long-term use is likely to be safe given the wide experience with deep brain and peripheral nerve stimulators. Recently, gastric pacing in humans was demonstrated to activate the hippocampus and other reward centers in the brain as assessed by positron emission tomography (PET) scanning.[39]

Limitations The extent of weight loss with electrical stimulation therapies is significant but modest compared to restrictive and malabsorptive procedures.[40] The mechanisms by which electrical stimulation of the stomach and vagal nerves reduces food intake are becoming more completely understood to involve central regulation of energy.[41] At present, the main limitation to electric impulse stimulation of the stomach and vagal nerves as a treatment of obesity is cost and reimbursement. It is not clear that insurance companies will bear the cost of this therapy until randomized trials show a clear advantage in cost and efficacy over current surgical approaches.

Analysis Experience with electrical pacing and vagal nerve stimulation therapies will continue as industry is perfectly positioned to exploit the knowledge base of electric heart therapies to the stomach. Even if the total amount of weight loss with the procedure is 10–30% of the excess body weight, the simplicity, non-deformity, and perceived positive physiologic effect has the potential for high demand for the development of this operation. The need for re-operations, replacement of electrical leads, re-programming, and generator replacement costs has the potential to retard acceptance of this therapy as it is likely that therapy will need to be permanent to ensure durability of weight loss. At present, the long-term maintenance costs of this approach versus the costs of a one-time operation cannot be anticipated. Lastly, the ethical issues surrounding informed consent for this procedure when the risks and benefits are so poorly defined have not been formally addressed.

Deep Brain Stimulation

Rationale A single case report from the University of Chicago has demonstrated that deep brain stimulation can profoundly affect appetite leading to massive weight loss (Fig. 4c; Frederick Brown, MD, personal communication). Deep brain stimulation to control excess food intake is technically feasible given the expanded use of this technology for other neurological disorders.

Limitations To date, studies have been limited to animals.[42] Infection or hemorrhage will challenge the ethics and appropriateness of this approach.

Analysis There will be major obstacles to implementing clinical trails both on ethical, economic, and risk assessment grounds. On an experimental basis, the industry will prove the feasibility of this approach; however, it will be unclear if deep brain stimulation can be implemented on regulatory and ethical grounds.

Pediatric Obesity Surgery

Rationale The prevalence of obesity has not escaped the pediatric patient population. In the past three decades, the number of children and adolescents with obesity has increased 300%.[43] Evidence shows that obese children are more likely to experience type 2 diabetes mellitus and hypertension and that obese adolescents are likely to develop into obese adults.[44] As such, pediatric obesity surgery has emerged as a treatment option with demonstrated success in achieving dramatic weight loss and control of eating. Surgical intervention for pediatric obesity has been limited to laparoscopic adjustable gastric banding and gastric bypass. As much as 50% estimated weight loss has been reported in studies, indicating that surgical intervention of either type is effective in adolescents.

Limitations The long-term clinical outcomes of surgical intervention in pediatric patients have not been adequately studied. While it is known that surgery effectively leads to weight loss in obese adolescents, the duration of this weight loss is unknown. Also, pediatric patients may still be developing, and the long-term effects of nutritional restriction on development are not known.[45] This is compounded by the fact that many complications related to obesity are not manifested until adulthood, further limiting the use of pediatric obesity surgery.

Analysis Pediatric obesity surgery is challenged by public acceptance, risk of developmental metabolic derangements, and major ethical concerns. Although currently there is no limitation on centers that can perform this procedure, surgery on adolescents should be performed in specialized centers and should be rigorously tracked with long-term follow-up for all patients.

Currently Available Tools to Comprehensively Analyze the Physiologic Basis of Bariatric Surgery: Moving Toward a More Scientific Understanding of Interventions

Important analytic tools are now available that could define a more precise basis for the rationale and success of bariatric surgery. Current technologies include functional MRI, PET scanning, satiety and hunger hormone proteomic profiling, continuous assessment of non-exercise activity thermogenesis (NEAT),[46] hand-held computer oral intake assessment tools, genetic screening for single nucleotide polymorphisms,[47] and comprehensive assessment of the intestinal microbiome via gene-wide phylotype analysis and metagenomics.[48] The current trend of using plasma hormone hunger/satiety peptides as putative markers for the efficacy of a given operation has led to widely varying reports and little insight into the mechanisms of the various operations. Many of these studies are poorly executed, uncontrolled for environmental noise, and reported as single measurements rather than the area under the curve of multiple measurements over time. The lack of recognition that sleep deprivation, diet, and stress have dramatic effects on gut satiety and appetite hormones and on the intestinal microflora, coupled with the observation that the intestinal microflora itself influences the gut endocrine profile, has resulted in an inadequate approach to properly interrogate the physiologic effects of bariatric surgery.[49,50] As energy balance is ultimately regulated centrally, only with a more comprehensive "readout" of peripheral and central elements involved in appetite/satiety regulation can the scientific basis for bariatric surgery be understood. Such a comprehensive readout between responders versus non-responders to the various operations would provide unique insight into the mechanisms of action of current operations and pave the way for a more rational development of newer, less invasive, and even non-surgical approaches. The currently held notion that patients who fail to lose weight after bariatric surgery are "non-compliant" with the dietary restriction imposed by the surgery, whereas those that succeed are universally compliant because of personal commitment and volition, is scientifically baseless. The complex interaction between the environment and genetics of both the host and its microbial flora must be tracked over the course of weight loss following a given procedure before any meaningful conclusion can be made regarding the mechanisms of action of a given operative intervention and its success or failure. Finally, while medical science continues to promise to make bariatric surgery obsolete, such a promise seems naive given the complex interactions between our every changing environment, our genes, and the multicomponent bioreactor of our intestinal microbial flora. The highly empirical nature of research in bariatric surgery today has permitted many missed opportunities to better define the science of weight loss following bariatric surgery and exploit this knowledge for novel therapies that are less invasive, less distorting, and ultimately more physiologic to the mechanisms that underlie the drive to eat in excess of energy expenditure at the peril of one's own health.

Ethical Considerations and Conclusions

Medical science is now technologically poised to better understand the puzzle of human obesity and clarify the mechanisms that underlie the success or failure with current and proposed surgical treatments. As obesity rises in the USA, the obese public will be reluctant to undergo a procedure that is disfiguring to the normal intestinal anatomy and that imposes a degree of food restriction or lifestyle that is perceived to be socially abnormal. Metagenomic/proteomic and PET/fMRI imaging with system-wide tracking of the central and peripheral elements that regulate energy balance at multiple points in time following the various bariatric operations will uncover the flaws and fallibility of the logic used to justify current bariatric procedures. The medical community will not continue to tolerate the performance of procedures that lead to metabolic complications such as vitamin deficiencies and chronic malabsorption. Insurance companies will not pay for "promising" surgical procedures and will continue to minimize their risk in the business of bariatric surgery. Surgical breakthrough therapies will be deemed so only under the most rigorously tested conditions with a clear understanding of their mechanism of action and long-term effectiveness. Medical science and medical ethics will need to converge to protect the morbidly obese from procedures that have not been rigorously analyzed for their long-term safety and durability. Although the practice of bariatric surgery will continue, it will be rationed, and attempts will be made to apply appropriate procedures to a select group of patients as an adjunct to a multidisciplinary approach to the problem. Political interest groups attempting to expand the indications and application of bariatric surgery to include all morbidly obese patients will be impeded by

the realization that the costs to bear will be too great and the science justifying such action too weak. A medical ethics consensus statement would be highly useful to protect patients against emerging surgical and endoscopic treatments that result in weight loss of uncertain duration and significance. A major theme to emerge from such a conference would be to explain to the public the scientific basis upon which the decision to operate is made. Results from such a conference should provide convincing evidence to the non-obese public that morbid obesity cannot be treated by methods that rely on human volition alone. A national referendum and funding mechanism to better understand the practice patterns of bariatric surgery will be necessary to balance the demands of the at-risk population requesting the surgical option with more rigorous guidelines on surgeon's indications and choice of procedures.[3]

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ORIGINAL ARTICLE

Nitroglycerin Protects Small Intestine from Ischemia–Reperfusion Injury via NO–cGMP Pathway and Upregulation of α-CGRP

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Abstract
Introduction Nitroglycerin (NTG) has been reported to possess preconditioning-like (PCL) protections on heart and other tissues. Our previous studies showed that NTG has acute PCL effects on rat small intestine. The present studies were designed to study whether NTG has delayed PCL protection on rat small intestine and to explore its mechanism(s).
Methods The intestine lesions were evaluated by histologic examination and serum lactate dehydrogenase (LDH) measurement. The effects of nitric oxide (NO), cGMP, and α-calcitonin gene-related peptide (CGRP) synthesis on the effects of NTG were analyzed.
Results Pretreatment with NTG (0.12 mg/kg i.v.) 24 h before ischemia–reperfusion (I/R) of super mesenteric artery significantly reduced histologic lesions and serum LDH with elevated blood levels of NO and CGRP. Inhibition of guanylate cyclase by methylene blue (30 mg/kg i.p.) or specific depletion of transmitters in capsaicin-sensitive sensory nerve by capsaicin (50 mg/kg s.c.) abrogated the protection conferred by NTG. Reverse-transcription polymerase chain reaction analysis showed that NTG upregulates the expression of α-CGRP messenger RNA (mRNA), but not β-CGRP mRNA in lumbar dorsal root ganglia.
Conclusion In conclusion, NTG prevents rat small intestine from I/R injury by delayed PCL effects 24 h after administration. The protective effects are mediated by NO–cGMP pathway and α-CGRP upregulation.

Keywords Nitroglycerin · Small intestine · Delayed preconditioning · CGRP (calcitonin gene-related peptide) · Nitric oxide (NO)

Introduction

Intestinal ischemia–reperfusion (I/R) is a potentially serious consequence of several clinical and pathophysiological conditions, including small bowel transplantation, cardiopulmonary bypass, trauma, and hemorrhage.[1,2] I/R injury can be attenuated by preconditioning, which renders cell, tissue, or organ resistant to subsequent severe I/R injury. The preconditioning phenomenon was also found in small intestine.[3–6] Ischemic preconditioning (IPC) is originally referred to as sublethal-brief-ischemia-induced protective condition against tissue injury induced by subsequent severe ischemia. Two phases of preconditioning (acute and delayed) have been recognized in IPC[7,8] and have been well studied in hearts and cardiac cells. The acute phase of IPC appears within minutes and confers a protection of 2–3 h, whereas the protection produced by the delayed phase develops 12 to 24 h later and persists for up to 3–4 days. Preconditioning-like (PCL) effects can be triggered by pharmacological agents.[9–12] Obviously, pharmacological preconditioning (PPC) is more practicable, less dangerous, and provides new ideas and exciting perspective for curing some refractory ischemic diseases. However, mechanisms underlying PPC, like IPC, remain to be elucidated, although

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a multitude of mediators have been investigated in various tissues and under different experimental conditions.

Calcitonin gene-related peptide (CGRP) is a principle transmitter in capsaicin-sensitive sensory nerves, which are widely distributed in the gastrointestinal tract. CGRP is suggested to play an important role in the mediation of preconditioning.[13–16] CGRP can be synthesized and released upon several stimulators, including nitric oxide (NO) or NO donor. NO has been widely accepted as both a trigger and a mediator of ischemic preconditioning.[17] The cardioprotection afforded by delayed IPC can be mimicked by the administration of a variety of pharmacological agents, including nitroglycerin (NTG)[11,12] and other NO-releasing agents.[18,19] As for NTG, both NO–cGMP pathway and CGRP have been reported to be involved in its PCL cardioprotective effects.[18] All these studies support that NTG confers a PCL effect on heart. However, little has been known as for whether and why NTG possesses a PCL effect on small intestine. Our previous work showed that pretreatment with NTG 5–20 min before I/R attenuated rat small intestine I/R injury with an elevated level of CGRP in the effluent and the plasma, suggesting that NTG produced an acute PCL protective effect, which may be mediated by CGRP.[20] As the delayed preconditioning is more relevant to protection, the present experiments were designed in an attempt to answer the question whether NTG confers a delayed PCL effect in rat small intestine, and if so, to explore its mechanisms by studying the effects of inhibition of guanylate cyclase or depletion of capsaicin-sensitive sensory transmitters on effects of NTG and effects of NTG on synthesis and release of CGRP isoforms (α and β).

Materials and Methods

Animals The protocols and procedures described below were approved by the Animal Care and Use Committee of the Shanxi Medical University and were in accordance with the guidelines on the care and use of animals required by the American Physiological Society. Male Wistar rats (Animal Facility Center of Shanxi Medical University, China) weighing 250–280 g were used.

Study Groups and Experimental Protocols The study consisted of two sets of experiments. The first set of experiments was designed to determine whether the administration of NTG reduces I/R injury of rat small intestine. The lesion grade, the serum lactate dehydrogenase (LDH), and the serum level of NO were measured after I/R. I/R was performed by occluding super mesenteric artery for 30 min of ischemia followed by 60 min of reperfusion. Rats were randomly assigned to receive one of the seven treatments: Sham, subjected to surgical procedures without I/R; I/R, subjected to I/R; NTG, pretreated with NTG (0.12 mg/kg i.v.) 24 h before I/R; MB, pretreated with methylene blue (MB, 30 mg/kg i.p.) 24 h before I/R; MB + NTG, pretreated with methylene blue and NTG 24 h before I/R; Cap + NTG, pretreated with capsaicin (Cap, 50 mg/kg s.c.) 4 days and with NTG 24 h before I/R; and Veh + NTG, same experimental procedures as in the Cap + NTG group except for substitution of Cap vehicle for Cap (Fig. 1).

Rats from all groups were anesthetized with urethane (1.2 g/kg, i.p.) and heparinized with sodium heparin (600U/kg, i.v.) after a 12-h starvation period. All rats except the Sham group underwent super mesenteric artery occlusion for 30 min and reperfusion for 60 min.

The second set of experiments was designed to examine the effect of NTG on the release and synthesis of CGRP. Rats were randomly assigned to three groups: NTG, MB + NTG, and Cap + NTG. The medications in these groups were same as in the corresponding groups of the first set of experiments. Blood samples were collected, and the lumbar dorsal root ganglia (DRG) were removed at 0 (control, before NTG), 8, and 24 h after administration of NTG.

Serum LDH, NO, and Plasma CGRP Measurements After I/R, blood samples were collected from the abdominal aorta. Serum LDH activity was measured spectrophotometrically, and the serum NO was determined indirectly as the concentrations of nitrate and nitrite as previously described.[21]

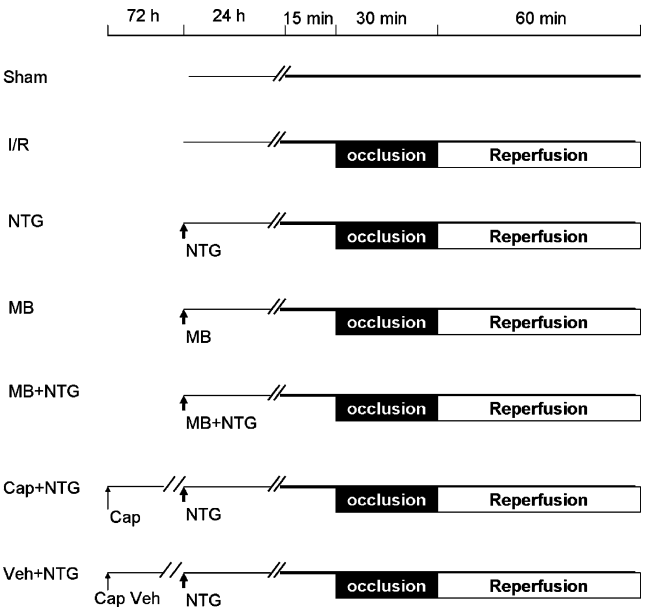

Figure 1 Schematic diagram of animal groups and experimental procedures. Twenty-four hours after pretreatment with NTG, anesthesia with urethane (1.2 g/kg, i.p.) and laparotomy were performed on all rats. And then, all rats except Sham group underwent super mesenteric artery occlusion for 30 min and reperfusion for 60 min (*I/R*). *NTG* nitroglycerin (0.12 mg/kg i.v.), *MB* methylene blue (30 mg/kg, i.p.), *Cap* capsaicin (50 mg/kg, s.c.), *Veh* vehicle for Cap.

Briefly, nitrate was converted to nitrite using aspergillus nitrite reductase, the total nitrite was measured with the Griess reagent, and the absorbance was determined at 540 nm.

To measure plasma CGRP, blood samples (3 ml) were collected in tubes containing 10% Na_2EDTA 40 μl and aprotinin 400 mU/l and centrifuged at 1,300×*g* for 20 min (at 4°C). The plasma concentration of CGRP-like immunoreactivity was determined using a radioimmuoassay kit with antiserum raised against rat CGRP, ^{125}I-labeled CGRP, and rat CGRP standard.

Histopathologic Examination Wedges of 1 to 2 cm from the ileum were excised, carefully cannulated, and gently flushed with normal saline solution. The tissue specimens were fixed by being immersed in 10% buffered formaldehyde solution, embedded with paraffin, and stained with hematoxylin and eosin. Mucosal injury, inflammation, and hyperemia/hemorrhage were assessed and graded in a blind manner by a pathologist using the histologic injury scale previously defined by Chiu et al.[22]

RNA Isolation In the second set of experiments, at 0, 8, or 24 h after administration of NTG, blood samples (3 ml) were drawn under anesthesia from the carotid artery for measurement of CGRP concentration. The lumbar DRG were then removed rapidly and homogenized in Trizol reagent. The individual tissue samples were incubated for 5 min at 20°C, and then, chloroform was added for phase separation. The upper (aqueous) phase was collected, and RNA was precipitated by mixing with isopropyl alcohol. The RNA pellet was washed once with ethanol, air-dried, and redissolved in RNase-free water. The purified RNA collected was confirmed by visualization of 28S and 18S ribosomal RNA bands after electrophoresis of RNA through a 1% agarose ethidium bromide gel, and the concentration of RNA was determined by absorbance at 260 nm in relation to that at 280 nm. RNA was stored at −70°C until it was used for the reverse-transcription polymerase chain reaction (RT-PCR).

RT-PCR The messenger RNA (mRNA) expression of CGRP in lumbar DRG was determined by RT-PCR. The RNA was reverse-transcribed using avian myeloblastosis virus reverse transcriptase (AMV-RT) at 42°C for 30 min. Negative controls for RT were made by deleting AMV-RT or RNA.

The primers had the following sequences (sense and antisense, respectively): for α-CGRP, 5′-AAGTTCTCCCCT TTCCTGGT-3′ and 5′-GGTGGGCACAAAGTTGTCCT-3′ (318 bp); for β-CGRP, 5′-TCAGCTTTGGAGAGCAGCCT-3′ and 5′-GGTGGGCACAAAGTTGTCCT-3′ (264 bp); and for β-actin, 5′-GAGACCTTCAACACCCCAGCC-3′, and 5′-TCGGGGCATCGGAACCGCTCA-3′ (422 bp).[23] The β-actin primers were used as an internal standard. The temperature cycling program was as follows: denaturation at 94°C for 30 s, annealing at 56°C for 30 s, and extension at 72°C for 45 s. The linear exponential phases for CGRP (α and β) and β-actin PCR were 28 cycles. Equal amounts of corresponding RT-PCR products were separated electrophoretically in a 1.5% agarose gel. Optical densities of ethidium-bromide-stained DNA bands were quantitated, and results were expressed as CGRP/β-actin ratios.

Reagents Cap and MB were purchased from Sigma (St Louis, MO, USA). NTG was purchased from Guangzhou Mingxing Pharmaceutical (Guangdong, PR China). NTG was diluted in 0.9% saline to the desired final concentration. Cap was dissolved in a vehicle containing 10% Tween 80, 10% ethanol, and 80% saline. LDH assay kits and NO assay kits were obtained from Nanjing Jiancheng Bioengineering (Nanjing, PR China). Radioimmunoassay kits for measurement of CGRP were purchased from Immunity Institute of Dongya (Beijing, PR China). Primers for PCR were synthesized by Sangon (Shanghai, PR China). Trizol reagent was obtained from Invitrogen (Invitrogen, Carlsbad, CA, USA). The RT-PCR kits were purchased from Division of TaKaRa (Dalian, PR China).

Statistical Analysis Results are expressed as mean ± SEM. Data were evaluated by one-way ANOVA, in which multiple comparisons were performed by using the method of Student Newman–Keuls test. Wilcoxon rank sum test was used to evaluate the morphological appearance of tissues. A value of $P<0.05$ was considered significant.

Results

Ischemic Reperfusion Injury of Rat Small Intestine I/R significantly increased serum LDH (I/R vs Sham, 693.49± 32.37 U/l vs 317.43±28.07 U/l, $P<0.01$) and induced more severe mucosa lesions (I/R vs Sham, 3.14 vs 0.29, $P<0.01$). Administration of NTG 24 h before I/R significantly reduced elevated serum LDH and abated the histological lesions induced by I/R. The protective effects of NTG were abrogated by either coadministration with MB or pretreatment with Cap pretreatment (Table 1 and Fig. 2).

Serum Concentration of NO Serum NO in the rats treated with NTG was significantly increased compared with the I/R group. Pretreatment with MB or Cap had no effect on the serum NO elevation induced by NTG (Table 1).

Plasma Concentration of CGRP Plasma concentrations of CGRP at 8 and 24 h after intravenous administration of

Table 1 Blood Levels of LDH, NO, CGRP, and Chiu's Lesion Grade of Rat Small Intestine at the End of Ischemia for 30 min and Reperfusion for 60 min (mean ± SEM, $n=7$)

	Serum LDH (U/l)	Serum NO (μmol/l)	Plasma CGRP (pg/ml)	Tissue lesion (Chiu's grade)
Sham	317.43±28.07	42.16±4.20	43.18±4.91	0.29
I/R	693.49±32.37[a]	51.46±3.66[a]	27.03±3.97[a]	3.14[a]
NTG	440.57±26.57[b]	90.01±6.29[b]	86.79±6.45[b]	1.43[c]
MB	692.26±32.84[d]	52.98±4.84[d]	33.68±6.26[d]	3.00[d,e]
MB + NTG	678.01±54.68[f]	81.82±7.50[f]	35.24±5.59[f]	2.86[d,g]
Cap + NTG	705.54±49.89[f]	79.31±8.52[f]	26.46±3.79[f]	3.29[f]
Veh + NTG	456.18±19.03[g]	88.51±5.27[g]	83.42±6.66[g]	1.71[g]

Abbreviations are same as in Fig. 1.
[a] $P<0.01$ vs Sham
[b] $P<0.01$
[c] $P<0.05$
[d] $P>0.05$ vs I/R
[e] $P<0.05$
[f] $P<0.01$
[g] $P>0.05$ vs NTG

NTG increased significantly (Table 1) in a marked time-dependent manner. The elevation of CGRP after NTG was abrogated completely either by concomitant administration of MB or by pretreatment with Cap (Fig. 3).

The Levels of CGRP mRNA To explore the relevance and causality among CGRP synthesis, NO elevation, and protection of NTG, the expression of CGRP mRNA in DRG was analyzed quantitatively. Levels of α-CGRP

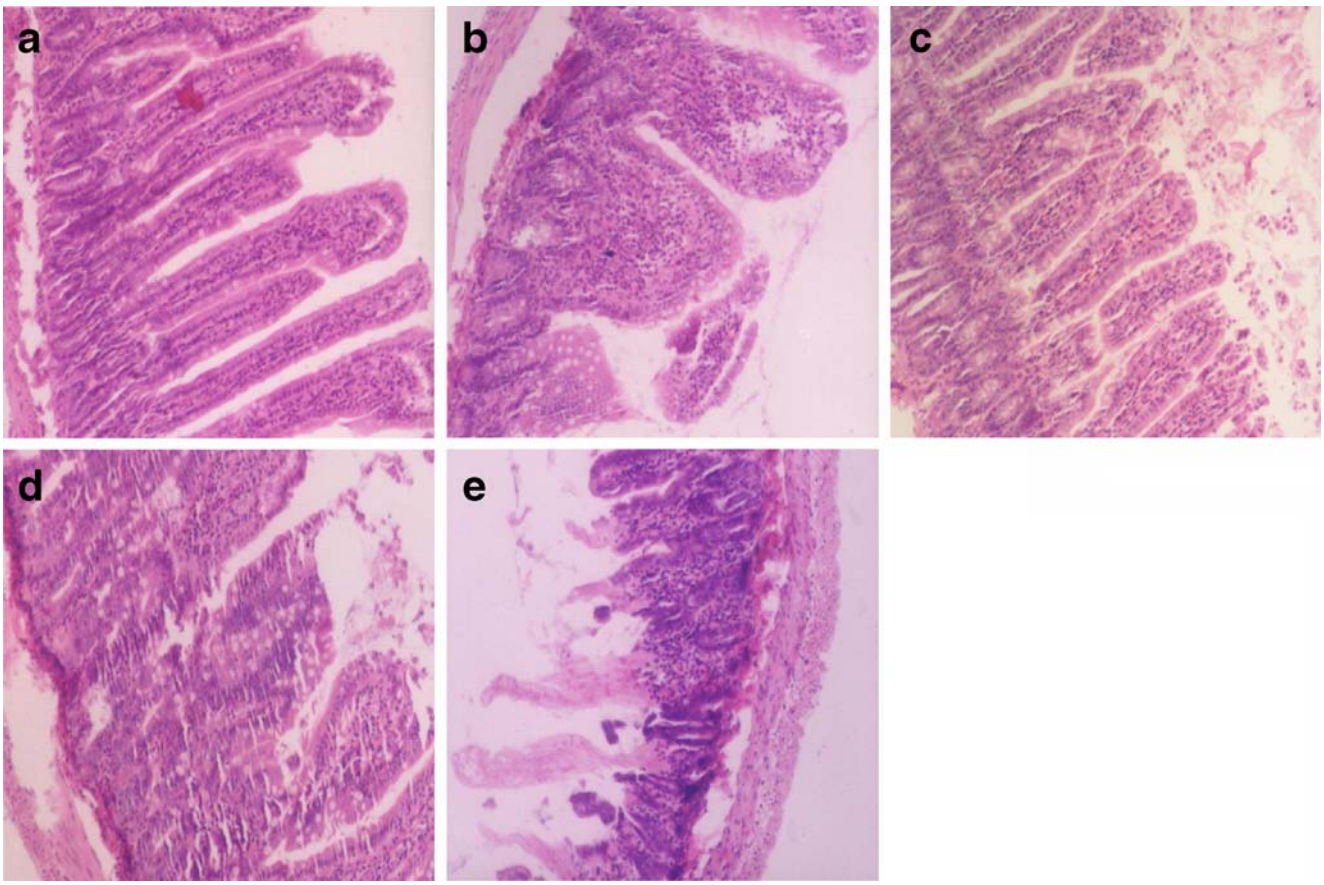

Figure 2 Photomicrographs of hematoxylin-and-eosin-stained sections of the small intestine (×100). **a** Normal histopathology in the Sham group. **b** Disintegration of lamina propria, hemorrhage, and ulceration in I/R group. **c** Normal intestinal mucosal villi and scattered hemorrhage area in NTG group. **d**, **e** Mucosal ulceration and necrosis with invasion of muscularis propria in MB + NTG group and Cap + NTG group. Abbreviations are same as in Fig. 1.

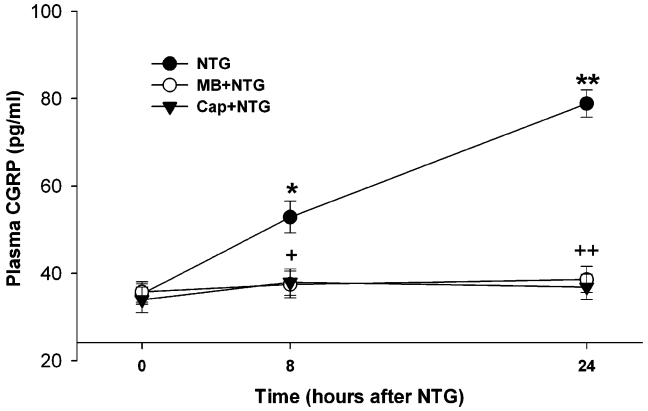

Figure 3 The time course of plasma CGRP level after NTG (0.12 mg/kg, i.v.) alone or with combined use of MB (30 mg/kg, i.p. simultaneously with NTG) or Cap (50 mg/kg, s.c. 72 h before NTG i.v.). Results are expressed as mean ± SEM, $n=5$; *$P<0.05$, **$P<0.01$ vs 0 h (before NTG); $^{+}P<0.05$, $^{++}P<0.01$ vs NTG at corresponding time point.

mRNA were significantly increased by 33.0% and 76.0% at 8 and 24 h after administration of NTG, respectively, as compared with 0 h (control, before NTG). The elevation of α-CGRP mRNA induced by NTG was completely abolished by MB or Cap (Fig. 4). In contrast, NTG had no effect on the level of β-CGRP mRNA at any time point mentioned above (Fig. 5).

Discussion

Growing evidence has suggested that NTG, a NO donor, can induce the acute and delayed preconditioning effect on heart and other organs. Recently, NTG has clinically been demonstrated to exert delayed preconditioning-mimetic effects in human heart.[12,24] Our early works demonstrated that pretreatment with NTG 5–20 min before I/R could produce the acute PCL protection on rat small intestine. In the present study, we have found that pretreatment with NTG 24 h before I/R induced delayed PCL protection on rat small intestine, as shown by the reduction of tissue injury and LDH release during periods of I/R. So, same effects on human intestine may be interestingly expected and called for further clinical investigations.

CGRP, a 37-amino acid peptide, is a principal transmitter in capsaicin-sensitive sensory nerves, and it is widely distributed in cardiovascular tissues.[25] Both experimental and clinical studies have demonstrated that CGRP is an endogenous protective substance and participates in the mediation of IPC and PPC.[26–29] Early studies have reported that NTG significantly evokes the release of CGRP in central and peripheral vessels. Our previous experiments showed that brief ischemia or administration of NTG 5–20 min before I/R prevented the rat small intestine from subsequent sustained I/R by the acute PCL effects. The protections were supposed to be mediated by endogenous CGRP based on elevated CGRP in the effluent and the

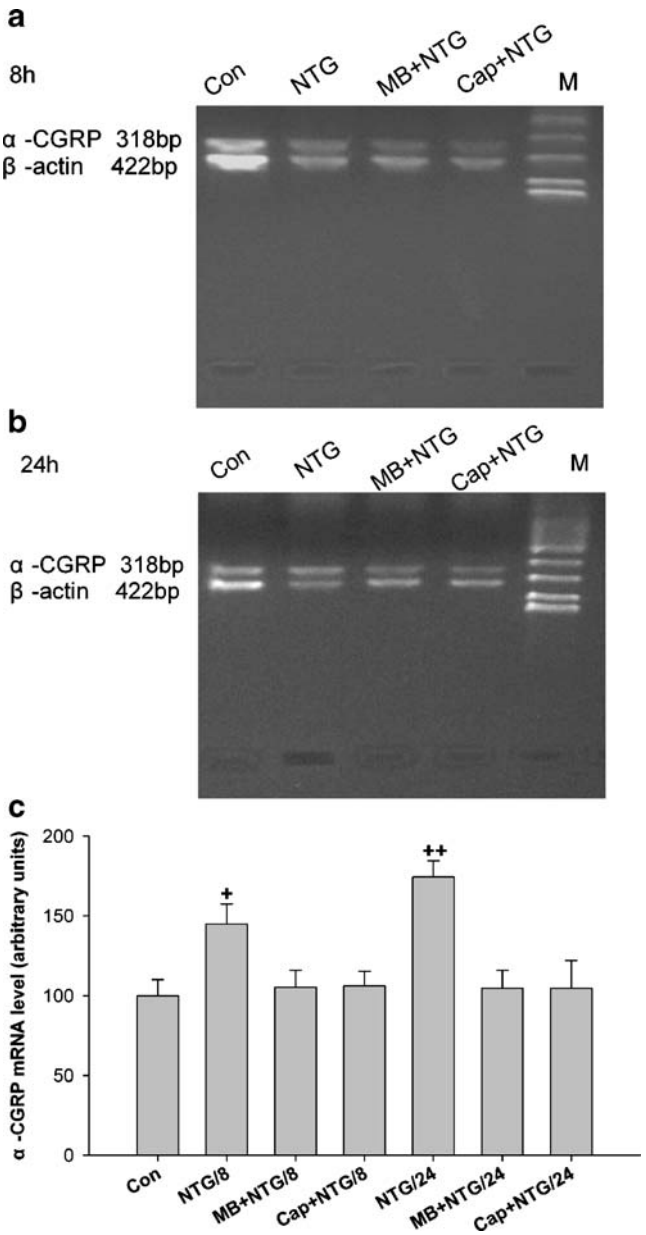

Figure 4 Levels of α-CGRP mRNA in lumbar DRG at 8 and 24 h after NTG (0.12 mg/kg, i.v.) alone or with combined use of MB (30 mg/kg, i.p. simultaneously with NTG) or Cap (50 mg/kg, s.c. 72 h before NTG i.v.). *M* PBR 322 DNA/Msp I marker. **a** and **b** are original results obtained by RT-PCR at the indicated time points after NTG. **c** Results of densitometric scanning ($n=5$) for DNA bands of each group at each time were expressed as α-CGRP/β-actin ratio. $^{+}P<0.05$, $^{++}P<0.01$ vs control (before NTG).

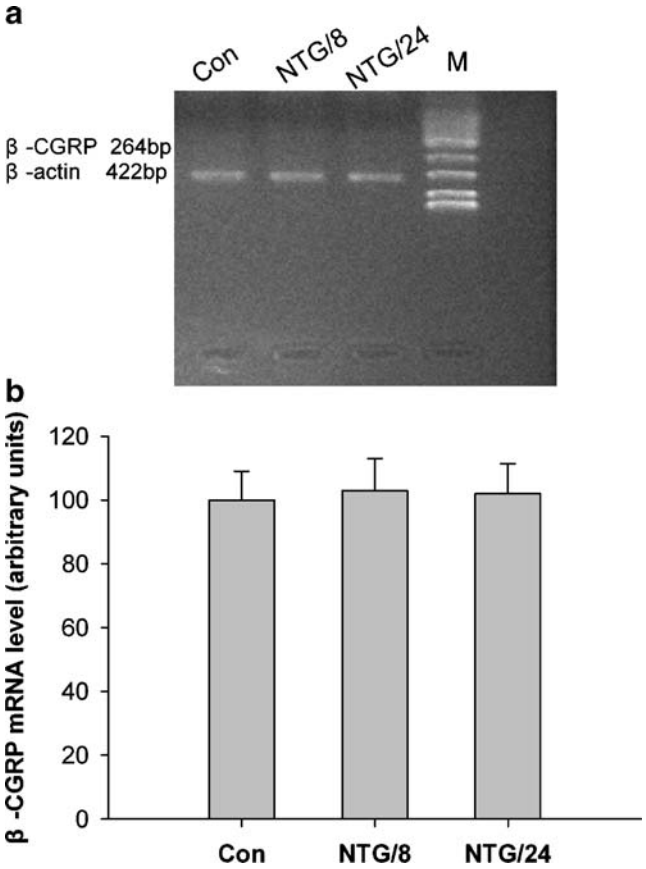

Figure 5 Levels of β-CGRP mRNA in DRG at 0, 8, and 24 h after administration of NTG (0.12 mg/kg, i.v.). *M* PBR 322 DNA/Msp I marker. **a** Original results obtained by RT-PCR at the indicated time points after NTG. **b** Results of densitometric scanning ($n=5$) for DNA bands of each group at each time were expressed as β-CGRP/β-actin ratio. No statistical significance was found among these groups.

plasma.[20] However, in these previous studies, the relations among the protection, NO, and CGRP synthesis were not well clarified. The conclusion that NTG protection is mediated by CGRP needs to be further demonstrated, because as a protein, CGRP synthesis needs time, and 20 min seems to be not long enough to produce enough amount of CGRP.

The present results revealed that in vivo pretreatment with NTG 24 h before I/R caused an increase in blood concentration of CGRP, concomitantly with reduced LDH level and alleviation in small intestine I/R injury. The elevation in CGRP level and the protective effects of NTG, however, were abolished by pretreatment with Cap, which depletes transmitters in sensory nerves. These findings support that NTG produces the delayed PCL protection mediated by endogenous CGRP in rat small intestine.

Mechanisms of the protective effects of delayed preconditioning should involve the production of one or more protective proteins.[30] In the delayed preconditioning offered by NTG in rat small intestine, we hypothesized that the elevated release of CGRP evoked by NTG was secondary to the increased synthesis of CGRP. CGRP has two isoforms (α- and β-CGRP) that are synthesized in the cell bodies of primary sensory neurons and transported axonally mainly to peripheral and also to central nerve terminals, where they are stored in large, dense-cored secretory granules.[25] Although α-CGRP differs from β-CGRP in rat or human in only one or three amino acids,[23,31] they have different biological activity on account of the differences in encoding gene and amino acid residues. Studies indicated that only α-CGRP mRNA has been detected in rat heart and the enteric nervous system of rat small intestine.[32] In contrast, rat T lymphocytes express only β-CGRP mRNA.[33] In the present study, by comparing the changes in the expression of α- and β-CGRP mRNA in DRG, a major site of CGRP synthesis, we found that levels of α-CGRP mRNA in DRG were increased significantly in the rat pretreated with NTG, whereas no changes in the expression of β-CGRP mRNA were observed. The increased expression of α-CGRP mRNA preceded the elevation of CGRP release. The protection of NTG in rat small intestine was completely blocked by pretreated with Cap. These results imply that the delayed preconditioning induced by NTG in rat small intestine is mediated mainly by α-CGRP. It supports the possibility that there are some unknown differences in biological actions between α- and β-CGRP.

Some investigations have showed that the release of CGRP is regulated by NO or NO derived from NTG.[26,34] Many of the biological actions of NO occur via the activation of soluble guanylate cyclase and the resulting increase in cGMP tissue levels. Previous reports had shown that NO participated in delayed cardioprotection via a cGMP-dependent mechanism.[35,36] In the present experiment, MB, an inhibitor of guanylate cyclase, was used to investigate the role of NO-dependent activation of guanylate cyclase in the delayed preconditioning induced by NTG in rat small intestine. The results revealed that in vivo pretreatment with NTG caused not only an increase in blood concentrations of both CGRP and NO but also the CGRP mRNA expression. However, both blood CGRP elevation and α-CGRP mRNA expression upregulation, but not blood NO elevation induced by NTG, were abolished by pretreatment with MB. These findings suggest that NO provided by NTG activates guanylate cyclase results in elevation of intracellular cGMP, and cGMP stimulates α-CGRP synthesis to mediate the protection.

However, the mechanisms whereby NO increment and enhanced CGRP biosynthesis mediate the protections remain far from clarification. The interaction of second messengers and the mechanisms by which NO releases CGRP needs further investigation. Growing evidence suggests that delayed preconditioning associated with

protein kinase C (PKC)-dependent signaling mechanism,[37] especially the activation of PKCε.[38] Du et al. reported that delayed cardioprotection afforded by NTG is mediated by the α-CGRP isoform via generation of NO derived from inducible nitric oxide synthase.[39]

Taken together, the present experiments extended our previous researches by demonstrating the delayed PCL effects of NTG on small intestine, verifying the involvement of CGRP, clarifying participation of α-CGRP, but not β-CGRP, and suggesting involvement of NO–cGMP pathway in the delayed PCL protection of NTG.

Conclusions

In conclusion, the present results demonstrate that NTG prevents rat small intestine from I/R injury by delayed PCL effects 24 h after administration. The protection is mediated by NO–cGMP pathway and α-CGRP upregulation.

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ORIGINAL ARTICLE

Radiofrequency Ablation vs. Resection for Hepatic Colorectal Metastasis: Therapeutically Equivalent?

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Abstract
Introduction The role of ablation for hepatic colorectal metastases (HCM) continues to evolve as ablation technology changes and systemic chemotherapy improves. Our aim was to evaluate the therapeutic efficacy of radiofrequency ablation (RFA) of HCM compared to surgical resection.
Methods A retrospective review of our 1,105 patient prospective hepatic database from August 1995 to July 2007 identified 192 patients with only hepatic resection or only ablation for HCM.
Results Patients who underwent RFA were similar to resection patients based on a similar Fong score (1.8 vs. 2.1 $p=0.28$), presence of extrahepatic disease (15% vs. 9% $p=0.19$), mean number of hepatic lesions (2.8 vs. 2.1 $p=0.14$), and prior chemotherapy (67% vs. 60% $p=0.33$). Median time to recurrence was shorter with ablation than resection (12.2 vs. 31.1 months; $p<0.001$). Recurrence at the ablation–resection site was more common with ablation than resection occurring 17% vs. 2% ($p\leq0.001$) of the time, respectively. Distant recurrence in the liver was also more common with ablation occurring in 33% of patients vs. 14% for resection ($p=0.002$).
Conclusions Surgical resection is associated with a lower chance of recurrence and a longer disease-free interval than RFA and should remain the treatment of choice in resectable HCM.

Keywords Radio frequency ablation · Hepatic resection · Colorectal liver metastasis

Introduction

Hepatic metastasis of colorectal cancer is quite common occurring at some time in 23% of all of the 190,000 colorectal patients diagnosed each year.[1] While systemic chemotherapy can slow growth and even cause regression of hepatic metastases, long-term survival without local therapy is unlikely. Surgical resection of hepatic metastases continues to remain the optimal first-line treatment for hepatic colorectal metastases. Other therapies that have been used are ethanol injection and cryotherapy which have been supplanted by radiofrequency ablation (RFA) and microwave ablation. The role of RFA of hepatic colorectal metastases continues to evolve as the technology evolves and experience with RFA matures.[2] There are many conflicting published series comparing efficacy of RFA and resection with some authors advocating a prospective trial comparing RFA and resection while others maintain that RFA is inferior to resection and patients should not be put at risk to compare the two therapies. The goal of this study was to evaluate the comparative therapeutic efficacy of RFA and surgical resection for hepatic colorectal metastases.

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Methods

A review of a 1,105 patient prospective hepatic–pancreaticobiliary database from August 1995 to July 2007 was done under IRB approval to identify patients who had

either only a resection or only an RFA of hepatic colorectal metastases. All patients included in this study had single lobar involvement. Patients who underwent combination resection and ablation or underwent extrahepatic organ resection and ablation or resection were excluded.

The decision to perform resection or RFA was determined by the treating surgeon at his discretion. In the patients undergoing hepatic resections, anatomic segmental liver resections were performed and classified as described by Couinaud[3]. Nonanatomical resections were performed when judged appropriate by the attending surgeon. For patients with disease that was felt to be unresectable because of the number, distribution, and/or location of the tumors or because of patient comorbid factors, ablation was performed. Standard preoperative evaluation of patients with metastatic colorectal cancer included three-phase computed tomography (CT) of the abdomen and pelvis and chest roentgenogram. Prior systemic chemotherapy of any type and duration was allowed. RFA was performed using intraoperative ultrasound guidance to ensure that at least a 1-cm ablation margin was achieved around the tumors.[4,5]

Postoperative complications and the length of hospital stay were prospectively evaluated. Complications were graded according to a standard five-point grading scale and have been utilized prospectively since June 2002.[4,6] All in-hospital and 90-day postoperative complications were evaluated with the highest severity level recorded. Perioperative complications were defined as complications occurring within 30 days of the operation. RFA patients had one early CT (<1 month from RFA) to ensure RFA success and were then imaged per standard while resection patients were imaged per standard. Standard CT follow-up was utilized every 3 months for the first year and then every 6 months thereafter. Data were censored at the last recorded patient contact if an end point was not reached. Recurrence was also evaluated using serological markers and positron emission tomography scan. A recurrence was the reoccurrence of viable tumor by radiologic CT criteria of a vascular mass. In the event of subsequent hepatic therapy for recurrence of disease, only the first procedure was used for the purposes of this study. Clinicopathologic data along with perioperative complications were recorded. Analysis of data was done using JMP 4.0 and SPSS version 16.0.

A review of all publications in peer review journals in the English Language from 1995 to 2007 was done. Unpublished studies and abstracts presented at national and international meetings were excluded. Trials were identified by conducting a comprehensive of Medline, Embase, Science Citation Index, Current Contents, and PubMed databases, using medical subject headings "colorectal liver metastasis," "radiofrequency ablation," "hepatectomy," "colorectal recurrence," and "comparative study." A manual search of the abstracts was performed to identify for inclusion in this review. Only articles that included a comparative evaluation of hepatectomy to radiofrequency ablation during the same time interval, ablation recurrence, nonablation recurrence, resection margin recurrence, disease-free survival, and overall survival were included.

Table 1 Demographics of RFA and Resection Patients for Hepatic Colorectal Metastasis

Baseline characteristic	RFA, *N*=66	Resect, *N*=126	*p* value
Age (mean)	63.5	61.9	0.35
Male	46 (70%)	69 (55%)	0.52
Months from resection of primary to RFA–resect (mean)	15.5	15.7	0.95
Fong score (mean)	1.8	2.1	0.28
Number of hepatic lesions (mean)	2.8	2.1	0.14
Largest hepatic lesion (mean, cm)	3.2	5.3	<0.001
>1 hepatic lesion	39 (59%)	51 (41%)	0.01
Nodal involvement of primary lesion	33 (50%)	79 (63%)	0.09
Extrahepatic disease at RFA–resect	10 (15%)	11 (9%)	0.19
Previous chemotherapy	44 (67%)	75 (60%)	0.33
Comorbidities			
Cardiac	8 (12%)	22 (17%)	0.32
Pulmonary	7 (11%)	7 (6%)	0.21
Diabetes	11 (17%)	12 (10%)	0.16
Ethanol abuse	2 (3%)	9 (7%)	0.22
Tobacco use	15 (23%)	32 (25%)	0.68
Hepatic disease	2 (3%)	2 (2%)	0.52
Hypertension	23 (35%)	35 (28%)	0.31
No comorbidities	1 (2%)	3 (2%)	0.68

Table 2 Hepatic Lesion Location

Segment	RFA, N=51	Resect, N=110	p value
I	6%	4%	0.53
II	16%	17%	0.80
III	16%	19%	0.60
IV	31%	27%	0.59
V	41%	53%	0.17
VI	45%	55%	0.22
VII	49%	43%	0.46
VIII	33%	34%	0.97
Number of involved segments (mean)	2.4	2.5	0.54

Results

Review of the database identified 308 patients who underwent hepatic resection and/or RFA for metastatic colorectal cancer with curative intent. One hundred and sixteen patients were excluded from this analysis because they had a concomitant resection and RFA at the time of their first hepatic procedure. Sixty-six patients had only hepatic RFA with curative intent while 126 patients underwent only resection with curative intent. Of the patients who had a resection, 106 had an anatomic resection; six had a nonanatomic resection; 12 had a combined anatomic and nonanatomic resection, and two had an unknown type of resection. The most common anatomic resection was a right lobectomy (N=73) followed by extended right hepatectomy (N=18) and left lateral segmentectomy (N=13), left lobectomy (n=10), extended left hepatectomy (n=4), central resection (n=5), caudate resection (n=4), segmentectomy (n=11), and bisegmentectomy (n=5). Patients who underwent RFA were more likely to have a smaller hepatic lesion (3.2 vs. 5.3 cm, p<0.001) and more likely to have more than one hepatic lesion (59% vs. 41%, p=0.01) than patients undergoing resection (Table 1). There was no difference in the location or the number of involved hepatic segments between the two groups (Table 2). All other clinicopathologic characteristics were similar between the two groups (Table 3).

While there was no difference in the percentage of patients experiencing any complication (Table 3), resection patients were more likely to have a major complication (29% vs. 10%, p=0.003). They also had a longer hospital stay (9.8 vs. 6.6 days, p=0.014) and were more likely to receive a blood transfusion during the hospital stay (21% vs. 3%, p<0.001).

The median follow-up for all patients was 20.0 months. Recurrence was more common in patients undergoing RFA compared to resection (71% vs. 46%, p<0.001). The patterns of recurrence were also different in patients who underwent RFA compared to resection. In the RFA group, recurrence was more common at the RFA–resection site (17% vs 2%, p<0.001), in the same lobe as the RFA–resection (42% vs. 3%, p<0.001), and in the liver distant to the RFA–resection (33% vs. 14%, p=0.002). There was no difference in the percentage of patients experiencing extrahepatic recurrence (Table 3). In addition to being more likely to have a recurrence, RFA patients also recurred earlier than resection patients (median 12.2 vs. 31.1 months, p<0.0005; Table 4, Fig. 1). When recurrence was stratified by extrahepatic recurrence, recurrence at the RFA–resection site, or distant hepatic recurrence, the median time to recurrence was always longer in the resection patients than the RFA patients.

Despite the differences in recurrence, there was no difference in survival with 49% of the RFA patients having died at last follow-up vs. 45% of the resection patients (p=0.67). There was a trend towards improved overall survival in the resection patients with an increased median survival (36.4 vs. 27.0 months); however, this was

Table 3 Complications, Recurrence, and Overall Survival in RFA and Resection Patients for Hepatic Colorectal Metastasis

Outcome	RFA, N=66	Resect, N=126	p value
Any complication	39 (59.1%)	68 (54.0%)	0.497
Major complication	5 (10%)	36 (29%)	0.003
Blood transfusion	2 (3%)	26 (21%)	<0.001
Length of hospital stay (mean days)	6.6	9.8	0.014
Chemotherapy after resection–RFA	7 (11%)	18 (14%)	0.47
Had a second RFA–resection	14 (21%)	13 (10%)	0.438
Months to second RFA–resection	10.8	11.8	0.445
Recurrence anywhere	47 (71%)	58 (46%)	<0.001
Recurrence at RFA–resection site	11 (17%)	3 (2%)	<0.001
Recurrence in same lobe as RFA–resection	28 (42%)	4 (3%)	<0.001
Hepatic recurrence distant to RFA–resection site	22 (33%)	17 (14%)	0.002
Extrahepatic recurrence	23 (35%)	42 (33%)	0.83
Median time to recurrence (months), 95% CI	12.2 (5.6-18.9)	31.1 (18.0–44.2)	<0.001
Median survival (months), 95% CI	27.0 (20.3-33.7)	36.4 (27.5–45.2)	0.31

Table 4 Comparison of Time to Recurrence: RFA Versus Resection

Group	Number	Median time to recurrence	95% CI	*p*
Overall RFA vs. resection				
RFA	66	12.2	5.6–18.9	<0.0005
Resect	122	31.1	18.0–44.2	
Patients with an extrahepatic recurrence				
RFA	23	9.8	4.1–15.5	0.577
Resection	42	16.4	9.1–23.8	
Patients without an extrahepatic recurrence				
RFA	43	12.8	4.6–21.1	<0.0005
Resection	84	>115	–	
Patients with a recurrence at RFA–resection site				
RFA	11	12.8	4.8–20.9	0.320
Resection	3	21.9	8.5–35.4	
Patients without a recurrence at RFA–resection site				
RFA	55	11.7	4.5–19.0	0.004
Resection	123	34.7	20.3–49.2	
Patients with a distant hepatic recurrence				
RFA	22	9.6	4.0–15.2	0.462
Resection	17	12.7	4.5–20.9	
Patients without a distant hepatic recurrence				
RFA	44	20.9	9.5–32.3	0.01
Resection	109	38.3	30.2–46.5	

not statistically significant (p=0.31; Fig. 2). When only patients who did not have extrahepatic disease at the time of RFA or resection were analyzed, the median survival was 26.4 months for RFA patients and 38.3 months for resection patients (p=0.13). The trend for increased survival was most evident when only patients who did not recur were analyzed with a median survival of 21.6 vs. 53.8 for patients undergoing RFA vs. resection respectively (p=0.10; Fig. 3). Overall 5-year survival was statistically the same at 21% for the RFA group and 23% for the resection group.

In a review of the peer-reviewed literature that met our inclusion criteria, three articles were identified (Table 5). In comparing the literature to our results, there were similar rates of recurrence for both RFA and non-RFA recurrence. In a summary of all the data reported, resection still has a lower rate of liver recurrence when compared to RFA (Table 5).

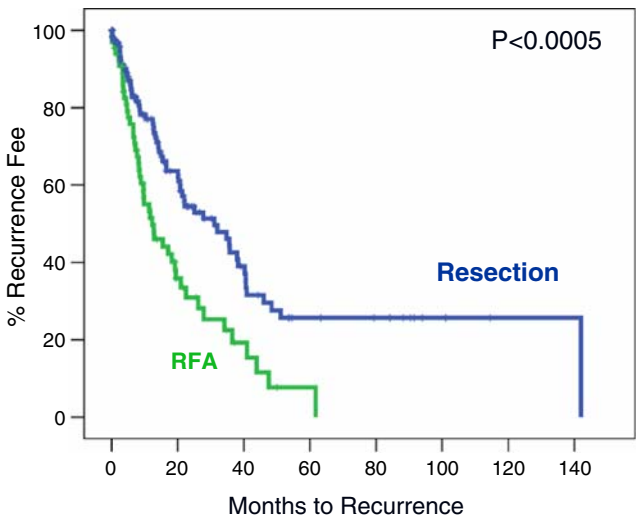

Figure 1 Time to recurrence.

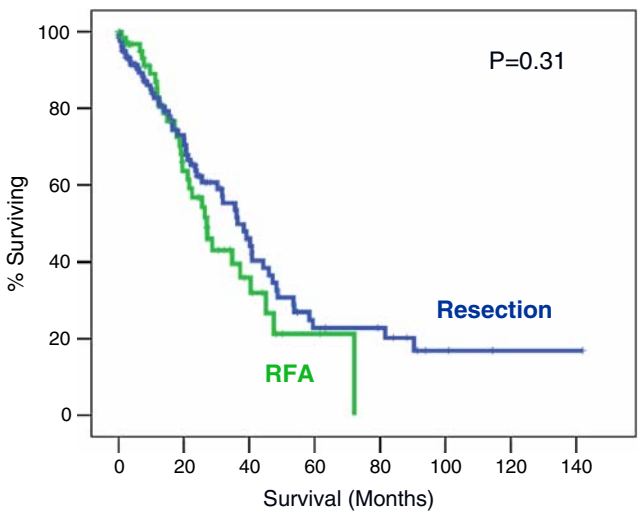

Figure 2 Overall survival.

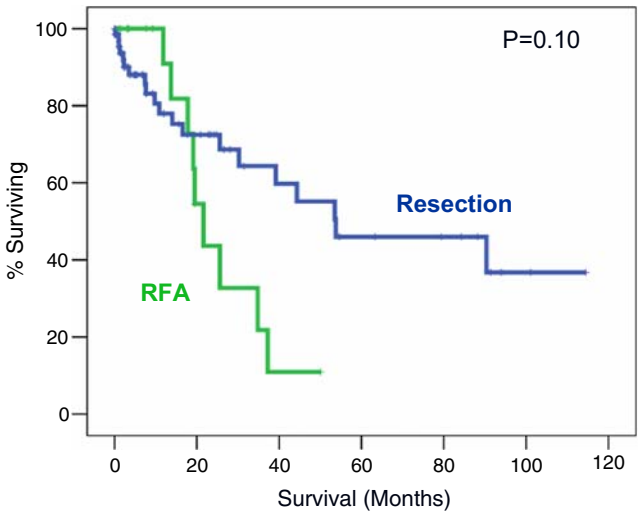

Figure 3 Survival of patients without a recurrence.

Discussion

Resection of colorectal metastases to the liver remains the treatment of choice when possible. Although there was not a difference in overall survival between RFA and resection in our study, there were consistent patterns that favored the resection group. Patients who underwent resection were less likely to recur and had a longer disease-free interval despite having a larger-sized lesion. The similarity of the Kaplan Meier survival curves for the first 60 months made the 9.4-month median survival advantage in the resection group nonsignificant. After 72 months, the curves separate with the RFA curve going to zero while the resection curve levels out and continues to 142 months at 17%. Potentially, with a larger number of patients and longer follow-up, differences in survival may become statistically significant.

It has already been shown that RFA can be safely done for unresectable hepatic tumors.[7,8] While some series have shown RFA to be equivalent to resection, others have found RFA to be inferior to resection based on overall survival.[9–11] All of these series, like ours, are case series comparing RFA for unresectable colorectal hepatic metastasis to resection and thus subject to a selection bias since the groups are not equivalent. The 5-year survival of 21% reported here is comparable to other published 5-year survival rates for unresectable hepatic colorectal metastasis treated with RFA of 14% to 31%.[10,12–14] Our 5-year survival of 21% following resection is also lower than others have reported.[9–11]

Our local recurrence at the RFA site of 17% fits well within the widely varying published rates of 2% to 40%.[7,9–11,14–18] All of our RFAs were done surgically (open or laparoscopic) allowing for accurate probe placement under ultrasound guidance. Our local recurrence rate of 2% following resection is at the low end of reported rates varying from 3.8% to 10.4% and indicates that our resections are adequate.[15,19]

In addition to differences in overall recurrence rates, the differences in the pattern of recurrence were interesting. Invariably, RFA patients were more likely to recur nearer the RFA site. This could be due to incomplete ablation secondary to lesion size, heat sink effect, or the limitations of the modality. Alternatively, the lower local failure rate with resection may be due to removing hepatic parenchyma that is at a higher risk than the rest of the liver for recurrence. Interestingly, RFA patients were also more likely to fail in the liver distant to the RFA site. As

Table 5 Meta-analysis Review of RFA vs Resection in Metastatic Colorectal Cancer

Author	Groups	*N*=(Pt's)	Margin recur	Nonmargin recur
Abdalla	Resection only	190	2 (2%)	78 (41%)
	RFA and resection	101	5 (5%)	37 (37%)
	RFA only	57	5 (9%)	23 (40%)
			p=0.02	p=NS
Aloia	Resection only	150	8 (5%)	27 (18%)
	RFA only	30	11 (37%)	5 (17%)
		p<0.001	p=0.86	
Elias	RFA only	63	11 (17%)	NA
	RFA + Wedge	36	4 (11%)	
	RFA + anatomic	44	4 (9%)	
			p=ns	
Our data	Resection only	126	3 (2%)	18 (14%)
	RFA only	66	11 (17%)	23 (33%)
			p<0.001	p=0.002
Summary	Resection only	466	13 (3%)	123 (26%)
	RFA only	150	38 (25%)	51 (59%)
			p=0.001	p=0.001

expected, local therapy in the liver did not affect the rate of or time to extrahepatic recurrence.

The lack of survival benefit despite a decreased risk of recurrence and increased time to recurrence in the resection group is likely multifactorial. First, when there is a hepatic recurrence in the absence of extrahepatic disease, a second RFA or resection can often be done. Second, the number of options and efficacy of adjuvant chemotherapy has increased dramatically over the recent years. Finally, there is a selection difference between the two groups even though it is not evident when the frequency of comorbidities is examined (Table 3). Our institutional bias has always been to "resect when possible." This has included systematic chemotherapy to downstage patients making them resectable, utilizing preoperative portal vein embolization to increase the size of the liver remnant and combining RFA with resection (these were excluded from this study). Some of the RFA patients would have been refused resection based on comorbidities. Perhaps this is best quantified by the shorter survival of the RFA patients when only patients who did not recur are analyzed. This difference is probably due to a higher severity of the comorbidities in the RFA group compared to the resection group. Unfortunately, there is no good scoring system to measure the overall severity of comorbidities in each group and do a statistical comparison.

In conclusion, RFA was associated with a higher hepatic recurrence rate and shorter time to recurrence but no difference in overall survival compared to resection.

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ORIGINAL ARTICLE

Clinicopathologic Characteristics of Hepatocellular Carcinoma with Bile Duct Invasion

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Abstract To clarify the characteristics of hepatocellular carcinoma (HCC) with bile duct invasion, we retrospectively analyzed clinical features and surgical outcome of HCC with bile duct invasion (b^+ group, n=15) compared to those without bile duct invasion (b^- group, n=256). In the b^+ group, four patients (27%) showed obstructive jaundice, and a diagnosis of bile duct invasion was obtained preoperatively in seven patients (47%). The levels of serum bilirubin and carbohydrate antigen 19–9 were significantly higher in the b^+ group. Macroscopically, confluent multinodular type and infiltrative type were predominant in the b^+ group (P=0.002). Microscopically, capsule infiltration (P=0.040) and intrahepatic metastasis (P=0.013) were predominant in the b^+ group. Portal vein invasion was associated significantly with the b^+ group (P=0.004); however, the frequency of hepatic vein invasion was similar (P=0.096). The median survival after resection was significantly shorter in the b^+ group than in the b^- group (11.4 vs. 56.1 months, P=0.002), and eight of 11 intrahepatic recurrences in the b^+ group occurred within 3 months after surgery. HCC with bile duct invasion has an infiltrative nature and a high risk of intrahepatic recurrence, resulting in poor prognosis.

Keywords Hepatocellular carcinoma · Bile duct invasion · Thrombus · Jaundice · Clinicopathologic characteristics

Introduction

We have reported that vascular invasion, especially portal vein invasion, is often present and recognized as a prognostic factor in patients with hepatocellular carcinoma (HCC).[1] However, bile duct invasion by HCC is rare, and it is not well characterized. Obstructive jaundice is occasionally caused by tumor invasion into the bile duct, and Lin et al.[2] first reported this type of HCC as the "icteric type of HCC" in 1975. Since then, several reports concerning HCC with obstructive jaundice have been published.[3–5] Surgical resection has generally been recommended as a curative treatment for patients with icteric-type HCC; however, the prognosis after surgery is controversial.[4–6] Moreover, most previous papers have described HCC with bile duct thrombus in the major biliary branches, and peripheral small bile duct invasion has not been considered.

We evaluated the clinicopathologic features of HCC with bile duct invasion, including microscopic invasion to the peripheral bile duct.

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Materials and Methods

From 1990 to 2006, 271 patients with HCC underwent hepatic resection at the Department of Surgery 1, Miyazaki

University Hospital, Japan. The medical records of these 271 patients were retrospectively reviewed. Of these 271 cases, macroscopic or microscopic bile duct invasion, including biliary tumor thrombus, was found in 15 cases (5.5%). We compared the characteristics of HCCs with bile duct invasion (b^+ group, n=15 cases) with those without bile duct invasion (b^- group, n=256 cases).

Laboratory data for patients were obtained at the time of admission before surgery. Tumors were evaluated by abdominal ultrasonography (US), computed tomography (CT), hepatic angiography, and magnetic resonance imaging. If necessary, direct cholangiography (percutaneous transhepatic cholangiography or endoscopic retrograde cholangiography) or magnetic resonance cholangiopancreatography (MRCP) was used before surgery to evaluate the extent of biliary invasion. Bile duct invasion by HCC was suspected when peripheral bile duct dilatation or tumor thrombus was detected on US or CT, and bile duct invasion was confirmed by the direct cholangiography or MRCP as obstruction or stenosis of the biliary trees.

Appropriate degree of hepatectomy was selected based on the location and extent of the tumor, liver function, and volume of liver parenchyma to be resected, which was calculated from CT findings.[7] Hepatectomies included partial resection, subsegmentectomy, segmentectomy, lobectomy, and extended lobectomy, and they were performed with the intent to remove the entire tumor. In all cases, intraoperative cholangiography via the cystic duct was performed to address the bile duct thrombus. When the tumor thrombus was extended to the common bile duct or contralateral hepatic duct, it was resected combined with extrahepatic bile duct or by cholangiotomy.

Resected specimens were evaluated macroscopically and microscopically according to the Japanese TNM Staging System from the Liver Cancer Study Group of Japan.[8] Clinicopathologic features of the patients, including degree of liver damage, tumor size, macroscopic classification of tumor, tumor differentiation, vessel invasion, capsule formation, and lymph node metastasis, were compared between the b^+ group and b^- group. Bile duct invasion was classified as b1 (invasion of the third order or more peripheral branches of the bile duct, but not of second order branches), b2 (invasion of the second order branches of the bile duct), b3 (invasion of the first order branches of the bile duct), or b4 (invasion of the common hepatic duct). The tumors without bile duct invasion were categorized as b0. Two pathologists were in agreement regarding the pathologic features of all cases, and we referred the pathological reports retrospectively.

Survival was measured from the time of hepatic resection, and death was the endpoint. Prognosis was examined in February 2007.

Statistical Analysis

Categorical and continuous variables were compared with chi-square test (Fisher's exact probability test) and Mann–Whitney U test, respectively. Survival curves were constructed with the Kaplan–Meier product-limit method and compared by log-rank test. Results are expressed as median (range). Statistical significance was defined as a P value$<$ 0.05. All statistical analyses were performed with JMP 6.03 software (SAS Institute, Cary, NC).

Results

Characteristics of the 15 HCC patients with bile duct invasion are shown in Table 1. The b^+ group comprised 12 men and three women with the median age of 66 years (range, 42–77 years). In the b^+ group, four patients (27%) showed obstructive jaundice. Preoperative diagnosis of the bile duct invasion was obtained in seven of 15 b^+ patients (47%), which comprised four of four patients with b2 and

Table 1 Demographics and Surgical Procedures in 15 HCC Patients with Bile Duct Invasion

Age (years)	66 (42–77)
Sex (M/F)	12/3
Chief complaint	
Icterus	4
Abdominal pain	3
General fatigue	2
Obstructive jaundice	
Positive	4
Negative	11
Bile duct invasion confirmed by preoperative imaging tools	
Positive	7
Negative	8
Resection	
Subsegmentectomy	2
Segmentectomy	4
Segmentectomy+EBR	1
Lobectomy	4
Lobectomy+EBR	2
Extended lobectomy	1
Extended lobectomy+EBR	1
Degree of bile duct invasion	
b1	5
b2	4
b3	6
b4	0

EBR extrahepatic bile duct resection; *b1* invasion of the third order or more peripheral branches of the bile duct, but not of second order branches; *b2* invasion of the second order branches of the bile duct; *b3* invasion of the first order branches of the bile duct; *b4* invasion of the common hepatic duct

three of six patients with b3. All of five b1 invasions and three of six b3 invasions were not diagnosed preoperatively. With respect to the diagnostic modalities, both US and CT demonstrated intrahepatic bile duct dilatation in all seven patients in whom bile duct invasion was diagnosed preoperatively. These patients were further assessed by direct cholangiography (six by endoscopic retrograde cholangiopancreatography and one by percutaneous transhepatic cholangiography), and the bile duct invasion was confirmed in all patients by demonstrating bile duct stenosis. MRCP was performed in three patients and drip-infusion cholangiography CT in two patients, and both modalities also could demonstrate bile duct stenosis when intrahepatic bile duct dilatation was observed. All five patients with b1 and three of six patients with b3 did not show intrahepatic bile duct dilatation by neither US nor CT. In these eight patients, bile duct invasion was not suspected and further work up for biliary assessment was not performed. Various degrees of liver resection with or without extrahepatic bile duct resection were performed as shown in Table 1.

The clinical features of the b^+ and b^- groups were compared as shown in Table 2. There was no difference between the b^+ group and the b^- group for age, sex, degree of liver damage, Child–Pugh classification, or presence of viral hepatitis. Levels of serum total bilirubin (1.4 mg/dl vs. 0.8 mg/dl, $P<0.001$), serum alkaline phosphatase (ALP) (411 vs. 268 IU/l, $P=0.001$), and carbohydrate antigen (CA) 19–9 in serum (36 vs. 15 U/ml, $P=0.002$) were significantly higher in the b^+ group than in the b^- group.

Table 2 Clinical Features of HCC Patients with and Without Bile Duct Invasion

	b^+ group	b^- group	*P* value
Age (years)	66 (42–77)	66 (18–83)	0.591
Sex (M/F)	12/3	192/64	1.000
Hepatitis viral status			0.920
HBV+/HCV+ /both/none	4/7/0/4	74/116/6/57	
Degree of liver damage[b]			0.168
A/B/C	7/8/0	176/77/2	
Child–Pugh classification			1.000
A/B/C	14/1/0	236/20/0	
Total bilirubin (mg/dl)	1.4 (0.4–9.7)	0.8 (0.2–2.2)	<0.001[a]
ALP (IU/l)	411 (212–1,462)	268 (53–1,368)	0.001[a]
Alpha-fetoprotein (ng/ml)	350 (1.5–303799)	47 (0–1,891,556)	0.236
PIVKA-2 (mAU/ml)	192 (0–12,900)	61 (0–443,000)	0.858
CA 19–9 (U/ml)	36 (2–6,564)	15 (0–1,153)	0.002[a]

HBV+, positive for hepatitis B surface antigen; *HCV+* positive for hepatitis C antibody; *ALP* alkaline phosphatase; *PIVKA* protein induced by Vitamin K absence; *CA19–9* carbohydrate antigen 19–9

[a] Statistically significant difference

[b] By the Liver Cancer Study Group of Japan

Table 3 Pathologic Features of HCC Patients with and Without Bile Duct Invasion

	b^+ group	b^- group	*P* value
Tumor size (cm)	5.0 (1.8–17.0)	4.0 (0.8–20.0)	0.087
Grade of differentiation			0.149
Well-differentiated HCC	1	49	
Except for well-differentiated HCC	14	192	
Gross classification			0.002[a]
Simple nodular type	3 (20%)	133 (52%)	
Simple nodular type with extranodular growth	3 (20%)	7 (28%)	
Confluent multinodular type	6 (40%)	30 (12%)	
Infiltrative type	3 (20%)	14 (5%)	
Growth type	0.308		
Expansive growth	7	190	
Infiltrative growth	5	64	
Capsule formation			0.157
Positive/Negative	13/2	172/83	
Capsule infiltration			0.040[a]
Positive/Negative	12/0	143/52	
Septum formation			0.056
Positive/Negative	11/3	161/80	
Serosal invasion			1.000
Positive/Negative	2/13	37/223	
Lymph node metastasis			0.087
Positive/Negative	1/14	4/252	
Invasion of the portal vein			0.004[a]
Positive/Negative	12/2	111/142	
Invasion of the hepatic vein			0.096
Positive/Negative	6/7	60/192	
Intrahepatic metastasis			0.013[a]
Positive/Negative	10/5	68/133	

[a] Statistically significant difference

The pathologic features of HCC patients with or without bile duct invasion are shown in Table 3. Tumor size did not differ significantly between the b^+ group and the b^- group (5.0 cm vs. 4.0 cm, $P=0.087$). With respect to the gross classification, confluent multinodular type (b^+ vs. b^-, 40% vs. 12%, respectively) and infiltrative type (b^+ vs. b^-, 20% vs. 5%, respectively) were predominant in the b^+ group ($P=0.002$). Microscopically, capsule infiltration was observed in all cases in the b^+ group (100% vs. 73% in the b^- group, $P=0.040$). Capsule formation, septum formation, serosal invasion, and lymph node metastasis did not differ significantly between the two groups. Intrahepatic metastasis was observed more frequently in the b^+ group (67% vs. 34%, $P=0.013$). Portal vein invasion was also observed

more frequently in the b^+ group (86% vs. 44%, P=0.004); however, the frequency of hepatic vein invasion was similar between the groups (P=0.096).

Eleven patients in the b^+ group experienced recurrence in the remnant liver, and recurrence occurred within 3 months after surgical resection in eight of these patients. The median survival time after surgery was significantly shorter in the b^+ group than in the b^- group (11.4 vs. 56.1 months, P=0.002, Fig. 1). The 1-, 3-, and 5-year overall survival rates were 46%, 23%, and 0% for the b^+ group and 80%, 63%, and 48% for the b^- group, respectively. The median survival times of patients with b1, b2, and b3 invasion were shorter than that of patients with b0 invasion, although statistical significance was obtained only between b1 and b0 patients (P<0.001, Fig. 2).

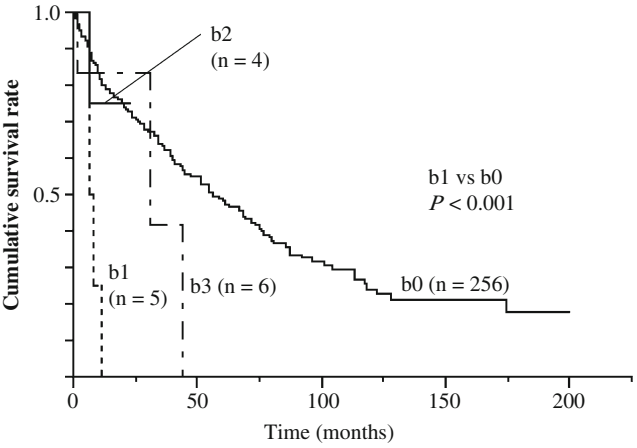

Figure 2 Survival of 15 HCC patients with bile duct invasion classified according the degree of invasion of the bile duct branches.

Discussion

Bile duct thrombosis by HCC is a rare event, and the incidence has been reported as only 0.8% to 12.9% of autopsy and surgical specimens (Table 4).[4–6,9–11] Thrombus involving a major biliary tree can cause obstructive jaundice, and this type of HCC was termed "icteric type of HCC" by Lin et al.[2] in 1975. Since then, a few sporadic reports concerning HCC with bile duct thrombi in a small number of cases have been published.[12–14] Many clinicians believed that patients with icteric-type HCC had a poor prognosis compared with that of HCC patients without bile duct thrombosis. Kojiro et al.[9] reported that the survival time of 24 patients with intraductal tumor growth was statistically shorter than that of controls among 238 autopsy and 21 surgical cases of HCC. Peng et al.[15] suggested that the poor prognosis of HCC with bile duct thrombi is due to low resectability and poor functional reserved associated with underlying liver disease and obstructive jaundice. However, with the development of better diagnostic tools and strategies to treat HCC with obstructive jaundice, successful liver resection with occasional long-term survival has been reported.[16,17] Lau et al.[17] reported that HCC patients with bile duct thrombi who received curative liver resection have better survival than those without resection (median survival, 25.3 vs. 2.1 months, respectively). Thus, the ideal treatment for icteric type of HCC has been recognized to perform aggressive hepatic resection when feasible. Satoh et al.[4] found no significant difference in the survival rate between patients with and without bile duct thrombi after hepatic resection, suggesting that the presence of bile duct thrombi may be less important as a prognostic factor. In contrast, Yeh et al.[5] reported that HCC patients with biliary tumor thrombi after surgery had significantly worse overall survival than those without thrombi (5-year survival, 6.7% vs. 33.0%, respectively). Surgical resection has been considered the preferred treatment for HCC with bile duct invasion; however, there is not yet a consensus regarding prognosis of between HCC with and without bile duct invasion. In our series, the median survival time of the b^+ group was 11.4 months, which was significantly worse than that of the b^- group. Our result was similar to that reported by Yeh et al.[5] In the present study, we found that the b^+ group included more confluent multinodular- and infiltrative-type HCC than the b^- group. HCCs in the b^+ group showed more capsule infiltration and portal vein invasion, although tumor size was similar to that of the b^- group. Intrahepatic metastasis was more frequently observed in the b^+ group. These findings suggest that HCC with bile duct invasion has specific particular infiltrative nature compared to that without bile duct invasion. The characteristic may be one reason that the prognosis for patients with this type of HCC was poorer despite curative resection.

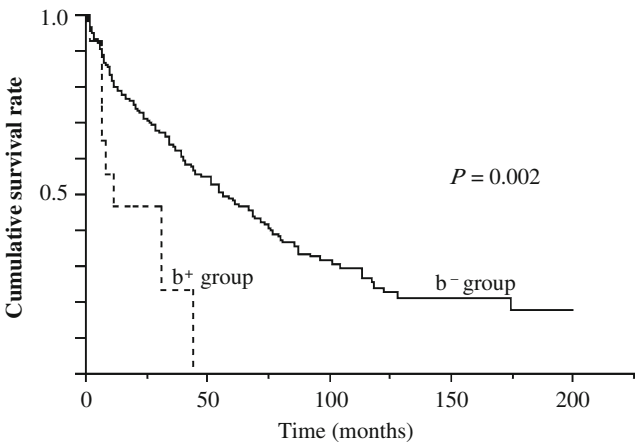

Figure 1 Survival of 15 HCC patients with bile duct invasion (b^+ group) vs. 271 HCC patients without bile duct invasion (b^- group).

Table 4 Previous Reports of HCC with Bile Duct Thrombus

Author	Year	Number of HCC patients with bile duct thrombus (frequency)	Case background	Outcome (overall survival)
Kojiro et al.[9]	1982	24 (9.3%)	Autopsy and surgical cases	Worse than HCC patients without bile duct thrombus
Lau et al.[6]	1997	49 (1.9%)	Surgical and non-surgical cases	Similar to HCC patients without clinical jaundice
Satoh et al.[4]	2000	17 (2.5%)	Surgical cases	Similar to HCC patients without bile duct thrombus
Shiomi et al.[10]	2001	17 (12.9%)	Surgical cases	Similar to HCC patients without bile duct thrombus
Yeh et al.[5]	2004	17 (3.0%)	Surgical cases	Worse than HCC patients without bile duct thrombus
Qin et al.[11]	2004	34 (0.8%)	Surgical cases	–
Our series		15 (5.5%)	Surgical cases	Worse than HCC patients without bile duct thrombus

HCC hepatocellular carcinoma

Most previous studies[4,10,11,15] have considered tumor invasion only to large bile ducts, such as the common bile duct up to the first branches of the hepatic duct, and peripheral bile duct invasion has not been well studied. In the present study, we evaluated HCC with bile duct invasion, including peripheral microscopic biliary invasion categorized as b1 and found that the prognosis of patients with b1 bile duct invasion was similar to that of patients with b2 and b3 bile duct invasion. We should note that even peripheral bile duct invasion has negative impact on the prognosis of HCC patients. In the Japanese TNM staging system,[8] bile duct invasion is considered when assigning stage. The presence of bile duct invasion increases the T classification by one grade. This differs from the TNM staging system of the American Joint Committee on Cancer/International Union Against Cancer,[18] which does not consider bile duct invasion when assigning stage. Recently, Minagawa et al.[19] reported that in Japanese patients, the prognostic stratification ability of the Japanese staging system is superior to that of the AJCC/UICC staging system. These findings and our present findings suggest that attention should be paid not only to biliary thrombus in the large branches but also to the small bile duct invasion.

Detecting bile duct invasion by HCC is still difficult despite recent improvements in imaging techniques. Qin et al.[11] reported that 18 (53%) of 34 HCC patients with bile duct thrombosis were suspected preoperatively to have bile duct obstruction. In our series, seven cases (47%) in the b^+ group showed peripheral bile duct dilatation on CT or US, and subsequent direct cholangiography confirmed the stenosis or obstruction of the biliary trees in all seven cases. All of these seven cases were b2 or b3, and none of the b1 cases were suspected preoperatively to have bile duct invasion. We believe that it would be difficult to detect peripheral bile duct invasion, and preoperative diagnosis of bile duct invasion by HCC is limited to grades b2–b4. In the present study, HCC patients with bile duct invasion were characterized by high levels of serum total bilirubin, ALP, and CA 19–9. Infiltrative findings on CT together with the serum laboratory test may raise the possibility of bile duct invasion. A deeper understanding of this type of disease is the key to improving further the preoperative diagnosis.

Qin et al.[11] reported that 50% of patients with bile duct thrombosis experienced intrahepatic recurrence within 1 year after curative surgery. In the present study, eight patients (53%) in the b^+ group suffered recurrences in the remnant liver within 3 months after surgery. In general, intrahepatic recurrence has been thought to be from the tumor migration through the portal vein. In our study, most of the tumors in the b^+ group had also portal vein invasion microscopically, and the recurrence of the b^+ group may be due to the tumor migration via the portal vein. However, all two cases without portal vein invasion in the b^+ group suffered multiple recurrences in the remnant liver. It indicates that the tumor migration of HCC via the bile duct may be one of the causes of the intrahepatic metastasis. We must notify that HCC with bile duct invasion has a high risk of early recurrence, causing poor prognosis. There is a report that surgical resection combined with chemotherapy is beneficial for advanced HCC with tumor thrombus. [20] Therefore, adjuvant chemotherapy for HCC with bile duct invasion may control postoperative recurrence and improve the prognosis of patients with this type of HCC. However, there is still no confirmatory evidence that adjuvant chemotherapy is effective for advanced HCC, including that with portal vein invasion, which is the strongest prognostic factor for HCC.[21] Peng et al.[15] reported that repeated liver resection yielded a good outcome for local

recurrence in patients with HCC with biliary tumor thrombus. Frequent follow-up evaluation should be planned for HCC patients with bile duct invasion to promote earlier detection of recurrence.

Although the further study with a larger number of patients is necessary to draw the final conclusion, our series demonstrated that HCC with bile duct invasion has unique characteristics compared to those of HCC without bile duct invasion. HCC with bile duct invasion has an infiltrative nature, resulting in poor prognosis even after curative resection. We should pay attention to peripheral bile duct invasion because it is an indicator of poor prognosis.

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ORIGINAL ARTICLE

One Thousand Laparoscopic Cholecystectomies in a Single Surgical Unit Using the "Critical View of Safety" Technique

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Abstract
Introduction Bile duct injuries have been substantially increased after the introduction of laparoscopic cholecystectomy (LC). They are accompanied by major morbidity, occasional mortality, lengthening of hospital stay, additional health costs, and deterioration of patients' quality of life and life expectancy. The aim of this study was to present the method of "critical view of safety" (CVS) as safe and feasible for the prevention of bile duct injuries during laparoscopic cholecystectomy.
Patients and Methods During a 6-year period from January 2002 till December 2007, 1,046 LCs (369 men and 677 women) were performed mainly for symptomatic gallstone disease. The CVS technique recommends clearing the triangle of Calot of fat and fibrous tissue and taking the gallbladder off the lowest part of its attachment to the gallbladder bed. The "infundibular" technique (identification of cystic duct and gallbladder junction) was used whenever CVS was not possible to perform.
Results The CVS was performed in 998 patients (95.4%). Overall, 27 patients needed conversion to the open approach (2.6%). This rate was higher in patients with acute inflammation undergoing early operation (nine of 128, 7%) compared with patients operated later or electively (18 of 914, 1.9%). There was no bile duct injury in the 1,046 cholecystectomies. Postoperatively, five patients had bile leaks which were transient and stopped spontaneously after 2–14 days. Two reoperations were performed because of severe bleeding.
Conclusion CVS clarifies the relations of the anatomic structures that should be divided, and therefore, it should be ideally and routinely applied in all LCs because of its highly protective role against bile duct injuries.

Keywords Laparoscopic cholecystectomy · Critical view of safety · Bile duct injury · Infundibular technique

Introduction

Following the introduction and rapid spread of laparoscopic cholecystectomy, there was a large increase in major bile duct injuries.[1,2] Considerable improvements in the equipment and the technique itself, as well as training of residents in the laparoscopic technique, resulted in the progressive decrease of this incidence today. Nevertheless, it continues to be two to three times more common compared to published major bile duct injury rates for open cholecystectomy,[3,4] which indicates that this is still an incompletely resolved problem. Bile duct injuries are accompanied by major morbidity and occasional mortality,[5–7] lengthening of hospital stay,[8] large additional health care costs,[9] substantial deterioration of patient's quality of life[10] and life expectancy,[11] and quite frequently, litigation.[9] Extensive medical publications have already dealt with many aspects of this problem. Improved understanding of the major responsible mechanisms for bile duct injuries during laparoscopic cholecystectomy has led experts to propose and describe several surgical tricks and techniques

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to prevent such catastrophes. The "critical view of safety" technique first described in 1995 by Strasberg et al. from Washington University in St Louis[2] is an easily applied and anatomically based approach to ductal identification which has been employed routinely by all surgeons in our Department since 2000. The aim of this study was to present our results with the use of this method in order to demonstrate the effectiveness of this technique in precluding bile duct injuries in clinical practice.

Methods

In the 6-year period from January 2002 to December 2007, 1,046 laparoscopic cholecystectomies were performed by five junior and senior consultant surgeons at the 1st Surgical Dept of Konstantopoulio Hospital. Results were stored prospectively in a database. Our intention was to apply the "critical view" technique (for the thorough dissection of Calot's triangle and cystic duct and artery identification) in all patients, even in straightforward cases. This technique recommends clearing the triangle of Calot of fat and fibrous tissue and taking the gallbladder off the lowest part of its attachment to the gallbladder bed (cystic plate). Only two structures will be connected to the lower end of the gallbladder once this is done. Raising the gallbladder off the lower part of the cystic plate is an important step. No attempt is made to expose the common bile duct or common hepatic duct. A picture of the critical view is shown in Fig. 1. This view provides a convincing demonstration that the two structures entering the gallbladder are the cystic duct and artery. The "infundibular" technique (identification of cystic duct and gallbladder junction) was used whenever "critical view" technique was not possible for any reason and in case the procedure was not converted to open. The recognition of the cystic and common bile duct junction or intraoperative cholangiography was used for ductal identification in only few cases. Special attention was always paid to avoid contact of the electrocautery with any metallic clip close to the hepatic hilum and to reduce power to less than 35 W during Calot's triangle dissection in order to avoid any undesirable thermal biliary disaster. One hundred and twenty-eight patients presenting with acute cholecystitis were operated within 2 days of admission, whereas others with that diagnosis had delayed surgical treatment 30 to 40 days later after the acute inflammation had subsided. Patients in whom there was a strong suspicion of choledocholithiasis were initially treated with an endoscopic retrograde cholangiopancreatography followed by cholecystectomy usually within 48 h. On the contrary, when there was a lesser suspicion of bile duct stones, preoperative magnetic resonance cholangiopancreatography or intraoperative cholangiography was performed. The use of a drain was elective, and when used, it was left in place for 24 h unless there was evidence or suspicion of hemorrhage or bile leakage. We performed a detailed review of the medical and operative records of all these patients and collected data regarding the indications for operation, the preoperative ultrasound (U/S) findings as well as the intraoperative findings, the rate of intraoperative cholangiography, the incidence of gallbladder rupture during the operation, evidence or report of biliary injury during the operation, incidence of intraoperative severe hemorrhage, and the overall conversion rate to open cholecyctectomy. In patients where the "critical view" technique was not feasible, the reason for that and the alternative method used for anatomy identification were also recorded.

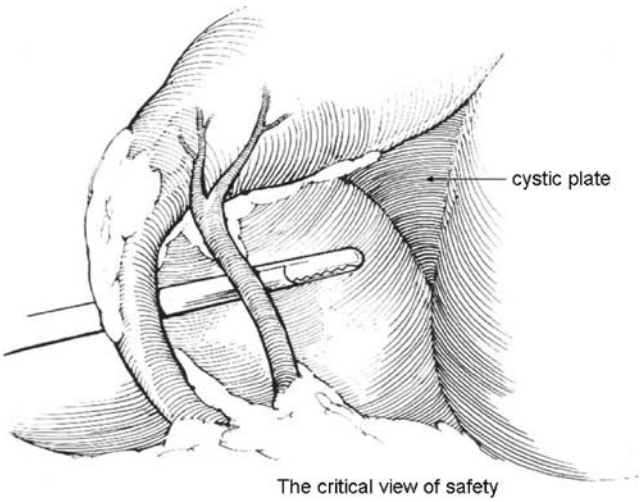

Figure 1 The "critical view of safety" technique—Calot's triangle is dissected free of all tissue except for the cystic duct and artery, and the base of the liver bed is exposed. When this view is achieved, the two structures entering the gallbladder can only be the cystic duct and artery. (figure used after permission from the Executive Editor of the *Journal of the American College of Surgeons*).

Results

Of 1,046 consecutive patients who underwent laparoscopic cholecystectomy from 1st of January 2002 to 31st of December 2007, 369 were men and 677 women. Mean patient age was 67.4 years (65.8 for men and 68.3 for women). The main surgical indication for cholecystectomy was symptomatic gallstones disease. All indications are listed in detail in Table 1.

In the group of patients with inflammatory conditions secondary to gallstones (acute cholecystitis, empyema, hydrops, pancreatitis), 128 patients (35.1%) were operated on during an acute gallbladder inflammation, while all the

Table 1 Surgical Indications for Laparoscopic Cholecystectomy

Indication	Number of patients	Percent
Biliary colic	326	31.1
Inspecific dispeptic disorders	191	18.3
Cholecystitis	157	15.0
Incidental gallstones in U/S	119	11.4
Pancreatitis	102	9.7
Hydrops	72	6.9
Jaundice	45	4.3
Empyema	34	3.2
Total	1,046	99.9

other 237 (64.9%) had a delayed surgical treatment. The remaining 681 patients had clinically significant gallstone-related inflammatory condition. In 302 patients, no surgical drain was needed, while in 744 patients, at least one vacuum or penrose drain was placed at the site of the gallbladder bed. A second drain was placed at the right subphrenic area in 27 patients. In total, 27 patients needed conversion from laparoscopic to open procedure accounting for an overall 2.6% conversion rate. As expected, this rate was more than three times higher in cases with acute inflammation having early operation (nine out of 128, 7%) compared to patients having a delayed or an elective surgical treatment (18 out of 914, 1.9%). The reason for conversion and the conversion rates are shown in Tables 2 and 3.

In 998 patients (95.4%), the "critical view" technique was successfully applied, but three of them had to be converted to open, two because of profound bleeding and one because of confusing anatomy. Twenty-two patients had their operation converted to open cholecystectomy very early, before any identification technique of the cystic and common bile ducts could be performed mainly because of firm adhesions, severe inflammation, or profound hemorrhage (Table 2). In those cases, after inspection of preliminary dissection, it was decided that

Table 2 Causes for Convention to Open Cholecystectomy

Etiology	Number of patients	Percent
Hemorrhage in surgical field	9	33.3
Firm adhesions	8	29.6
Unfamiliar anatomy	4	14.8
Adhesions from previous operations	3	11.1
Severe tissues inflammation	2	7.4
Visceral trauma	1	3.7
Total	27	100

Table 3 Conversion Rates

Patient groups	Patients	Patients converted	Percent
Acute inflammation–early operation	128	9	7.0
Scheduled or delayed operations	914	18	1.9
Total	1,046	27	2.6

laparoscopic cholecystectomy could not be performed safely. In 19 patients, the "infundibular" technique was applied, and four more had their laparoscopic cholecystectomy performed after cystic and common bile duct junction identification. In only three patients, a diagnostic perioperative cholangiography was needed. Two out of these three patients had a conversion, both because of doubtful anatomy. Perioperative cholangiography was performed in an additional 31 patients for possible common bile duct stones identification and not for anatomic safety reasons.

There was no bile duct injury in the 1,046 cholecystectomies. Bile leaks from gallbladder bed or from the cystic duct were recorded in five patients and were transient, and all stopped spontaneously after 2–14 days. They should be better classified as surgical complications rather than true bile duct injuries. All bile leaks occurring in patients with drains stopped spontaneously without any other interventions. Two re-operations were performed in two patients for severe hemorrhage, one from a trocar site and one from the gallbladder bed. No major vascular injury was reported in all patients. Finally, the gallbladder was ruptured intraoperatively in 188 of 914 patients, and in 29 of these, there was stone spillage in the peritoneal cavity. For the rest of the 132 patients, there is no such relevant information reported. More than half of all the operations (555) have been performed by young surgical registrars but always under the "hands-on" supervision of a consultant.

Discussion

Several surgical techniques reported in the literature[12–14] have attempted to describe a reliable technique for ductal identification during laparoscopic cholecystectomy. This relatively new surgical challenge emerged after the significant increase in bile duct injury rates that have been perceived soon after the rapid and worldwide expansion of the laparoscopic technique. The "infundibular" technique[13] which is the intraoperative recognition of cystic duct and gallbladder junction, the "critical view" technique that has been described earlier in this paper, the recognition of cystic and common bile duct junction, and last, the routine

use of intraoperative cholangiography are the four main techniques that, at least theoretically, intend to minimize the risk of such injuries. The aim of all these techniques is to establish an undisputable surgical method that could clearly distinguish the anatomical structures of that area in an objective way, unbiased by subjective delusions.

It is not only the number of these complications that has been changed in the laparoscopic era, but the pattern of bile duct damages has unfortunately been altered as well. The new technology has changed the mechanism of these injuries, and as a result, severe and complicated bile duct injuries like complete bile duct transection, thermal injuries, or central injuries towards the hepatic hilum occur more frequently in 31% of all injury cases compared to 12% before laparoscopy.[15] In addition, almost in one fourth of bile injury cases that happen during laparoscopic cholecystectomy, hepatic vascular injury coexists that further complicates final treatment.[16,17]

Three large population-based studies[18–20] have already dealt with the potential protective effectiveness of the intraoperative cholangiography from bile duct injuries. Although the role of cholangiography in the early recognition of a bile duct injury is strongly documented, the results of these restricted statistical significance studies are partially confusing in respect with the desirable prevention from these injuries. Additionally, this technique, which requires special technologic support on a 24-h basis, is technically more demanding than a simple cholecystectomy and increases the total cost and duration of the operation.[2] Its sensitivity in identifying a right accessory bile duct (a common anatomic variation) is low, and last but not least, a small hole in what the surgeon believes to be the cystic duct is needed for its accomplishment. A wrong initial subjective anatomic assessment would already have result in a bile injury.

As far as we know, there is no published data on the true value of the "critical view" technique in avoiding injuries of the bile ducts in clinical practice. The technique is known and well described since 1995 by Strasberg et al.[2] and has been rapidly adopted by many surgeons including all consultants in our Surgical Department in "Konstantopoulio" Hospital in Athens, Greece. We found the technique surgically correct and logical, easy to perform, and possible to be applied in the great majority of patients, even in those with acute biliary inflammation, with no aggravation in surgical time and cost. We perform all laparoscopic cholecystectomies by adjusting the "critical view" step even in the very easy cases. Our results are excellent not only because of the reported zero complications regarding the bile duct injuries but also because of the firm confidence this technique offers to the surgeons that such an injury has definitely been avoided. In clinical practice, less than 5% (48 patients) of all our patients were not reported to have "critical view" technique. Actually, only 26 patients (2.5%) had other techniques for anatomical structures visualization as the 22 remaining were very soon converted to open surgery after the laparoscopic camera insertion and before any technique could be tried.

During the same 6-year period in our department, we have also performed 132 open cholecystectomies. The main reasons for choosing the open procedure were severe cholecystitis, complicated cholecystitis (gangrenous, emphysematous, empyema), preoperative suspicion for gallbladder malignancy, previous upper abdominal surgery, or the presence or severe comorbidity that prohibited the use of general anesthesia. Again, no bile duct injury has happened in this open cholecystectomy group.

During the first 5 years after the first laparoscopic cholecystectomies, unbelievable bile injury rates up to 4% have been reported.[1,2] Hopefully today, this rate is much lower and ranges between 0.3% and 0.8% but remains two to three times up the injury rates reported for open cholecystectomy.[21] Considerable improvements in laparoscopic apparatus, better surgical training, advanced laparoscopic performance of almost all abdominal operations, and experience gained over the years are mostly responsible for this gratifying evolution. In total, due to the vast number of laparoscopic cholecystectomies performed annually all over the world, the absolute number of bile duct injuries is quite high, making this a significant problem for patients, surgeons, and health systems.[6,22,23] Still, there is enough room for improvement on that field, and efforts should be focused on the pre- and perioperative prevention of these injuries by any possible mean. Simple and formulizing surgical techniques like the "critical view" one can be proved to be of substantial importance in order to avoid such injuries, especially the ones that happen because of surgeons' technical errors.

Three main risk factors have been identified to increase the bile injury probability during a laparoscopic cholecystectomy.[12]. The surgeon's experience, the difficult inflammatory local conditions, and the not-so-rare biliary tree anatomical variations all play a distinct role whenever such a sad event occurs. Bile duct injuries take place three times more often in patients with tough local conditions due to active acute cholecystitis compared to subjects without inflammation.[24,25] The way surgical experience affects causatively an injury is not very clear. Despite the fact that few studies showed a definite decline of the injury rate after the first 50 cases of a surgeon, other studies concluded that only 30% of all injury cases happened within the 60 first cases of every participating surgeon.[26,27] It is important for

all surgeons to possess a realistic self appreciation of their limits, not only to be able to perform and complete a cholecystectomy laparoscopically but also to be able to realize when an operation needs to be converted. Once an injury takes place, though, it is strongly suggested that it should be managed by an experienced hepatobiliary surgical team.[28] Early injury diagnosis and treatment affects positively the final outcome. Data from North America and Europe show that over half of these cases are unfortunately managed by the injuring surgeon and that these cases acquire an increased long-term mortality risk which is 11% for the first 9 years from injury.[4,29,30]

In conclusion, the strict application of the "critical view" technique simplifies the correct identification of the anatomic structures that should be divided and should be ideally used in all laparoscopic cholecystectomies. Our single surgical department experience has shown, in addition, that the technique has a highly protective role against bile duct injuries during laparoscopic cholecystectomies.

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ORIGINAL ARTICLE

Does CT Influence the Decision to Perform Colectomy in Patients with Severe Ulcerative Colitis?

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Abstract
Purpose The purpose of this study was to evaluate the impact of abdominal computerized tomography (CT) on the decision to perform colectomy in patients with severe acute ulcerative colitis (SAC).
Methods Patients with SAC admitted to a single hospital between 2002 and 2007 were reviewed. The criteria for SAC were ≥6 bloody bowel movements per day plus fever >37.8°C, pulse >90, or hemoglobin <10.5 g/dL. Study patients were given a SAC score of 2–4 based on these criteria. Clinical and laboratory parameters, medication use, abdominal X-ray, and endoscopic findings in SAC patients who did or did not have an abdominal CT were compared. Chi-squared, Fisher exact test, and Wilcoxon rank sum test were used as appropriate.
Results Ninety-two consecutive patients with SAC were evaluated. CT was performed in 26 (28%). The SAC score, laboratory values, abdominal X-ray, and endoscopic findings were similar in patients who did or did not have a CT. Colectomy was performed in 32 (48%) and 10 (38%) patients who did or did not have a CT, respectively ($p=0.4$). The CT findings were similar in patients who required colectomy and those who did not require colectomy. In two (8%) of the patients who underwent CT, the CT findings clearly influenced the decision to perform or defer colectomy.
Conclusion CT has a minor impact on the decision to perform colectomy in patients with severe acute ulcerative colitis.

Keywords Ulcerative colitis · CT · Colectomy

Introduction

Severe acute or "toxic" ulcerative colitis (SAC) is characterized by frequent blood bowel motions, fever, tachycardia, and anemia.[1] Treatment decisions in SAC are based on clinical assessment of the patient, laboratory tests, endoscopic studies, and plain abdominal X-ray (AXR).[2,3] Intravenous steroids and supportive care are the cornerstones of SAC treatment.[4–6] When there is an inadequate response to steroid therapy, cyclosporine or infliximab may be used to induce disease remission and may prevent the need for urgent colectomy.[7–12] Failure of medical therapy in SAC is characterized by continued frequent bloody bowel movements, clinical stagnation, or clinical deterioration. Travis et al. demonstrated that on day 3 of medical therapy for SAC, 85% of patients with eight or more daily bowel movements or three to eight bowel movements per day together with a C-reactive protein >45 mg/l would require same admission colectomy. In Travis's study and similar studies of moderate to severe ulcerative colitis, both the determination of disease severity and the therapeutic decisions were based on clinical parameters, laboratory values, and in some cases, endoscopic findings.[1,7–17] While abdominal computerized tomography (CT) has proven useful in the management of Crohn's disease, diverticulitis, and appendicitis, its utility in SAC has not been established.[18–21] The purpose of this study was to evaluate the impact of abdominal CT on the decision to perform same admission colectomy in patients with SAC.

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Methods

We performed a retrospective study of consecutive patients with a diagnosis of SAC admitted to the Cleveland Clinic between 2002 and 2007. Severe acute ulcerative colitis was defined as ulcerative colitis with six or more bloody bowel movements per day and one or more of the following parameters: fever >37.8°C, heart rate >90 beats per minute, or hemoglobin <10.5 g/dL.[1,4] The index admission for SAC was defined as the initial inpatient admission for the diagnosis and treatment of SAC. To the best of our ability, patients with Crohn's, ischemic, and infectious colitis were excluded from the analysis. Patients were given a SAC score (2–4) based on the number of SAC parameters present at the time of SAC diagnosis (one point for each parameter). By definition, all study patients had a SAC score of 2, 3, or 4. The medical records of each study patient were used to obtain clinical, laboratory, radiological, endoscopic, and surgical data. Megacolon was defined as transverse colon diameter greater than 6 cm or cecal diameter greater than 9 cm on AXR. In patients who underwent sigmoidoscopy or colonoscopy, the endoscopic findings were reported using the modified Baron score: 0 = normal (normal mucosa), 1 = mild (erythema, decreased vascular pattern), 2 = moderate (marked erythema, loss of vascular pattern, mucosal friability), and 3 = severe (spontaneous bleeding, ulceration).[22]

The standard but nonprotocol treatment for SAC at our hospital, during the study period, was intravenous fluid resuscitation, stool *Clostridium difficile* testing, daily AXR, intravenous hydrocortisone 100 mg every 8 h or solumedrol 20 mg every 8 h, liquid diet, serial examinations, sigmoidoscopy, and cooperative management of the patient by a gastroenterologist and colorectal surgeon. Infliximab or colectomy was considered in patients who did not completely respond to this regimen. Cyclosporine was not used in any of the study patients. There were no defined study criteria to guide the recommendation for colectomy. In all patients who underwent index admission colectomy, a subtotal colectomy with ileostomy and subcuticular implantation of the distal sigmoid colon stump was performed. Patients who responded adequately to medical therapy were transitioned to oral steroids and were discharged at the discretion of their physicians.

Abdominal CT performed at anytime during the SAC index admission were included and each was re-read by a study radiologist (M.B.). The following CT features of the colon were evaluated at the time of the re-read: colitis extent (pan-colitis, left-side colitis, proctosgmoiditis), maximum colon diameter and colon wall thickness, colon wall enhancement pattern, the presence of "comb" sign (engorgement of the vasa recta), and haustral fold appearance.

The primary aim of our study was to determine the impact of CT on the decision to perform same admission colectomy in patients with SAC. Secondary aims were to compare the CT findings in patients who required colectomy to those who did not require colectomy and to compare AXR and CT findings in patients who underwent both of these radiological studies. The Cleveland Clinic Institutional Review Board approved the study.

Statistical Analysis

Categorical data were summarized by frequencies and percentages, and quantitative data were summarized by medians and range. Fisher's exact, chi-square, or Wilcoxon rank sum test was used to assess associations between both groups. A significance level of $p=0.05$ was used for individual tests.

Results

Ninety-two patients with SAC were evaluated. CT was performed in 26 (28%) patients during their index admission for SAC. In the CT and no-CT patient groups, patient age, SAC score, admission laboratory values, intravenous steroid use, infliximab use, the use of abdominal X-ray, sigmoidoscopy, or colonoscopy, and the duration of hospitalization were all similar. There was no difference in the rate of same admission colectomy in the CT (38%) and no CT (48%) groups ($p=0.4$; Table 1).

Of the 42 patients who underwent colectomy, the indication for surgery was failure of medical treatment in 36 (86%), peritonitis in four (10%), and megacolon in two (5%) patients. There were no differences in the indication for colectomy in patients who did or did not have a CT. Thirty-six patients (86%) had surgery within 2 days of admission (range: 0–23 days). Of the 26 patients who had a CT, 18 (69%) underwent the CT during the first 2 days of their hospitalization (range, 0–19 days). In the ten patients who had a CT before colectomy, the median interval between CT and colectomy was 2 (0–13) days. The median hospital stay in the CT and no-CT groups of patients was 7 (3–40) and 6 (3–23) days, respectively ($p=0.2$). There were no deaths in the study population.

The most common indication for CT was abdominal pain in 23 (88%) patients. In the other three (12%) patients, CT was performed for each of the following indications: to evaluate an elderly, atypical patient who incompletely responded to medical therapy, to confirm a diagnosis of suspected acute pancreatitis, and to further evaluate pneumatosis detected by AXR. Colitis was identified in 26 (93%) of patients who underwent CT.

Table 1 Comparison Between CT Patients and No CT Patients

	No CT (n=66)	CT (n=26)	p value
Age[a]	37 (17–74)	34 (17–83)	0.6
Gender			
Female	36 (55%)	11 (42%)	
Male	30 (45%)	15 (58%)	0.3
SAC score[a]	3 (2–4)	3 (2–4)	0.9
Hemoglobin (g/dL)[a]	10.2 (4.5–14.7)	10.9 (7.3–14.6)	0.07
WBC (k/μL)[a]	10.2 (3.7–26)	10.4 (4–24.9)	0.4
Albumin (g/dL)[a]	3.1 (1.7–4.9)	3.2 (2.2–4.4)	0.4
IV steroid	56 (85%)	25 (96%)	0.3
Infliximab	5 (8%)	5 (19%)	0.1
Abdominal X-ray	55 (83%)	22 (81%)	1
Endoscopy	41 (62%)	18 (69%)	0.5
Modified Baron score			
1 (mild)	1 (2%)	1 (6%)	
2 (moderate)	18 (44%)	11 (61%)	
3 (severe)	22 (54%)	6 (33%)	0.3
Same admission colectomy	32 (48%)	10 (38%)	0.4
LOS (days)[a]	6 (3–23)	7 (3–40)	0.2

CT computed tomography, *SAC* severe acute colitis, *WBC* white blood cell count, *IV* intravenous, *LOS* length of hospital stay
[a] Median and ranges reported as indicated

By CT, the extent of colitis was pancolitis, left-sided colitis, and proctosigmoiditis in 18 (69%), four (15%), and two (8%), respectively. In two (8%) patients, CT revealed no signs of colitis. The CT findings were similar in patients who did or did not require colectomy (Table 2).

Twenty-one patients (23%) underwent both AXR and CT. The AXR and CT findings differed in two patients: (1) AXR with pneumatosis, CT without pneumatosis and (2) AXR with no pneumoperitoneum, CT with pneumoperitoneum. In two of the 26 (8%) patients who underwent CT, the CT result directly influenced the treatment plan. The first patient was an elderly woman, who incompletely responded to several days of medical therapy for SAC, did not have clinical signs of peritonitis, and colectomy was not planned. Pneumoperitoneum, intra-abdominal abscess, and pancolitis were detected on CT. A colectomy was performed in this patient. The second patient also had no clinical signs of peritonitis and underwent CT to confirm an AXR finding of pneumatosis. The CT revealed colitis without pneumatosis, and colectomy was deferred in this case.

Discussion

In patients with severe acute ulcerative colitis, the effectiveness of medical treatment is measured by the clinical condition of the patient, laboratory values, and the findings on daily AXR. The utility of these parameters in the management of patients with SAC is well established.[1,2,4–17] On the contrary, the utility of abdominal CT in the management of SAC has not been clearly established. While CT has proven useful in the diagnosis of pericolonic and extra-colonic abnormalities, which infrequently occur in SAC, it has not been used to determine disease severity or to guide medical or surgical treatment.[23,24] Despite this, in our hospital, we observed that CT was being obtained with increased frequency in patients with SAC. The primary aim of our study was to determine the impact of CT on the decision to perform urgent colectomy in patients with SAC. Secondary aims were to compare the CT findings in patients who required colectomy to those who did not require colectomy and to compare AXR and CT findings in patients who underwent both of these radiological studies.

In our study, there was no difference in the rate of same admission colectomy for SAC patients who did or did not have a CT. In addition, the findings on CT were similar in patients who did or did not require a colectomy. In the subset of patients who had both AXR and CT, the results of these studies differed in less than 10% of patients. A clear impact of CT on the decision to perform or defer colectomy was observed in only two of 26 patients.

Our study has several limitations. As this was a retrospective study, the evaluation and treatment of patients was not protocol-based. Rather, the use of diagnostic

Table 2 Comparison of CT features between SAC patients who did or did not require colectomy

	No colectomy (n=16)	Colectomy (n=10)	p value
Wall thickness (cm)[a]	0.75 (0.1–1.7)	0.7 (0.3–1.4)	0.7
Colon diameter (cm)[a]	3.25 (1.6–5.1)	3.45 (2.4–4.5)	0.5
Enhancement pattern			
Homogeneous	9 (56%)	3 (30%)	
Target	7 (44%)	5 (50%)	
Unknown	0	2 (20%)	0.1
Comb sign	14 (88%)	7 (70%)	0.2
Disease extension			
Pancolitis	11 (70%)	7 (70%)	
Left-side colitis	1 (6%)	3 (30%)	
Proctosigmoiditis	2 (12%)	0	
Normal	2 (12%)	0	0.2
Folds			
Effaced	7 (44%)	6 (60%)	
Nodular	4 (25%)	2 (20%)	
Nodular and effaced	1 (6%)	0	
Normal	3 (19%)	0	
Unknown	1 (6%)	2 (20%)	0.4

CT computed tomography
[a] Median and ranges reported as indicated

studies, including CT, and the decision to perform colectomy were at the discretion of the treating physicians and surgeons. The absence of a treatment algorithm for SAC may at least partially explain why, despite similar disease severity, laboratory values, medications, AXR, and endoscopic findings, some patients had CT, while others did not. This was a retrospective analysis and thus suffers from all of the deficiencies attributable to a retrospective study, including confounding and selection bias. It is quite possible that there were unmeasured clinical findings or laboratory results that prompted the use of CT in certain cases and were not detected in our analysis. Despite these limitations, we found that there were no differences in clinical parameters, laboratory values, medical treatments, endoscopy use, indication for colectomy, rate of colectomy, or length of stay in the patients who had or did not have CT. In the patients who did have CT, there were no differences in the CT findings in the patients who did or did not require colectomy.

In conclusion, we have shown that CT had little impact on the decision to perform colectomy in patients with SAC. Until there is more robust evidence to support its use, we suggest that clinicians carefully consider the yield of CT, before it is obtained, and that they continue to rely on the established clinical, laboratory, radiologic, and endoscopic parameters to guide their management of patients with SAC.

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ORIGINAL ARTICLE

Surgical Site Infections Following Colorectal Surgery in Patients with Diabetes: Association with Postoperative Hyperglycemia

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Abstract
Introduction Postoperative glycemic control reduces sternal infections following cardiac surgery in patients with diabetes mellitus (DM). The objective of this study was to examine the relationship between postoperative glycemic control and surgical site infections (SSI) in patients with DM undergoing colorectal resection.
Discussion A cohort of patients with DM who underwent colorectal resection (April 2001–May 2006) at our institution were reviewed. SSI were defined by Centers for Disease Control criteria. From a study cohort of 149 patients, 24% had poor postoperative glycemic control (defined as a mean 48-h postoperative capillary glucose (MCG) >11.0 mmol/L or 200 mg/dL), and these patients developed SSI at a significantly higher rate than those with a 48-h MCG ≤11.0 mmol/L (29.7% vs. 14.3%; odds ratio (OR) 2.5, $p=0.03$). On multivariate logistic regression, 48-h MCG >11.0 mmol/L was significantly associated with SSI (OR 3.6, $p=0.02$), independent of the dose and regimen of postoperative insulin administration. In conclusion, 48-h MCG >11.0 mmol/L (200 mg/dL) was independently associated with increased SSI following colorectal resection in patients with DM. Prospective studies are required to validate this relationship, address the role of preoperative glycemic control, and examine strategies to improve glycemic control following colorectal resection.

Keywords Diabetes mellitus · Colorectal surgery · Surgical wound infection · Hyperglycemia · Insulin

Introduction

Diabetes mellitus (DM) has a prevalence approaching 20% and accounts for an increasing proportion of healthcare expenditures. DM is recognized as an independent risk factor for surgical site infections (SSI) in general surgery and SSI occur following 5–26% of colorectal resections.[1–5] SSI lengthen hospital stay and increase use of community nursing resources.[3,6] There are major quality improvement campaigns currently underway in both the USA and Canada aimed at reducing the incidence of SSI and their associated costs.[7,8] Recent implementation of quality improvement protocols have demonstrated some efficacy in reducing SSI following colorectal surgery; however, the proportion of this early success attributable to improved glucose control is not known.[9,10]

In the cardiovascular surgery and surgical intensive care patient populations, improved glucose control during the 48-h immediately following surgery has been clearly linked with a reduction in major infections.[11–13] This association appears to be independent of preoperative glycemic control and the dose of insulin infused postoperatively.[13,14] These findings have led to implementation of routine intensive insulin therapy in cardiac and surgical ICUs, with the goal of maintaining capillary glucose levels between 4.5 and 6.0 mmol/L.

The noncardiac, non-ICU literature contains an increasing number of studies investigating the impact of postoperative hyperglycemia on morbidity including surgical site

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infections.[15–20] The American Diabetes Association and the Canadian Diabetes Association recommend maintaining random serum glucose values ≤11.0 mmol/L in the perioperative period for all noncardiovascular surgeries.[21,22]

This study sought to examine whether 48-h postoperative glycemic status among patients with DM undergoing colorectal surgery was associated with SSI. Secondary end points were clinically significant anastomotic leak (CAL), length of stay (LOS), and mortality.

Materials and Methods

After receiving approval from the Institutional Ethics Review Board (CDHA REB #2006-105), medical records for all patients undergoing resection with primary anastomosis involving the colon and/or rectum at a single tertiary care center between April 1, 2001 and May 31, 2006 were reviewed. Inclusion criteria were:

1. A diagnosis of DM listed in the preoperative anaesthesia assessment and/or discharge summary
2. Capillary blood glucose values recorded at least twice daily for 48 h postoperatively
3. Treatment for hyperglycemia ordered within 48 h postoperatively

Patients who underwent emergency colorectal surgery for indications such as sepsis, perforation, or complete obstruction were excluded. Patients undergoing closure of a loop colostomy without a separate clean surgical site (i.e., midline incision) were also not included.

Detailed pre-, peri-, and postoperative data were extracted from each medical record including age, body mass index, HgA1C level, Charlson Comorbidity Index,[23] operation performed, duration of operation, surgeon caseload (≥20 vs. <20 colorectal cases per year),[24,25] surgical wound classification,[26] American Society of Anesthesiology (ASA) score,[26] capillary glucose readings during 48-h postoperatively, and medication types and doses (e.g., insulin, oral antihyperglycemics, antibiotics). Our institution has a protocol for calibration of glucometer machines but given the retrospective nature of this study, no quality assurance data regarding capillary glucose readings is available. Data regarding antibiotic use was collected for three time periods—the immediate preoperative period, the immediate postoperative period, and within 30 days postoperatively for a defined non-SSI, non-CAL infection (e.g., pneumonia, urinary tract infection). Patients were classified into two groups based on the calculated mean 48-h capillary glucose (MCG) value, using 11.0 mmol/L (200 mg/dL) as the threshold value. For simplicity's sake, only the international units (mmol/L) are used in the remainder of this report.

Data regarding the primary and secondary end points were also collected from each medical record. SSI was defined by Centers for Disease Control (CDC) criteria[26] as the presence of all of the following: purulent drainage; at least one of pain, tenderness, localized swelling, redness, or heat; and deliberate opening of the incision by the surgeon at the bedside. It did not include organ or deep space infections as defined by the CDC. CAL was defined as clinical findings suggestive of an anastomotic leak (e.g., ileus, abdominal pain, fever, leukocytosis) supported by either conclusive radiographic evidence (fluid collection adjacent to the anastomosis on computed tomography scan or extravasation on contrast enema) or intraoperative findings. The LOS was defined as the number of days spent in hospital following surgery, including the day of discharge. Perioperative mortality was defined as death occurring during the index hospitalization and/or within 30 days of surgery. A thorough search for records of outpatient clinic and emergency visits, as well as readmissions to hospital, was conducted to identify all such SSI, CAL, and mortalities.

The data were collated and analyzed using SPSS software (version 15.0, Chicago). Chi-square or Fisher's exact (categorical variables), *t* test or analysis of variance (continuous normally distributed variables), and Mann–Whitney *U* (continuous nonnormally distributed variables) tests were used to analyze univariate relationships. Multivariate logistic analysis was conducted incorporating variables which were significant or near significant ($p \leq 0.15$) on univariate analysis for each end point.

Prior to undertaking data collection, a baseline power calculation was performed. Using a conservative baseline estimated SSI rate of 7%, assuming that a 50% increase in SSI would be clinically significant, using one-tailed $\alpha = 0.05$, and adding 30% for confounding variables, our available estimated sample size of 150 patients would result in a power of 87%.

Results

The study cohort consisted of 149 consecutive patients with DM undergoing colorectal surgery. Descriptive and operative characteristics are presented in Table 1, along with the results of univariate analysis for SSI.

Postoperative management characteristics and outcomes are summarized in Table 2, along with the corresponding univariate analysis. Capillary glucose values were recorded, on average, nine times within the 48-h postoperative period (range 4–25). Of the 132 patients who received insulin for postoperative treatment of hyperglycemia, 109 received subcutaneous insulin sliding scale alone, six received sliding scale plus longer-acting insulin, and 17 received an insulin infusion. Poor glycemic control, defined as a mean

Table 1 Demographic and Operative Parameters—with Univariate Analysis Results (n=149)

		Number	Univariate analysis for surgical site infection[b]	
			%	p value
Age[a]	≥75 years	47	10.6	0.1
	<75 years	101	21.6	
Gender	Male	85	16.5	0.5
	Female	64	20.3	
Body mass index[a]	0–29.9 kg/m^2 (nonobese)	78	14.1	0.1
	≥30.0 kg/m^2 (obese)	65	24.6	
Charlson Comorbidity Index	1–4 (mild)	87	19.5	0.6
	≥5 (moderate–severe)	62	16.1	
Preoperative DM treatment	None/oral medications	115	17.4	0.7
	Insulin	34	20.6	
Operative indication	Malignancy	110	16.4	0.4
	Benign disease	39	23.1	
Anastomotic type	Ileocolonic/rectal	67	9.0	p=0.009
	Colocolonic/rectal	82	25.6	OR 3.5
Surgeon caseload[a,b]	≥20 colorectal cases/year	107	15.9	0.4
	<20 colorectal cases/year	40	22.5	
Surgery duration[a]	<90 min	49	6.1	p=0.007
	≥90 min	99	24.2	OR 4.9
ASA classification[a]	1–2	85	16.5	0.3
	3–4	50	24.0	
Wound classification[a,c]	Contaminated/dirty	13	15.4	0.7
	Clean/clean-contaminated	131	19.1	
Bowel preparation	Yes	129	19.4	0.3
	No	20	10.0	
Antibiotics given <60 min preoperatively[c]	Yes	122	17.2	0.5
	No	27	22.2	
Antibiotics stopped within 24 h preoperatively[a,c]	Yes	98	19.4	0.9
	No	3.9	20.5	
Hair removal[a,c]	None/clipper	124	19.4	0.6
	Shave	20	15.0	
Perioperative transfusion[a]	Yes	47	14.9	0.4
	No	98	20.4	
Recovery room body temperature 36.0–38.0°C[a,c]	Yes	71	21.1	0.9
	No	52	20.0	

[a] Missing data points result in category totals less than the total sample size
[b] Chi-squared testing (Fisher's exact testing if count <5 in any cell)
[c] Components of surgical site infection quality improvement campaigns in the USA and Canada

postoperative 48-h capillary glucose value >11.0 mmol/L, was found in 36 (24.2%) patients. SSI occurred in 27 (18.1%) patients and CAL occurred in nine (6.0%) patients. Among patients with SSI, 26% were recognized after discharge from hospital whereas all CAL were recognized during the index hospitalization. Nineteen percent of patients had another infection (non-SSI, non-CAL related) requiring antibiotics within 30 days postoperatively. The median LOS was 10 days, with a range of 5 to 161 days. The 75th percentile for LOS was 14 days and 33 patients had an extended LOS using this as a benchmark. Only one patient died perioperatively.

On univariate analysis for the end point of SSI, patients with a postoperative 48-h MCG >11.0 mmol/L had a greater likelihood of SSI compared to patients with a postoperative 48-h MCG≤11.0 mmol/L (29.7% vs. 14.3%, odds ratio (OR) 2.5, p=0.03). Other factors significantly associated with SSI on univariate analysis were duration of surgery ≥90 vs. <90 min (OR 4.9, p=0.007), colocolonic or colorectal vs. ileocolonic or ileorectal anastomosis (OR 3.5, p=0.009), and absence of another infection requiring antibiotics within 30 days postoperatively (OR 1.3, p=0.006). On multivariate analysis, only a 48-h MCG >11.0 mmol/L (OR 3.6; 95% confidence interval (CI) 1.3, 9.9; p=0.02) and the absence of another infection requiring antibiotics within 30 days postoperatively (OR 11.1; 95% CI 1.3, 93.5; p= 0.025) were significantly associated with SSI (Table 3).

Table 2 Postoperative Management and Outcomes—with Univariate Analysis Results (n=149)

		Number	Univariate analysis for surgical site infection[a]	
			%	p value
48-h postoperatively				
Mean capillary glucose value	≤11.0 mmol/L	113	14.3	p=0.03
	>11.0 mmol/L	36	29.7	OR 2.5
Treatment received for hyperglycemia	None/oral medications	17	23.5	0.5
	Insulin	132	17.4	
30-days postoperatively				
Mortality	Yes	1	0	1.0
	No	148	18.2	
Clinically significant anastomotic leak	Yes	9	22.2	0.7
	No	140	17.9	
Other infection requiring antibiotics	Yes	28	0	p=0.006
	No	121	22.3	OR 1.3
Postoperative length of stay	≤75th percentile	116	19.0	0.6
	>75th percentile	33	15.2	

[a] Chi-squared for 2×2 (Fisher's exact test if count <5 in any cell)

Of the 17 patients who received no insulin postoperatively, none were receiving insulin preoperatively, and none had a 48-h MCG >11.0 mmol/L. These patients may be a subgroup with "borderline" DM who were not truly part of the intended cohort. The statistical analysis was repeated after excluding these 17 patients. Among the "insulin receivers" (n=132), use of an insulin infusion was associated with receipt of larger amounts of insulin within the initial 48-h postoperative period (75 vs. 21 units, p=0.003) and a lower mean 48-h MCG (9.0 mmol/L vs. 10.3 mmol/L, p=0.02), when compared to use of a sliding scale insulin regimen. On multivariate logistic analysis, poor postoperative glycemic control (48-h MCG >11.0 mmol/L) was associated with use of a sliding scale insulin regimen (OR 6.6, 95% CI 1.6, 26.9; p=0.009) and receipt of ≥25 units of insulin within the 48-h postoperative period (OR 19.9, 95% CI 6.3, 56.8; p<0.001).

When the multivariate analysis for the SSI end point was repeated for this subgroup of insulin receivers, the results were essentially unchanged. Both 48-h MCG >11.0 mmol/L (OR 3.9, 95% CI 1.4, 11.3; p=0.01) and absence of another infection requiring antibiotics (OR 10.4, 95% CI 1.2, 88.4; p=0.03) were significantly associated with SSI. The type of insulin regimen used and the number of units of insulin received were not significantly associated with SSI.

In terms of secondary end points, patients with 48-h MCG value >11.0 mmol/L were not more likely to have a CAL compared to those with 48-h MCG ≤11.0 mmol/L (8.1% vs. 5.4%; p=0.54). Length of stay was similar between patients with a 48-h MCG >11.0 mmol/L and those with a 48-h MCG

Table 3 Surgical Site Infection—Multivariate Analysis (n=149)

		SSI rate (%)	p value	RR
Age	≥75 years	10.6	–	1.0
	<75 years	21.6	0.8	1.2
Body mass index	0–29.9 kg/m^2 (nonobese)	14.1	–	1.0
	≥30.0 kg/m^2 (obese)	24.6	0.3	1.7
Surgery duration	<90 min	6.1	–	1.0
	≥90 min	24.2	0.07	3.6
Anastomotic type	Ileocolonic/rectal	9.0	–	1.0
	Colocolonic/rectal	25.6	0.07	2.9
Mean 48-h capillary glucose	≤11.0 mmol/L	14.3	–	1.0
	>11.0 mmol/L	29.7	0.02	3.6
Other infection requiring antibiotics	Yes	0	–	1.0
	No	22.3	0.025	11.1

Logistic regression using enter method and incorporating all variables with p<15 on univariate analysis

≤11.0 mmol/L (median 10 days in each group, $p=0.9$). LOS was not significantly increased in patients with SSI (median 12 vs. 9 days, $p=0.09$).

Analysis for the mortality end point was not conducted as only one patient died. This patient had a 48-h MCG of 8.3 mmol/L, no SSI, no CAL, and a LOS of 27 days. The cause of death was pneumonia.

Discussion

The most clinically significant finding of this study was that 48-h postoperative MCG >11.0 mmol/L was associated, on multivariate analysis, with a greater than threefold increased risk of SSI among diabetic patients undergoing colorectal surgery. The retrospective, nonrandomized nature of this data prevents any conclusion regarding causality but this finding parallels those in the cardiac literature, where several authors have shown an approximately threefold decrease in sternal wound infections when 48-h postoperative glucose levels were kept below 11.0 mmol/L.[11,13] Conflicting results have been published by Estrada et al. who found no relationship between postoperative hyperglycemia and overall infections, which occurred in 5.0% of their 1,574 patients. The study was adequately powered to detect a 50% change in this infection rate but was markedly underpowered to detect a true change in sternal wound infections given that only 0.8% of their sample developed such an infection.

Outside the cardiac surgery and intensive care literature, the question of postoperative hyperglycemia and SSI has been studied in several retrospective analyses. Among vascular surgery patients who underwent infrainguinal reconstruction, postoperative hyperglycemia (48-h MCG >7.4–8.4 mmol/L) was associated with a five- to 14-fold increase in infectious wound complications.[18,19] Parallel relationships have been found in spinal surgery,[15] pancreatic surgery,[16] and following mastectomy.[17] Patients undergoing esophageal resection have also been studied.[20] No significant association between postoperative hyperglycemia and infectious complications was found, although the sample size was small (151), only six patients had a diagnosis of DM, and postoperative MCG values were analyzed by quartiles, making the numbers in each group quite small.

In the current multivariate analysis, the increased risk of SSI with postoperative hyperglycemia was independent of the type of antihyperglycemic treatment received pre- or postoperatively, as well as other clinical factors (surgical wound classification, appropriately timed perioperative antibiotics, and hair removal technique) which have been proposed as SSI risk factors in the literature and targeted by current quality improvement programs.[7,8] Even on univariate analysis, none of these factors were significantly associated with SSI although the study was not powered to detect smaller, but real, differences in SSI that may be associated with such factors. In addition, there may be other factors, not captured in the current data set, which may have contributed to SSI risk. For instance, surgery duration >90 min was associated with SSI on univariate, but not multivariate, analysis. Perhaps there is some factor or factors, such as the involvement of trainees, tumor size, or technical complications, which were at work here but not captured with our retrospective data collection technique. Such factors should be considered for inclusion in any future studies.

Among the subgroup of patients who received insulin, SSI was not related to the type of insulin regimen used, nor the number of units of insulin administered. This suggests that glycemic control, and not insulin regimen or dosage, is the mediator of the association with SSI. The biological basis for this proposed relationship is not yet fully understood but may be related to the cellular effects of hyperglycemia in the immediate postoperative period when the wound is in the inflammatory phase of healing. This phase requires local vasodilation, opsonisation of bacteria, antigen presentation by monocytes, and neutrophil chemotaxis and phagocytosis. In vitro studies have demonstrated that even short-term (6–24 h) exposure to hyperglycemia impairs all of these functions.[27,28] Both animal[29] and clinical[14] studies support this hypothesis, providing evidence that normoglycemia, rather than the physiological effects of insulin, is responsible for decreased morbidity and mortality postoperatively. While there is some evidence that insulin may have independent benefits on endothelial and hormonal function which affect mortality, the effect on wound healing is unknown.[30]

In the current study, patients with poor glycemic control were, appropriately, receiving the largest number of units of insulin in the immediate postoperative period. It also suggests that use of an insulin infusion was associated with better postoperative glycemic control. However, the great majority of cohort patients received only sliding scale insulin, and these patients were at higher risk for poor postoperative glycemic control and thus, in turn, for SSI. Current endocrinology literature strongly recommends against the use of insulin sliding scale in isolation and suggests that a regimen including scheduled doses of longer-acting insulin (such as NPH) provides better control.[31] The small number of patients in this study ($n=6$) who received such a combined regimen made analysis of its benefits impossible but this is an important area for future study given that insulin infusions are unlikely to become widely used on postoperative general surgery wards.

It is conceivable that the observed relationship between MCG >11.0 and SSI actually represents a hyperglycemic response caused by the presence of an infection. However, the SSI were diagnosed at least 3–4 days (and in many cases

7–14 days) postoperatively, whereas the hyperglycemia was recorded within the first 48 h postoperatively. In addition, prospective data from the cardiac surgery literature suggests that postoperative hyperglycemia *contributes* to infectious complications, rather than the other way around.[11,13]

The definition of "poor" glucose control used in this study (48-h MCG >11.0 mmol/L) was chosen on the basis of current Canadian and American guidelines for the perioperative management of patients with DM[21,22] and in an effort to match recently implemented quality improvement protocols.[9,10] In our cohort, 24% of patients had poor postoperative glucose control by this definition. This may reflect a lower priority and greater difficulty associated with control of hyperglycemia on a general surgical ward compared to the critical care setting that is typically studied in the cardiac literature. Given that the majority of colorectal patients will continue to spend their initial postoperative 48-h in a nonintensive care situation, a threshold of 11.0 mmol/L is probably a more reasonable goal than the current standard threshold of 6.0 mmol/L used in cardiac surgery.

Patients who received antibiotics within 30 days postoperatively for a defined non-SSI, non-CAL related infection developed no SSI, and this relationship was significant on univariate and multivariate analysis. Interestingly, a similar relationship did not exist between SSI and postoperative use of >24 h of "prophylactic" antibiotics. Although data concerning the clinical reasoning for prescription of >24 h of postoperative antibiotics were not collected, its use was associated, on post hoc univariate analysis, with surgery duration >90 min (p=0.01) and receipt of perioperative transfusions (p=0.05)—suggesting that a longer duration of postoperative antibiotics was prescribed in the more complex surgical patients. These relationships have not been reported previously and warrant further study in a prospective fashion.

Given the strength of the relationship between SSI and antibiotics for another defined infection within 30 days postoperatively, a post hoc univariate analysis was undertaken for this factor. It showed that other infections diagnosed and treated within 30 days postoperatively were significantly more common in women than men (26.6% vs. 12.9%, OR 2.4, p=0.03), patients whose surgery lasted >90 compared to <90 min (24.2% vs. 8.2%, OR 3.6, p=0.02), among patients who received >24 h of postoperative prophylactic antibiotics rather than ≤24 h of such antibiotics (30.8% vs. 12.2%, OR 3.2, p=0.01), and in patients whose LOS was >75th percentile rather than less (30.3% vs. 15.5%, OR 2.4, p=0.05). The development of other non-SSI, non-CAL infections was not significantly associated with 48-h MCG (p=0.9), nor with insulin usage pre- or postoperatively (p=0.4 and p=0.1, respectively). These findings suggest that the relationship between hyperglycemia and SSI may not apply to other infectious complications but this certainly warrants further prospective study.

Patients with left-sided anastomoses and those with a surgery duration ≥90 min were more likely to develop SSI on univariate analysis. Neither of these relationships attained statistical significance on multivariate analysis but both are strong enough to warrant further study.

The subgroup of patients with nonmalignant ("benign") disease included patients with diverticular disease and patients with Crohn's disease and/or colocutaneous fistulae. This group may therefore be considered at higher risk of postoperative infections than the subgroup of patients with a malignant indication for surgery. Univariate analysis did not show a significant relationship between surgical indication and SSI (Table 1). Post hoc analysis showed no significant relationship between surgical indication and either postoperative prophylactic antibiotic use (p=0.4) nor 30-day incidence of non-SSI, non-CAL infection (p= 0.9). Based on this, it seems reasonable to generalize the results of this paper to both groups of patients and to include both in any future studies.

Postoperative hyperglycemia was not associated with a significant increase in CAL although this study was statistically underpowered to examine this uncommon outcome. However, it is questionable whether the observed difference in CAL rate between patients with 48-h MCG >11.0 vs. ≤11.0 mmol/L (8.1% vs. 5.4%, respectively) is clinically significant.

Limitations of this study are largely related to its retrospective design. Firstly, we may not have identified every patient with DM who was undergoing colorectal surgery. We chose to use the preoperative anesthesia assessment record and the discharge summary (which includes a list of preadmission comorbidities) to identify our cohort because we wished to include patients who would have generally been considered "diabetic" by the surgical team and thus would be candidates for more intensive glycemic control measures if such a protocol were implemented. The validity of the DM diagnosis in the included patients is supported by the fact that each one had capillary glucose monitoring ordered at least twice daily during the postoperative period.

Secondly, it is possible that not every SSI was captured on retrospective analysis. However, the overall rate of SSI in this cohort (18.1%) is consistent with data reported by others (5–26%) who applied similar definitions to broad samples of colorectal surgery patients.[1–4] We are also confident that we captured all SSI based on the concerted effort made to identify SSI diagnosed after discharge from hospital, which accounted for 26% of all SSI in this study. It is well recognized that a methodical approach to post-discharge surveillance is necessary to capture all SSI.[3,32]

Retrospective data capture resulted in some variables not being available for all cohort members. For example, only

18% of patients had a preoperative serum albumin level in their chart, only 46% had their intraoperative FiO_2 recorded, and 22% were missing a value for their body temperature in the recovery room (there was no protocol regarding perioperative normothermia in place during the period of this study). These factors have all been associated with SSI in previous studies[1,33–35] but our ability to control for them in this study was limited. Similarly, only ten (6.7%) of patients in this cohort had a HgA1C value available from the 3 months preceding surgery, and thus, our multivariate analysis could not include preoperative glycemic control as a covariate. However, the cardiac surgery literature contains analyses similar to our own, but where HgA1C was collected routinely. These studies suggest that postoperative hyperglycemia is the operand, not preoperative glycemic control.[13] This study used a cohort from a single tertiary care academic center and thus may not be generalizable to other health care settings.

Finally, this cohort of patients underwent surgery before laparoscopic techniques were widely used at the study institution. Only five (3.3%) cohort patients had a laparoscopic approach to their surgery and all had a midline incision for removal of the specimen. These patients were included in the overall cohort but not subjected to subgroup analysis, given their small numbers. The question of whether equivalent SSI associations occur in laparoscopic colorectal resection awaits further study. Initial results suggest overall SSI rates with laparoscopic colorectal surgery are within the range quoted for open procedures.[36]

Conclusion

Mean 48-h postoperative capillary glucose >11.0 mmol/L was associated with SSI following colorectal surgery in patients with DM, independent of the route and dose of insulin received during the immediate postoperative period. The retrospective, nonrandomized nature of the data used in this study prevent conclusions regarding causality. However, given the strength of the demonstrated relationship, the solid correlating data from the cardiac surgery literature, the significant morbidity and cost associated with SSI, and the current quality improvement initiatives focused on reducing SSI incidence, improved postoperative glycemic control deserves further attention as a possible point of intervention following colorectal surgery. Prospective studies are required to validate the association observed here, to address the role of preoperative glycemic control, and to evaluate reasonable treatment options to improve postoperative glycemic control in the colorectal surgery population.

Disclaimers None

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ORIGINAL ARTICLE

Colonic Diverticular Bleeding with Comorbid Diseases may Need Elective Colectomy

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Abstract
Background Colonic diverticular bleeding can usually be managed with conservative treatment. However, in a selected group of patients under conditions of recurrent, persistent bleeding influencing quality of life or causing life-threatening shock, it should be managed with surgery. This is a retrospective study to clarify the risk factors relating to colectomy for colonic diverticular bleeding.
Methods Between 1997 and 2005, a retrospective chart review of 73 patients with colonic diverticular bleeding was undertaken. Univariate and multivariate logistic regression analyses were performed to identify the relevant risk factors correlating to colectomy.
Results The mean age of the 73 patients was 70 years (range, 22–90 years). Most colonic diverticular bleeding could be managed with conservative treatment (n=63, 86.3%), and urgent colectomy was performed in ten patients (13.7%). The bleeding site could not be well identified in six of those ten patients and so underwent total abdominal colectomy with ileorectal anastomosis, and the other four underwent right hemicolectomy after a diagnosis of right-sided colon diverticula with bleeding. There were two deaths in the surgical group and one death in the nonsurgical group. The overall mortality rate in the series was 4.11% and 20% among patients undergoing urgent colectomy. Multiple logistic regression analysis showed that the presence of comorbidities and daily maximum blood transfusion requirement were risk factors for urgent colectomy for colonic diverticular bleeding.
Conclusion Preoperative comorbid diseases may increase operative risk in urgent surgery, and the outcome is poor. To avoid high mortality and morbidity relating to the urgent colectomy, we suggest that patients of colonic diverticular bleeding with comorbid diseases, especially subgroups of patients with diabetes and gouty arthritis, may need early elective colectomy.

Keywords Colonic diverticular bleeding · Risk factor · Colectomy

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Introduction

Diverticulosis involving the large intestine is a common disorder. A diverticulum is the herniation of the mucosa and submucosa through the muscular layers of the colon and occurs because of increased intraluminal pressure and weakness in segments of the colonic wall.[1] Although various complications of diverticular disease can occur, bleeding is one of the most common.[2] The vasa recta, the blood vessels from the mesentery that supply the mucosa and submucosa of the colon, run from the mesentery in the subserosa toward the antimesenteric tiniae on either side of the bowel wall and on each side penetrate the circular muscle at two points between the mesenteric and anti-

mesenteric tiniae. Mucosal herniations can occur through the vascular portals in the circular muscle into the subserosa.[3] Mucosal ulceration results in bleeding that is gradual and mild. In contrast, erosion of the vasa recta, which are in close apposition to the diverticula as they traverse the circular muscle, may lead to brisker hemorrhage. The incidence of bleeding has been estimated to be between 4% and 50% in patients with this condition.[4] The severity of bleeding varies from intermittent and minimal to massive and life-threatening. Although the overwhelming majority of diverticular bleeding episodes resolve spontaneously with conservative treatment, surgical intervention cannot be avoided under certain circumstances, such as persistent bleeding, repeated bleeding, and even hypovolemic shock. Approximately 25% of patients who initially bleed with diverticulosis will develop further episodes of bleeding, which create difficult management decisions.[5] The aim of this study was to identify risk factors for urgent colectomy to manage colonic diverticular bleeding (CDB) in order to determine patients who may benefit from early elective colectomy.

Materials and Methods

The charts of 250 patients who had been admitted to the Tri-Service General Hospital, Taipei, Taiwan, between1997 and 2005, with a diagnosis of lower gastrointestinal bleeding were reviewed, and the selected subgroup of 73 patients with a diagnosis of CDB were identified and analyzed retrospectively.

Data were collected with regard to age, sex, albumin level, colon bleeding site, history of recurrent bleeding, shock episode during hospitalization, daily maximum blood transfusion requirement, hemoglobin level on admission, preoperative comorbidity, coagulation function, use of medication associated with coagulation or wound healing, treatment policy, morbidity, and mortality (Table 1). The determination of colonic diverticular bleeding was based on the findings of barium enema, and the bleeding site was localized by angiography, which was complementary to colonoscopy and tagged red blood cell scanning. Bleeding sites in the cecum, ascending colon, or transverse colon were categorized as right-sided colon bleeding, whereas those in the descending colon or sigmoid colon were categorized as left-sided colon bleeding. A hemoglobin level below 10 g/dL or persistent lower gastrointestinal bleeding with unstable hemodynamics were the circumstances under which blood transfusions were deemed to be necessary. Urgent colectomy was indicated in patients in whom conservative treatment (resuscitation, angiography with selective embolization, colonoscopic procedure with vasopression injection) failed and who suffered hypovolemic shock or persistent bleeding. The latter was defined as continuous bleeding within the first 24 h of hospitalization and/or recurrent bleeding after 24 h of stability or readmission for CDB within 1 week of discharge. Preoperative comorbid diseases included cardiovascular diseases (hypertensive

Table 1 Characteristics of Patients with Colonic Diverticular Bleeding

Variable	Surgery group (n=10)	Non-surgery group (n=63)
Age (range)	69 (53–84)	70 (22–90)
Male/female ratio	7/3	36/27
Bleeding site	R-4UI-6	R-22 L-32 UI-9
Recurrent bleeding	9 (90)	23 (37)
Hemoglobin on admission (g/dL)	9.6	10.3
Blood transfusion (max unit/day)	4.7	1.8
Albumin (<3 g/dL)	4 (40)	5 (8)
Cardiovascular disease	6 (60)	42 (67)
Type 2 diabetes mellitus	5 (50)	10 (16)
Liver disease	3 (30)	9 (14)
Peptic ulcer	3 (30)	11 (18)
Pulmonary disease	2 (20)	6(10)
Gouty arthritis	6 (60)	11 (18)
Uremia	2 (20)	4 (6)
Shock symptom	1 (10)	2 (3)
Coagulopathy	3 (30)	4 (6)
Anticoagulant use	5 (50)	12 (19)
Steroid use	2 (20)	1 (2)
Mortality	2 (20)	1 (2)

Data are numbers with ranges or percentages in parentheses unless otherwise indicated
R right-sided colon, *L* left-sided colon, *UI* unidentified

cardiovascular disease, coronary artery disease), diabetes, liver disease (cirrhosis of the liver, fatty liver), peptic ulcer disease (gastric ulcer, duodenal ulcer), pulmonary disease (chronic obstructive pulmonary disease, asthma), gouty arthritis, and uremia. Coagulation function was assessed from the prothrombin time and the partial thromboplastin time. Medications in use included anticoagulants and steroids.

Statistical analysis was performed with Statistics Package for Social Science (SPSS) 11.5 software. Data were initially analyzed with univariate logistic regression. Variables with a P value of <0.1 on univariate analysis were subjected to multivariate logistic regression. Statistical significance was set at $P<0.05$.

Results

Seventy-three patients were admitted with a diagnosis of CDB. The mean age of the 73 patients was 70 years (range, 22–90 years); 43 of the 73 patients were men (59%).

Most bleeding episodes from colonic diverticulosis could be managed with conservative treatments of blood transfusion and hemostatics ($n=63$, 86.3%), but urgent colectomy was performed in ten patients (13.7%). Four of the ten patients underwent a right hemicolectomy after a diagnosis of right-sided colon diverticula with bleeding. The other six underwent a total abdominal colectomy with ileorectal anastomosis because of uncertainty of the exact bleeding site. There were two deaths in the surgical group, one secondary to colonic diverticulosis complicated with hypovolemic shock and the other from postoperative lobar pneumonia complicated with septic shock and acute respiratory distress syndrome. The one death in the nonsurgical group was the result of empyema complicated with septic shock during hospitalization. The overall mortality rate was 4.11% ($n=3$), and it was 20% ($n=2$) in the group that underwent urgent colectomy. Two patients with wound infections and anastomal bleeding after a total abdominal colectomy with ileorectal anastomosis were returned to the operating room for surgical debridement and suppression of bleeding. The morbidity rate in the urgent surgery group was 20% ($n=2$).

Univariate analysis with logistic regression indicated that the factors associated with a greater likelihood of having an urgent colectomy were albumin level [odds ratio (OR), 0.129, $P=0.010$), comorbidity with type 2 diabetes (OR, 5.300, $P=0.021$) or gouty arthritis (OR, 7.091, $P=0.007$), use of anticoagulants (OR, 4.250, $P=0.041$) or steroids (OR, 15.500, $P=0.032$), coagulopathy (OR, 6.321, $P=0.032$), daily maximum blood transfusion requirement (OR, 1.509, $P=0.003$), and recurrent bleeding (OR, 15.652, $P=0.011$; Table 2). On multivariate analysis with logistic regression, only preoperative comorbid diseases, including cardiovascular disease, type 2 diabetes, liver disease, peptic ulcer, pulmonary disease, gouty arthritis, and uremia (OR, 2.375, $P=0.029$), and daily maximum blood transfusion requirement (OR, 1.386, $P=0.031$) remained risk factors for urgent colectomy for CDB, independent of all other variables.

Discussion

Colonoscopy is the standard diagnostic technique for lower gastrointestinal bleeding. Arteriography is reserved for patients in whom colonoscopy cannot be carried out or is inconclusive and in whom bleeding persists for localization. In severe acute lower gastrointestinal bleeding, it is difficult to determine clinically which cases will be cataclysmic and which are self-limiting. Approximately 10–25% of patients require urgent surgery for hemodynamic instability.[6] Morbidity and mortality have been reported to be 17% and 8.3%, respectively, in patients with acute lower gastrointestinal bleeding who have undergone urgent surgery.[7]

The colonic origins of lower gastrointestinal hemorrhage are, in order of decreasing incidence, diverticulosis, inflammatory bowel disease, including ischemic and infectious colitis, colonic neoplasia, benign anorectal disease, and arteriovenous malformations.[8] In our study, colonic bleeding was determined by angiography or tagged red blood cell

Table 2 Risk Factors for Urgent Colectomy for Colonic Diverticular Bleeding on Univariate Analysis

Variables	*B*	SE	OR(95%CI)	*P* value
Blood transfusion (max U/day)	0.412	0.140	1.509 (1.146–1.987)	0.003
Coagulopathy	1.844	0.862	6.321 (1.167–34.25)	0.032
Recurrent bleeding	2.751	1.086	15.652 (1.862–131.5)	0.011
Type 2 diabetes mellitus	1.668	0.720	5.300 (1.292–21.75)	0.021
Gouty arthritis	1.959	0.726	7.091 (1.710–29.41)	0.007
Anticoagulant use	1.447	0.709	4.250 (1.259–17.06)	0.041
Steroid use	2.741	1.281	15.500 (1.259–190/9)	0.032
Albumin level	−2.046	0.796	0.129 (0.027–0.616)	0.010

scanning. The colonoscopy and angiography studies were performed to exclude the etiology of lower gastrointestinal bleeding other than colonic diverticulosis. The pathology reports proved colonic diverticular bleeding in surgery group patients, while barium enema studies were performed in all non-surgery patients to confirm the diverticulosis of colon. Current medical and surgical texts report that CDB stops spontaneously in 70–80% of cases. However, 15% of patients who experience further bleeding episodes after conservative treatment are treated surgically.[9] A number of distressing and vexing problems confront the surgeon, with controversies concerning the possibility of re-bleeding from colonic diverticulosis after patient discharge, conservative versus surgical forms of management during hospitalization, and the risks of urgent surgery for elderly patients. The clinical courses and predictors of re-bleeding in patients with CDB requiring surgery have not been determined. This might cause a delay in outpatient treatment, with consequent resource waste or re-bleeding after discharge, which influences quality of life.

The variables analyzed in our study were selected after consideration of the factors that affect the tendency to bleed and nutrition status, which is associated with colonic mucosal repair in CDB patients. Comorbidity was also included because it is a potential risk factor for mortality in severe acute lower gastrointestinal bleeding for which the most frequent etiology is colonic diverticulosis.

No difference has been found in the distribution of colonic diverticulosis between the sexes,[10] which is the same for CDB requiring surgery. The ages of patients with CDB had no significant association with surgery ($P>0.05$).

A patient's nutritional status upon admission affects the length of hospital stay for patients with colonic diverticulosis. The length of a patient's stay in hospital is an indication of the patient's recovery rate. Serum albumin levels correlated negatively with the length of hospital stay.[11] In our study, 40% of CDB patients in the surgery group had albumin levels below 3 g/dL, whereas this was true of only 8% of patients in the non-surgery group.

Among comorbidities, type 2 diabetes mellitus and gouty arthritis had an independent impact in predicting re-bleeding in colonic diverticular disease. It is well established that diabetes mellitus has a negative effect on wound integrity and the dehiscence of the gastrointestinal tract.[12] Gouty arthritis was another comorbidity that significantly predicted a bleeding tendency in patients with colonic

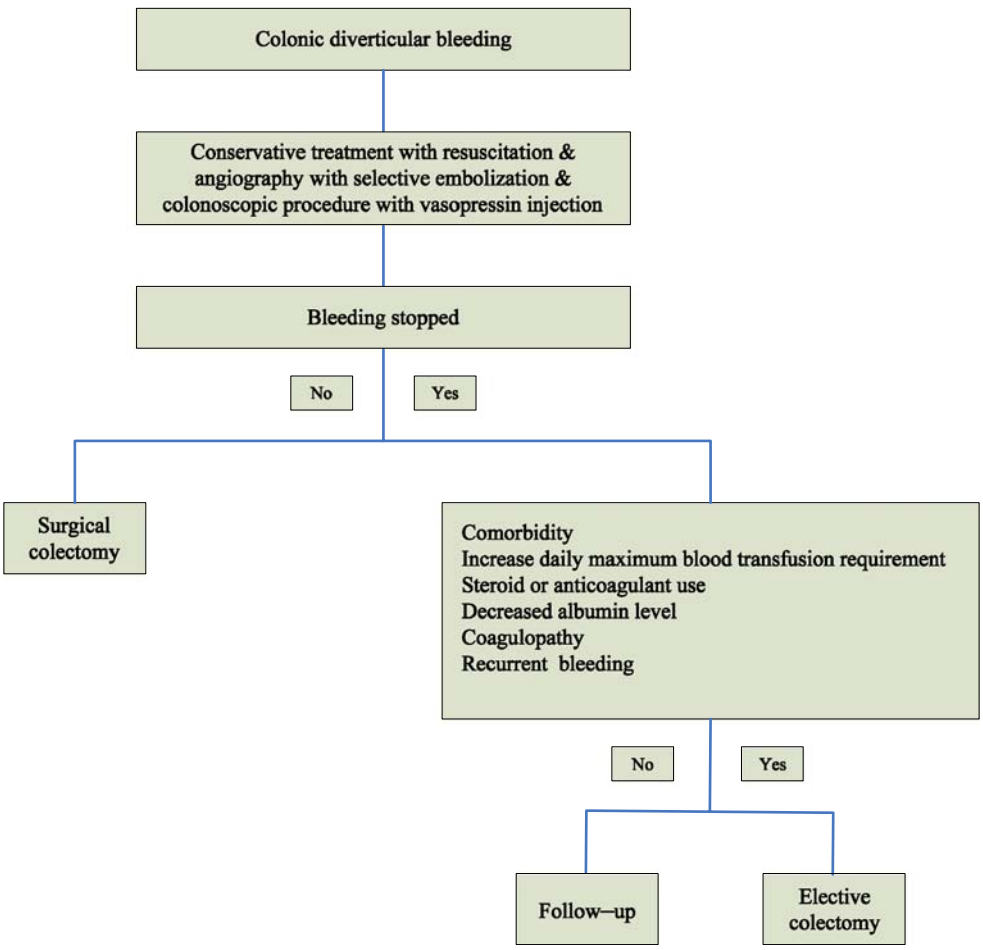

Figure 1 Management of patients with colonic diverticular bleeding.

diverticulosis. It has become increasingly clear that non-steroidal anti-inflammatory drugs may cause damage to both the upper gastrointestinal tract and the small and large intestines, including colonic colitis, ulcerations, and erosions. The inhibition of prostaglandin synthesis has been suggested to be responsible for the pathogenic mechanism.[13] In patients with gouty arthritis, continuation of their non-steroidal anti-inflammatory treatments was highly likely to impair colonic mucosal repair. Steroid treatment also has a negative effect on mucosal regenerative activity,[14] as was evident in our series. Of the other comorbidities examined, liver disease and uremia, which have obvious effects on the clotting process, did not significantly predict diverticular re-bleeding. This is probably because the number of patients with uremia in our series was small, and the severity of most liver cirrhosis in the patients in our sample was mild.

In the study by McGuire[15] published in 1994, bleeding stopped spontaneously in 75% of episodes and in 99% of patients requiring less than 4 U of transfusion per day, whereas bleeding continued in 25% of episodes and in most patients who required four or more units per day. In our patients, the maximum blood transfusion requirement was 4.70 U of packed red blood cells (PRBC) per day in the urgent surgery group and 1.81 U of PRBC per day in the conservative treatment group of CDB patients. The occurrence of recurrent bleeding and an increased requirement for blood transfusion predicted urgent colectomy in patients with CDB.

We used a further multivariate logistic regression analysis in which only preoperative comorbid diseases, including cardiovascular disease, type 2 diabetes, liver disease, peptic ulcer, pulmonary disease, gouty arthritis, and uremia (OR, 2.375, P=0.029), and the daily maximum blood transfusion requirement (OR, 1.386, P=0.031) had significant importance.

The main risk factor for mortality and morbidity in severe acute lower gastrointestinal bleeding is the presence of associated comorbidities.[7] In our results, comorbid diseases, which is permanent and cannot be omitted, is one of the risk factors relating to urgent colectomy. There were 13.7% of patients with CDB who had to receive urgent colectomy despite aggressive conservative treatment including angioembolization or urgent colonoscopic procedure. The mortality and morbidity rates in operated group are up to 20% each.

Conclusions

Approximately 25% of patients with CDB may develop further episodes of bleeding, and our data showed that 13.7% of patients needed urgent colectomy. On the basis of a multivariate analysis, it showed that the presence of comorbid diseases and increase daily maximum blood transfusion requirement are risk factors for urgent colectomy for CDB, and the mortality and morbidity are all very high (20%). Therefore, we suggested that elective surgical colectomy should be considered for patients exhibiting comorbid diseases, especially diabetes and gouty arthritis, after an episode of colonic diverticular bleeding which was stabilized conservatively in order to avoid the high mortality and morbidity rates of the urgent procedure (Fig. 1). The patients might have to take more risks in receiving urgent colectomy if they had more comorbid diseases. A limitation of our study is that the overall number of patients included in this study is not large, which this might be because minor colonic diverticular bleeding patients would not admit to the hospital. Nevertheless, the results of this retrospective study would reflect the patients of CDB who required surgical intervention mostly. Besides, as no data are available for the mortality and morbidity associated with elective surgery in CDB patients, a further study is required to confirm these results.

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ORIGINAL ARTICLE

Safety of Laparoscopic Total Mesorectal Excision for Low Rectal Cancer with Preoperative Chemoradiation Therapy

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Abstract
Introduction Total mesorectal excision (TME) with preoperative chemoradiation therapy is an accepted standard treatment for low rectal cancer. Although the laparoscopic approach is accepted for the treatment of colon cancer, its value for low rectal cancer is unknown. The purpose of this study was to evaluate whether preoperative chemoradiation therapy exerted an adverse influence on laparoscopic TME for low rectal cancer.
Methods We studied 125 consecutive patients who underwent laparoscopic TME for low rectal cancer. Twenty patients with preoperative chemoradiation therapy (CRT-Lap group) were compared with 105 patients without chemoradiation therapy (non-CRT-Lap group).
Results Operating time in the CRT-Lap group (276 min, range 160–390 min) was no different from that in the non-CRT-Lap group (263 min, range 143–456 min). The CRT-Lap group had more blood loss during the operation (70 *vs*. 37 ml), but mean blood loss was <100 ml. The distal tumor margin was longer in the CRT-Lap group (25.8 *vs*. 18.6 mm). The number of lymph node harvested did not differ between the groups (14.5 *vs*. 15.4). Conversion to open surgery was necessary only in one case in the non-CRT-Lap group. There was no anastomotic leakage in the CRT-Lap group, whereas three patients (3.1%) had anastomotic leakage in the non-CRT-Lap group.
Conclusion Laparoscopic TME with preoperative chemoradiation therapy is a safe procedure with reasonable operating time and does not appear to pose any threat to the surgical and oncologic outcomes.

Keywords TME · Laparoscopic · Low rectal cancer · Preoperative chemoradiation

Introduction

Laparoscopic resection of the colon is an accepted option for surgical treatment of colon cancer.[1,2] However, no comparable evidence is available to support laparoscopic surgery of rectal cancer at this time. Initial data in the MRC CLASICC trial showed a high conversion rate to open surgery (34%) and impaired short-term outcomes after laparoscopic anterior resection of rectal cancer, which do not justify its routine use. This indicates that laparoscopic rectal surgery is a technically difficult operation that requires advanced laparoscopic surgical skills.[2] While several non-randomized studies have suggested that laparoscopic surgery of rectal cancer is safe and feasible,[3–9] its use for rectal cancer remains controversial.

Total mesorectal excision (TME) is a standard procedure for low rectal cancer that has resulted in decreased local recurrence.[10] Recently, preoperative chemoradiation therapy for low rectal cancer has been shown to increase the probability of tumor resectability, improve sphincter preservation rate, decrease local recurrence, and improve both disease-free and overall survival.[11–13] However, recent

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studies have reported that operating time, blood loss, and the postoperative complication rate increase in TME with preoperative irradiation.[14–16] However, there are few reports about the effect of preoperative chemoradiation therapy on laparoscopic surgery. The purpose of this study was to evaluate whether preoperative chemoradiation therapy exerted an adverse influence on laparoscopic TME for low rectal cancer.

Materials and Methods

Patient Selection

From July 2005 to July 2008, 125 consecutive patients underwent laparoscopic TME for low rectal cancer with a distal margin less than 8 cm from the anal verge, following preoperative chemoradiation therapy (CRT-Lap group) or without preoperative chemoradiation therapy (non-CRT-Lap group). The indications for laparoscopic surgery in our institution include maximal tumor size <6 cm; no evidence of synchronous resectable liver metastasis; no evidence of invasion to adjacent organs; no evidence of ileus; and no evidence of lateral lymph node metastasis. Pre-treatment clinical staging was performed by using a combination of physical examination, cross-sectional imaging with either computed tomography or magnetic resonance imaging. Indications for neoadjuvant therapy were full-thickness rectal cancers (T3 or T4) staged by magnetic resonance imaging and/or node-positive disease; no evidence of distant metastases; and no history of prior radiation therapy to the pelvis. In practice, preoperative chemoradiation therapy tended to be selected to the patients with very low (tumor distance from the anal verge≤40 mm) locally advanced tumors to increase the chance of sphincter-preserving surgery in our institution. All patients received 5-fluorouracil (5-FU)-based chemoradiation with a total dose of 4,500 cGy of pelvic irradiation, which was administered five times weekly, with a daily fraction of 180 cGy. Twelve patients received concurrent oral 5-FU [doxiflurisine (5'-DFUR)], and two patients received intravenous 5-FU administration during irradiation. Surgical treatment was performed 4–8 weeks after the completion of preoperative chemoradiation. Pathological staging of the patients was performed according to the postoperative pathology report using the standard tumor–node–metastasis system and pathological complete response was defined as the absence of viable tumor cells in the specimen.

Informed consent was obtained from each patient. Data were prospectively collected for age, gender, body mass index, tumor staging, duration of operation, amount of blood loss, intraoperative blood transfusion, conversion to open surgery, and postoperative data including pathology, hospital stay, 30-day morbidity, and mortality.

Surgical Procedure

A five-port technique was employed: a 10-mm port below the navel, 5-mm ports on the upper right and left abdominal quadrants, and 12-mm ports on the lower right and left quadrants. The port on the right lower quadrants was positioned as low as possible, paying attention not to damage the femoral and inferior epigastric vessels. Medial-to-lateral retroperitoneal dissection of the mesocolon and early division of the inferior mesenteric vessels were performed, which preserved the inferior mesenteric plexus and superior hypogastric plexus. We used an Opti4™ Laparoscopic Handset and Electrodes with Curved Spatula Tip (Valleylab, Boulder, CO, USA) for the precise dissection. The dorsal dissection was performed in the avascular plane between the mesorectum and the parietal pelvic fascia, with preservation of the hypogastric nerve, sufficiently down to the floor of pelvis. In the dorsal dissection, we were careful not to damage the pelvic splanchnic nerve. Next, lateral dissection was completed by recognizing and preserving the hypogastric nerve and inferior hypogastric (pelvic) plexus. The dissection progressed to the endopelvic fascia and levator ani muscle. Great care was taken to preserve the neurovascular bundle in the anterolateral dissection. Thus, autonomic-nerve-preserving surgery was performed in principle, except in four cases in the non-CRT-Lap group, in which direct invasion to the neural plexus was suspected. In laparoscopic low or superlow (anastomotic site within 2 cm from the dentate line) anterior resection, we used an ENDOPATH Endo-Cutter or Echelon60 (Ethicon Endo-Surgery, Cincinnati, OH, USA) for rectal resection. Normally, two cartridges are used for complete resection. When the port is placed sufficiently caudally, the cartridge can be inserted at a right angle to the long axis of the rectum without changing the angle of its edge, as reported previously.[17] The specimen was extracted through the left quadrant port, which was extended to about 4 cm, and the anastomosis was completed intracorporeally by the double stapling technique. In intersphincteric resection, the specimen was extracted through the anus, and a handsewn coloanal anastomosis was performed. In cases of abdominoperineal resection, the specimen was retrieved through the perineal incision in the traditional fashion. The perineal wound was closed primarily and a terminal colostomy was constructed at the left lower quadrant site. All operations were performed under the supervision of a well-experienced board-certified laparoscopic colorectal surgeon (H.K.).

Statistical Analysis

Analysis was performed using Fisher's exact test, χ^2 test, and Mann–Whitney U test, when appropriate, to test

differences between the groups. Analysis was performed with SPSS software (Chicago, IL, USA) and $P \leq 0.05$ was considered to be significant.

Results

Over a 36-month period, a total of 125 consecutive patients who underwent laparoscopic resection for low rectal cancer were evaluated. Patient characteristics are summarized in Table 1. The mean age, gender, body mass index, and tumor size were comparable between both groups. The CRT-Lap group had a significantly lower distance from the anal verge to the lowest border of the tumor (32.5 *vs*. 49.1 mm) and higher T-staging. Four patients had pathological T0 disease, one had T1, six had T2, eight had T3, and one patient had T4 in the CRT-Lap group.

The surgical background is summarized in Table 2. The operative procedures were significantly different in both treatment groups. Rate of low or superlow anterior resection was 30.0% (six patients) in the CRT-Lap group and 74.3% (78 patients) in the non-CRT-Lap group. Rate of intersphincteric or abdominoperineal resection was 70.0% (14 patients) in the CRT-Lap group and 25.7% (27 patients) in the non-CRT-Lap group; these resections were undertaken because the tumor locations were too low. The rate of creating a diverting ileostomy was significantly higher in the CRT-Lap group than in the non-CRT-Lap group (100% *vs*. 36.8%). The mean operating time was comparable (276 *vs*. 263 min). The amount of estimated blood loss was significantly higher in the CRT-Lap group (70.3 *vs*. 37.3 ml). The longitudinal resection margins were longer in the CRT-Lap group than in the non-CRT-Lap group (25.8 *vs*. 18.6 mm). Only one positive longitudinal resection margin was detected in the non-CRT-Lap group (1.0%) for a patient who underwent intersphincteric resection. Positive circumferential resection margins were not identified in either group. The number of lymph nodes harvested was similar (14.5 *vs*. 15.4). Only one patient (1.0%) underwent intraoperative conversion to open surgery in the non-CRT-Lap group, due to bleeding from the internal iliac vein and additional dissection of lateral lymph nodes. No patients required intraoperative blood transfusion in either group.

The surgical outcome is summarized in Table 3. The rate of postoperative complications did not differ significantly between groups. Anastomotic leakage was observed in three cases (3.1%, excepting cases of abdominoperineal resection) in the non-CRT-Lap group. The rate of wound infection tended to have a higher incidence in the CRT-Lap group. The three cases of wound infection in the CRT-Lap group were perineal wound infection following abdominoperineal resection. One patient (5.0%) from the CRT-Lap group had ileus of >5 days duration and needed nasogastric tube decompression. Other complications in the non-CRT-Lap group include three cases of enterocolitis, one port site hernia, and two anastomotic bleeding. Three patients (2.9%) required re-operation in the non-CRT-Lap group; two patients underwent stoma construction for anastomotic leakage; and one patient underwent herniorrhaphy for port site hernia. No patients died in the hospital in either group. The mean length of hospital stay was comparable (21.2 *vs*. 18.4 days).

Table 1 Patient Characteristics

	CRT-Lap (n=20)	non-CRT-Lap (n=105)	P value
Mean age (year) (range)	61.1 (42–74)	61.4 (33–87)	0.6444
Male/female ratio	14/6	54/51	0.1476
Mean body mass index (kg/m^2) (range)	23.5 (19.6–31.7)	22.3 (15.4–33.4)	0.1925
Mean tumor size (mm) (range)	32.2 (10–45)	29.4 (7–90)	0.1170
Mean tumor distance from the anal verge (mm) (range)	32.5 (20–60)	49.1 (10–60)	<0.0001
Tumor stage[a]			<0.0001
Tis	0 (0%)	1 (1.0%)	
T1	0 (0%)	48 (45.7%)	
T2	0 (0%)	28 (26.7%)	
T3	19 (95.0%)	26 (24.8%)	
T4	1 (5.0%)	2 (1.9%)	
Nodal stage			0.8133
N0	16 (80.0%)	77 (73.3%)	
N1	3 (15.0%)	22 (21.0%)	
N2	1 (5.0%)	6 (5.7%)	
Grade of differentiation			0.1199
Well/moderately	18 (90.0%)	103 (98.1%)	
Poorly/mucinous	2 (10.0%)	2 (1.9%)	

[a] Tumor stage in the CRT-Lap group was preoperative stage

Discussion

Although laparoscopic colorectal resection is well established for colonic and upper rectal cancers, there are technical limitations with resection of middle and low rectal cancers.[2,3] In our hospital, however, laparoscopic TME has been positively employed for the treatment of rectal cancer, since it has the advantage of providing a good view, even in a narrow pelvis, and allowing us to perform more precise autonomic nerve preservation.[17]

There were different characteristics in both groups, including lower tumor location from the anal verge and more locally advanced tumor in the CRT-Lap group. This explains the higher rate of intersphinceric and abdominoperineal resection and construction of diverting ileostomy

Table 2 Surgical Backgrounds

	CRT-Lap (n=20)	non-CRT-Lap (n=105)	P value
Operative procedure			0.0011
Low anterior resection	0 (0%)	17 (16.2%)	
Superlow anterior resection	6 (30.0%)	61 (58.1%)	
Intersphincteric resection	8 (40.0%)	17 (16.2%)	
Abdominoperineal resection	6 (30.0%)	10 (9.5%)	
Temporary diversion	14/14 (100%)	35/95 (36.8%)	<0.0001
Mean operating time (min) (range)	276 (160–390)	263 (143–456)	0.2103
Mean estimated blood loss (ml) (range)	70.3 (0–235)	37.3 (0–740)	0.0290
Mean distal tumor margin (mm) (range)	25.8 (5–60)	18.6 (5–45)	0.1256
Invasion distal margin	0 (0%)	1 (1.0%)	1
Invasion circumferential margin	0 (0%)	0 (0%)	
Mean no. of lymph nodes harvested (range)	14.5 (10–26)	15.4 (8–52)	0.1295
Conversion to open surgery	0 (0%)	1 (1.0%)	1

in the CRT-Lap group. In open TME, shorter tumor distance from the anal verge is thought to be a major factor elongating operative time.[18] Nevertheless, the present study showed that both CRT-Lap and non-CRT-Lap groups had comparable operating times (276 *vs*. 263 min). Intraoperative blood loss was significantly higher in the CRT-Lap group, but average blood loss was <100 ml in both groups. Increased blood loss in the CRT-Lap group was partially explained by increased exudates, due to tissue inflammation and edema following chemoradiation therapy. Furthermore, although the preoperative chemoradiation therapy blurred the dissection plane due to fibrosis in some cases, nerve-preserving TME was successfully performed in all CRT-Lap cases. These results suggest that laparoscopic TME following CRT is safe and feasible.

In the present study, overall postoperative complication rate was comparable between both groups, and there were no serious complications or operative mortality. There was no anastomotic leakage in the CRT-Lap group and only three cases (3.1%) in the non-CRT-Lap group. These three cases underwent superlow anterior resection, one with covering ileostomy and two without covering ileostomy. The absence of anastomotic leakage in the CRT-Lap group may be explained by construction of covering stoma in all cases. Previous studies have reported much higher leakage rates in patients with laparoscopic resection for rectal cancer (13.5–17%).[4,8,9] Intracorporeal rectal transection and anastomosis are two of the most important and difficult parts of laparoscopic low anterior resection, and the technique is completely standardized in our institution, as reported previously.[17] Furthermore, a single experienced laparoscopic surgeon performed or supervised all the operations. This may explain the low incidence of anastomotic leakage in our institution, together with appropriate operating time, low blood loss, and very low conversion rate.

Table 3 Surgical Complications

	CRT-Lap (n=20)	non-CRT-Lap (n=105)	P value
Postoperative complication	4 (20.0%)	12 (11.4%)	0.4320
Anastomotic leakage	0 (0%)	3 (3.1%)	
Wound infection	3 (15.0%)	3 (2.9%)	
Persistent ileus	1 (5.0%)	0 (0%)	
Other	0 (0%)	6 (5.7%)	
Reoperation	0 (0%)	3 (2.9%)	1
Mean postoperative hospital stay (days) (range)	21.2 (11–52)	18.4 (5–123)	0.1411

The rate of wound infection was higher in the CRT-Lap group. A previous study has reported that preoperative irradiation is one of the risk factors for developing surgical site infection.[14] However, wound infections in the CRT-Lap group were perineal wound infections following abdominoperineal resection. These results suggest that a higher rate of wound infection may not be due to preoperative chemoradiation, but differences in operative procedures in the present study.

There are several important limitations of this study to be noted. First, this was not a randomized study; therefore, a longer follow-up is required to assess the true incidence of local recurrence and cancer-free survival. Second, the comparable operating time between both groups may be caused by the small sample size and different operative procedures performed. Particularly, different rate of abdominoperineal resection between both groups makes simple comparison difficult. However, supervision of all operations by a single experienced surgeon in a single surgical team can avoid the risk of bias within the early phase of the learning curve, or the intercenter variability of a multicenter trial. We believe that our study suggests that, with careful case selection and expertise, laparoscopic TME for low

rectal cancer following chemoradiation therapy is a safe procedure with a reasonable operating time and does not confer any oncological disadvantage.

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ORIGINAL ARTICLE

Laparoscopic Restorative Proctocolectomy with Ileal Pouch Anal Anastomosis: A Comparative Observational Study on Long-term Functional Results

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Abstract
Purpose Long-term results after laparoscopic ileal pouch anal anastomosis (IPAA) have not been thoroughly evaluated. Our study prospectively compares short- and long-term outcomes of laparoscopic and open IPAA.
Methods Between October 2002 and November 2007, 73 laparoscopic and 106 open IPAA patients were enrolled. Patient- and disease-specific characteristics and short- and long-term outcomes were prospectively collected.
Results There were no differences in demographics, treatment, indication, duration of surgery, and diversion between groups. Laparoscopic patients had faster return of flatus ($p=0.008$), faster assumption of a liquid diet ($p<0.001$), and less blood loss ($p=0.026$). While complications were similar, the incidence of incisional hernias was lower in the laparoscopic group ($p=0.011$). Mean follow-up was 24.8 months. Average number of bowel movements was 6.8±2.8/day for laparoscopy and 6.3±1.7 for open ($p=0.058$). Overall, 68.4% of patients were fully continent at 1 year, up to 83.7% long term without differences between groups. Other indicators of defecatory function and quality of life remain similar overtime.
Conclusions Laparoscopic IPAA confers excellent functional results. Most patients are fully continent and have an average of six bowel movements/day. When present, minor incontinence improves over time. Laparoscopy mirrors the results of open IPAA and is a valuable alternative to open surgery.

Keywords Ulcerative colitis · Laparoscopic surgery · Quality of life · Surgical outcomes

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Introduction

Despite significant advances in the medical treatment of ulcerative colitis (UC),[1,2] surgery still remains the definitive option for UC patients who fail medical management or are diagnosed with neoplastic degeneration. Restoration of intestinal continuity with an ileal pouch anal anastomosis (IPAA) is uniformly considered the gold standard of modern management of UC patients in need of surgical treatment. A laparoscopic approach to IPAA has been proposed not only in the adult[3,4] but also in the pediatric population.[5] While long-term function after conventional open IPAA has been extensively analyzed,[6,7] the results of laparoscopic IPAA have been reported only as single institution series[8] with short follow-up[9] or in small prospective randomized trials.[10,11]

From the limited data available, it is clear, however, that laparoscopic IPAA offers significant advantages over the open conventional procedure in terms of body image and

cosmesis.[11,12] Although these findings may have been expected, cosmesis and body image are important factors in the acceptance of surgery in this young patient population. The results of postoperative return of bowel function and analgesic requirements after laparoscopic IPAA have been less concordant. Although several authors have reported faster return of bowel function after laparoscopy, often associated with decreased use of narcotic pain medications,[9] these findings did not always translate into a shorter hospital stay.[10]

On the other side of the argument, concerns have been raised regarding the longer duration of surgery often reported even by very experienced laparoscopic colon and rectal surgeons.[9,10] Although this finding may in part reflect the learning curve of the surgical team, in studies comparing costs, longer duration of surgery often resulted in higher expenses.[10]

Though feasibility and safety remain the main issues when proposing a new procedure, especially for a benign condition in a young patient population, efficacy and functional results ought to be analyzed as well. Data on long-term sequelae after laparoscopic IPAA, such as the incidence on incisional hernias and bowel obstruction, have not to our knowledge been published. The same applies to pouch function and quality of life with very few studies reporting adequate follow-up.[8,9,11,12]

The number and quality of studies available does not allow us to draw any definitive conclusions on this topic to date. Clearly this is a procedure that requires a dedicated surgical team with highly sophisticated skills and expertise. To justify the additional training and expenses, long-term results of this procedure and the tangible benefits for our patients need to be further characterized. Since 2002 when laparoscopic IPAA was first introduced in our practice, we have been prospectively collecting data to answer some of these questions. In light of the need for long-term functional data on this topic, our current study was designed to prospectively analyze short- and long-term outcomes after laparoscopic IPAA in comparison with contemporary open IPAA from the same tertiary practice.

Materials and Methods

Patients and Operative Technique

Consecutive UC patients that were referred for surgery between August 2002 and November 2007 were evaluated for inclusion in this study. The decision to offer a laparoscopic approach was left to the surgeon's assessment. No formal inclusion or exclusion criteria were defined for this study; the decision to offer laparoscopy was left to the surgeon's judgment and experience. Although obesity and previous abdominal operations often make laparoscopic colorectal procedures difficult to complete, they were not considered absolute contraindications to laparoscopy in our study. As experience with the laparoscopic approach increased, laparoscopic-assisted IPAA has become the procedure of choice in our practice.

The indications for a stapled versus hand-sewn IPAA in our practice have been previously described[13] and were applied to both the open and the laparoscopic group. Briefly, hand-sewn IPAA with a transanal mucosectomy starting at the dentate line was recommended to patients whose colonoscopic biopsy showed evidence of dysplasia, irrespective of location and severity. Stapled IPAA was recommended only after the presence of dysplasia had been ruled out by multiple endoscopic biopsies.[13]

Although a hand-assisted approach is a valuable alternative to laparoscopic-assisted surgery, it has not been offered to any of our patients in this series.

All the patients underwent the procedure under elective circumstances. For our laparoscopic operations we used a five, 5-mm trocar approach (Fig. 1). In case of a previous abdominal colectomy, we would start the operation by taking down the ileostomy and gaining access to the peritoneal cavity through the ileostomy site where a 12-mm trocar would be placed. All the proctectomies were performed laparoscopically with intracorporeal vessel ligation after having identified the left ureter. The specimen was exteriorized through a suprapubic Pfannenstiel incision

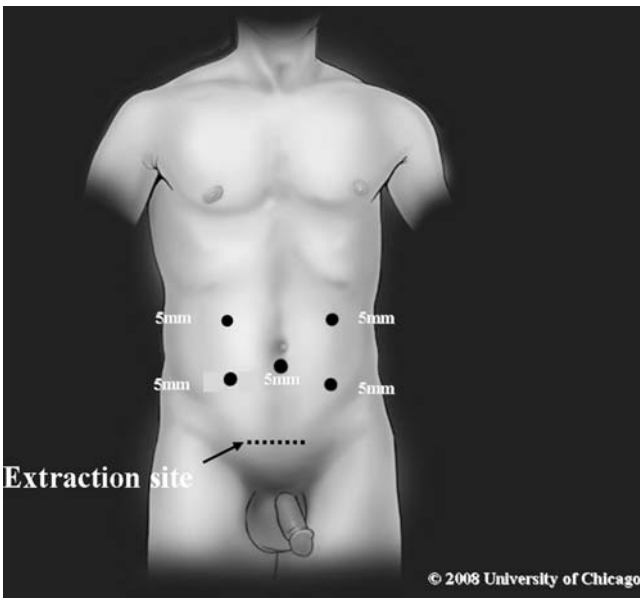

Figure 1 Trocars placement. Specimen extraction site. Five, 5-mm trocars are used for our laparoscopic approach. The specimen is exteriorized through a suprapubic incision. The vascular division is performed intracorporeally. The rectal transection, pouch construction, and the anastomosis are performed under direct vision through the Pfannenstiel incision.

(Fig. 1). The pouch was constructed according to the technique previously described.[14] The rectal transection, pouch construction, and anastomosis were performed under direct vision through the Pfannenstiel incision. Since an incision was needed to extract the specimen, we elected to place it in the suprapubic area as a classic Pfannenstiel incision to decrease the incidence of incisional hernia and to allow the transection of the specimen and the anastomosis to be performed under direct vision. We consistently used an open stapling device, as an endoscopic stapler often requires multiple applications to divide the rectum and thus leaves overlapping staple lines. The decision to construct a diverting ileostomy was left to the surgeon's intraoperative assessment in both groups, with ileostomy being performed when there was judged to be moderate or severe tension on the anastomosis. Conversions were defined as any diversion from the surgical plan involving early placement of an incision, irrespective of the size of the incision, or any completion of the mobilization of the specimen through the extraction site.[15]

Postoperative management did not follow a formal care path, but patients from both groups were treated similarly. Diet was advanced as bowel function resumed, with clears given upon passage of flatus and solids given after patients had a bowel movement. Pain was controlled with parenteral narcotics through patient-controlled analgesia, which was weaned as patient pain could be controlled with oral medications. Early postoperative mobilization was implemented equally for both groups, and patients were discharged once they were tolerating solid food, having bowel movements, and not requiring intravenous narcotics.

Patients' demographics, disease-specific characteristics, intraoperative variables, short-term perioperative results, and long-term postoperative outcomes were analyzed. The study was approved by the Institutional Review Board of the Division of Biologic Sciences of the University of Chicago.

Questionnaires and Data Analysis

Patients completed a previously validated two-part questionnaire at 3, 6, 9, 12, 18, and 24 months after the procedure and yearly thereafter.[7] Part I evaluated bowel habits and functional parameters as well as quality of life and adjustment to the new lifestyle following the operation. Part II consisted of a week-long diary of daily frequency, timing, and consistency of bowel movements, in addition to the timing and severity of any fecal incontinence episodes.

These surveys were followed by clinic visits in which the answers were evaluated, and diet and medications reviewed. Suggestions were made to improve functional results, but the surveys were not changed. The diary results for each patient were averaged over the 7-day period and expressed as mean number of daily bowel movements, daytime and nighttime bowel movements, and percentage of bowel movements that were solid, pasty, or liquid. Additional follow-up data, including long-term complications and need for additional surgery, were collected at the clinic visits.

The results were initially analyzed comparing the open and the laparoscopic groups, along with subgroup analyses when indicated, based on body mass index (BMI) and anastomotic technique (hand-sewn versus stapled) within and between the two groups.

Statistical Analysis

Statistical analysis was performed using SPSS 14.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using independent samples t tests, and categorical variables were analyzed with the Pearson χ^2 test. The Fisher Exact Test was used for categorical variables when there were fewer than five observations in a particular group. For questionnaire measures with more than two categories, the responses were dichotomized prior to analysis. A p value of less than 0.05 was considered to indicate statistical significance.

Results

Demographics

Of the 179 ulcerative colitis patients who underwent IPAA during the study period, 106 (59.2%) received an open IPAA and 73 (40.8%) a laparoscopic procedure. The percentage of patients undergoing a laparoscopic procedure has increased throughout the study period (Fig. 2). One laparoscopic patient required conversion to an open procedure for adhesions leaving a conversion rate of 1.4%. He was included in the laparoscopic group for intent to treat analysis (Table 1).

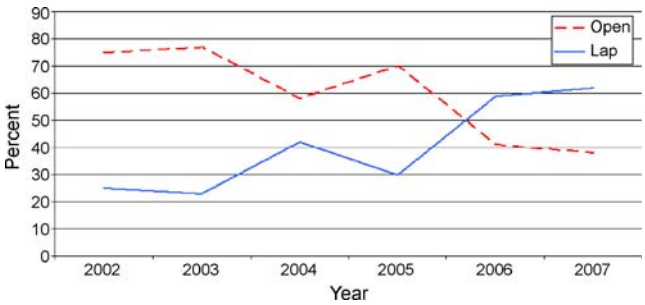

Figure 2 Distribution of the surgical procedures during the study. Over the course of the study, laparoscopic IPAA has become the preferred approach in UC patients in our practice.

Table 1 Patients' Demographics

	OPEN 106	LAP 73	*p* value
Age	36.9	36.3	0.719
Gender (% male)	57.8%	50.7%	0.348
Body mass index	24.6	23.6	0.059
Indication (failure of medical Tx)	83.3%	82.2%	0.675
Previous abdominal colectomy	54.9%	50.7%	0.581
Diverting ileostomy	71.6%	67.1%	0.528
Stapled IPAA	56.9%	79.5%	0.002

There were no significant differences in age, gender distribution, BMI, indication for surgery, percentage of patients that had undergone previous abdominal colectomy, and the use of a temporary diverting ileostomy between the groups. More patients in the laparoscopic group received a stapled IPAA (79.5% versus 56.9%, $p=0.002$). The mean follow-up was 24.8 months (range=3–60 months) and there was no difference in the length of follow-up between the two groups.

Perioperative Results

The duration of surgery was not different between groups, and blood loss was significantly less in the laparoscopic group ($p=0.026$). While the overall length of stay did not vary between groups, laparoscopic IPAA patients reported passage of flatus and tolerated a liquid diet approximately 1 day earlier than the open patients ($p=0.008$ and <0.001, respectively). The amount and duration of administration of parenteral narcotic pain medications were notably lower in the laparoscopic group but did not reach statistical significance (Table 2).

Postoperative Complications

There was a postoperative mortality in the laparoscopic group. The incidence of delayed return of bowel function, small bowel obstruction before or after closure of the ileostomy, and the need for surgical intervention to relieve bowel obstruction did not differ between groups. Also, the incidence of septic anastomotic complications or anastomotic strictures requiring mechanical dilatation did not differ between groups. While no patients in the laparoscopic group developed an incisional hernia, nine open IPAA patients (8.8%) were diagnosed with a hernia ($p=0.011$) and eight (7.8%) required surgical repair during the study period ($p=0.022$). Of these patients, 88.9% had a BMI >25. Pouch failure requiring excision was needed only in four open IPAA patients (3.9%), all for septic anastomotic complications. Three were suspicious for Crohn's disease and were converted to a permanent end ileostomy and one had her pouch reconstructed. This difference was not statistically significant (Table 3).

Frequency and Consistency of Bowel Movements

The overall average number of daily bowel movements for the two groups was not significantly different, nor was the average number of daytime or nighttime bowel movements. In the laparoscopic group, the fraction of bowel movements that were pasty in consistency was higher than the open group ($p=0.026$), while in the open group the fraction of bowel movements that were liquid in consistency was higher ($p=0.016$). To eliminate the potential bias of having a higher percentage of hand-sewn anastomosis patients in the open group, we performed a subgroup analysis of the hand-sewn and the stapled IPAA patients separately. Laparoscopic hand-sewn IPAA patients had more pasty bowel movements than the open group (70% versus 48%, $p=0.003$). The fraction of liquid bowel movements was not statistically different. Laparoscopic stapled IPAA patients had fewer liquid bowel movements than the open group (15.3% versus 22.9%, $p=0.008$), but the difference in pasty bowel movements was not statistically significant (Table 4).

Table 2 Perioperative Results

	OPEN 106	LAP 73	*p* value
Length of procedure (min)	321.5	335.4	0.233
Blood loss (ml)	305.0	231.5	0.026
First flatus (POD)	3.6	2.6	0.008
First bowel movement (POD)	4.8	4.8	0.988
Liquid diet (POD)	3.8	2.4	<0.001
Solid diet (POD)	5.4	5.5	0.822
Total amount of MSO_4 equivalent (mg)	304.5	247.8	0.140
Duration of parenteral narcotic (days)	4.9	4.4	0.177
Hospital stay (days)	7.4	8.3	0.135

Table 3 Postoperative Complications

	OPEN 106	LAP 73	*p* value
Hospital mortality	0.0%	1.4%	0.408
Prolonged ileus	2.9%	4.1%	0.695
SBO before ileostomy closure	1.0%	5.5%	0.162
Late SBO	12.7%	15.1%	0.660
Surgery for SBO	4.9%	9.6%	0.226
Anastomotic septic complications	11.8%	19.2%	0.174
Stricture requiring mechanical dilation	25.5%	19.2%	0.327
Incisional hernias	8.8%	0.0%	0.011
Surgery for incisional hernia	7.8%	0.0%	0.022
Pouch failure	3.9%	0.0%	0.141

SBO small bowel obstruction

Table 4 Frequency and Consistency of Bowel Movements

	OPEN 106	LAP 73	*p* value
Number of bowel movements/day	6.3	6.8	0.058
Daytime bowel movements	5.3	5.7	0.081
Nighttime bowel movements	1.0	1.1	0.171
Formed bowel movements	29.0%	25.6%	0.351
Pasty bowel movements	49.1%	57.1%	0.026
Liquid bowel movements	21.8%	16.3%	0.016

Continence

No significant differences in fecal continence were noted between the two groups. During the entire study period, only 20.8% of the laparoscopic patients and 21.9% of the open patients experienced some degree of incontinence. Similar were the fraction of patients with minor leakage (18.5% in the laparoscopic group and 20.2% in the open) and the fraction with major loss of stool (6.9% in the laparoscopic and 7.1% in the open). In line with our previous data, an improvement of continence function was evident over time in both groups.[7] There were no differences in continence results within the hand-sewn and the stapled IPAA groups or within the overweight group (Table 5).

Defecatory Function

Protective pad usage mirrored the consistency of bowel movements data, with fewer laparoscopic IPAA patients wearing pads during the daytime ($p<0.001$) and nighttime ($p<0.001$), likely as a consequence of their lower fraction of liquid bowel movements. There was also a significantly lower fraction of patients reporting frequent perianal rash in the laparoscopic IPAA patients ($p=0.021$). No significant differences were noted between the two groups for the other indicators of defecatory function. In the subgroup analysis, more overweight open IPAA patients wore protective pads at night than overweight laparoscopic patients (35% versus 16.3%, $p=0.024$) and more patients in the stapled open IPAA group wore protective pads at night than in the stapled laparoscopic (20% versus 10%, $p=0.041$; Table 6).

Table 5 Continence

	OPEN 106	LAP 73	*p* value
Fully continent—entire follow-up	78.1%	79.2%	0.817
Fully continent—1 year	68.5%	68.3%	0.981
Fully continent—>1 year	83.1%	84.6%	0.837
Minor leakage—entire follow-up	20.2%	18.5%	0.699
Minor leakage—1 year	29.6%	26.8%	0.764
Minor leakage—>1 year	15.4%	15.4%	1.000
Major leakage—entire follow-up	7.1%	6.9%	0.951
Major leakage—1 year	11.1%	9.8%	1.000
Major leakage—>1 year	4.6%	2.6%	1.000

Table 6 Defecatory Function

	OPEN 106	LAP 73	*p* value
Wear pad during day	25.6%	7.6%	<0.001
Wear pad during night	33.3%	14.4%	<0.001
Frequent perianal rash	44.6%	31.8%	0.021
Frequent rectal itching	68.7%	64.0%	0.367
Frequently able to delay BM	89.8%	90.5%	0.842
Frequently able to distinguish flatus from stool	38.3%	43.0%	0.392
Use medications to control BM	68.7%	63.7%	0.344
Alter diet to control BM	57.6%	57.7%	0.987
Change eating times to control BM	41.4%	40.4%	0.859

BM bowel movements

Quality of Life

In both groups, the large majority of patients similarly rated their quality of life as "better" or "much better" compared to before their IPAA or to before the ileostomy closure. There were no significant differences between groups in the percentage of patients who reported "excellent" or "good" satisfaction with the operation or in the fraction whose adjustment to the new lifestyle imposed by the operation was rated as "excellent" or "good". In both groups, the large majority of patients would recommend the procedure to others. There were no differences in quality of life or satisfaction results within the hand-sewn and the stapled IPAA groups or within the overweight patients group (Table 7).

Discussion

We have very meticulously collected data on pouch function and outcomes in our UC patients for over two decades,[7,14,16–19] for a better understanding of the correct indications for this life-changing operation and to better

Table 7 Quality of Life

	OPEN 106	LAP 73	*p* value
QOL (better or much better)	82.1%	87.2%	0.215
QOL compared to the ileostomy (better or much better)	95.2%	95.0%	0.965
Satisfaction (excellent or good)	91.5%	85.7%	0.103
Adjustment (excellent or good)	87.1%	85.7%	0.726
Recommend operation	98.9%	95.2%	0.067

QOL quality of life

educate our patients. When laparoscopic IPAA was introduced in our practice in 2002, we designed this study to expand our knowledge and analysis to this new surgical approach. At the beginning of our experience, very limited data on laparoscopic IPAA were available and relatively little has been written on this topic since then.[3,4,8–12,20,21]

Our study offers a detailed analysis of the results of the last 5 years of laparoscopic pouch surgery for UC in a tertiary referral practice compared with the results of the contemporary open pouch surgery group. Overall, the two groups had very similar patient characteristics despite the lack of randomization. Even though the laparoscopic group includes the early phases of our learning curve, perioperative results are quite comparable between the two groups. The longer duration of laparoscopic surgery noted by many authors[9,21] was not present in our series, despite similar BMI and incidence of previous colectomy between groups. The higher number of hand-sewn anastomoses in the open group may appear to have affected this result, but even when hand-sewn patients are eliminated from both groups for analysis, the operative times remain similar.

In the perioperative period, we observed a faster return of bowel function, represented by passage of flatus and assumption of a liquid diet, in the laparoscopic group, as has been previously described.[4,9] However, these findings did not translate into a shorter hospital stay despite similar percentages of patients with a diverting stoma and similar incidence of postoperative complications between the two groups. Other authors have found the same discrepancy[10] between return of bowel function and hospital stay.

The incidence of incisional hernia after laparotomy has been reported to be as high as 20% after a 10-year period.[22] More recent studies have reported an incidence after colorectal surgery of between 12.9% and 14.7% with a follow-up up to approximately 5 years.[23,24] Both studies have also reported a significant lower incidence of incisional hernias after laparoscopic colorectal resections.[23,24] Based on anecdotal experience, we believe the incidence of incisional hernias to be significantly higher than reported after open surgery in the inflammatory bowel disease population with increased risk associated with malnutrition, long-term steroid use, chronic illness, and obesity that is not an uncommon finding even in inflammatory bowel disease patients. In our study, we found 8.8% of the open group with incisional hernias, with a follow-up of 24.8 months. We are expecting the incidence of incisional hernias in these patients to increase with the length of follow-up. With these concerns in mind, we have planned our laparoscopic approach to include a Pfannenstiel incision for both the extraction site and for pouch construction and anastomosis. A classic Pfannenstiel incision is a true muscle sparing incision that causes minimal weakening of the abdominal wall, thus in part explaining the fact that we have not seen any incisional hernias in the laparoscopic IPAA patients, even in those that have required an ileostomy closure. We will continue to follow these patients.

Another advantage of the Pfannenstiel incision is the ability to transect the rectum under direct vision using an open stapling device, thus avoiding multiple applications often needed with an endoscopic stapler with the resulting overlapping staple lines. Furthermore, through the Pfannenstiel, we are able to truly construct the pouch in the same way as we have described for the open approach[14] and to complete the anastomosis under direct vision. By keeping the pouch construction and anastomosis consistent between the two groups, we have been able to duplicate the results previously published in our large open series.[7] The difference noted in consistency of bowel movements and pad usage in favor of our laparoscopic IPAA group is difficult to explain and we will continue to investigate it during further follow-up.

One of the major limitations of the study is the lack of randomization. Additionally, as we have become increasingly comfortable with laparoscopic IPAA since adopting it in 2002, we have offered this approach to more patients, so we were not able to maintain formal inclusion or exclusion criteria for laparoscopy over the course of this study. These methodological drawbacks, however, did not result in significant differences between the characteristics of the two groups, so we believe the results we obtained are valid and valuable. Although some patients in our study did have as much as 5 years of follow-up, the average follow-up for all patients was only slightly over 2 years. While we will continue to follow these patients, we have reason to believe from our previous study[7] that functional results after a 12- to 18-month adjustment period generally remain stable over the years to come, so the results from this study are likely to reflect the outcomes that would be found over an even more extended follow-up period.

Conclusions

Our study, like others currently available in the literature, supports the use of laparoscopy in UC patients in need of an IPAA. Laparoscopic IPAA provides comparable results to the traditional open approach, offers some short-term and very promising long-term benefits, and confers excellent functional outcomes.

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MULTIMEDIA ARTICLE

Totally Transumbilical Laparoscopic Cholecystectomy

Andrew A. Gumbs · Luca Milone · Prashant Sinha · Marc Bessler

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Abstract A recently convened Consortium at the Cleveland Clinic agreed on the term Laparo-Endoscopic Single-Site (LESS) surgery to describe minimally invasive techniques that use a single incision to accomplish laparoscopic procedures. These procedures are done by using either a single port through one fascial incision or multiple ports placed through separate fascial incisions. Because of cost containment issues and the lack of widespread availability of a single port, we currently use multiple reusable ports placed through three separate fascial incisions via a transumbilical incision. As opposed to standard laparoscopic cholecystectomy, a deflecting laparoscope and one articulating instrument are utilized to improve the safety and ease of this procedure. Presented in this video are the steps necessary to perform a LESS cholecystectomy via a transumbilical incision with commercially available instruments.

Keywords Single port surgery · SPA · Transumbilical endoscopic surgery · TUES · Single incision surgery

Introduction

With the advent of natural orifice transluminal endoscopic surgery (NOTES), and the acknowledged limitations of the current technology, single port access (SPA) has emerged as a viable and more widely applicable minimally invasive technique.[1–3] Unfortunately, access to a single port that allows for SPA has been limited to small numbers of academic centers.[4,5] In an effort to exploit the benefits of single-incision laparoscopic surgery, some centers have begun performing minimally invasive surgery in this manner to further improve cosmesis and potentially reduce postoperative pain.[6,7] Presented here are the steps necessary to perform totally transumbilical laparoscopic cholecystectomy (TTLC) with the use of commercially available technology.

Material and Methods

As with all new technology, patient selection is paramount during the initial period of one's experience. To perform TTLC we make a 2-cm incision through the umbilicus until the fascia is identified. Using three separate fascial sites, three 5-mm reusable trocars are placed after pneumoperitoneum to 15 Torr is obtained using the Veress needle. Intra-abdominal visualization should be obtained with a 5-mm deflecting laparoscope (LTF-VP Deflectable Tip Video Laparoscope, Olympus Surgical America, Orangeburg, NY, USA). The deflecting scope is necessary to minimize external interference of the instrument handles. Because only two other instruments are used, it is imperative to grasp the gallbladder in the "sweet spot," to enable the exposure of both the Triangle of Calot and retract the cystic duct off of the common bile duct. Because all instruments are transumbilical, at least one articulating instrument (Realhand, Novare Surgical Systems, Cupertino, CA, USA) will be necessary to accomplish this and stay out of the line of view of the optic port. A straight laparoscopic instrument can then used to perform the dissection just as in a standard laparoscopic cholecystectomy.

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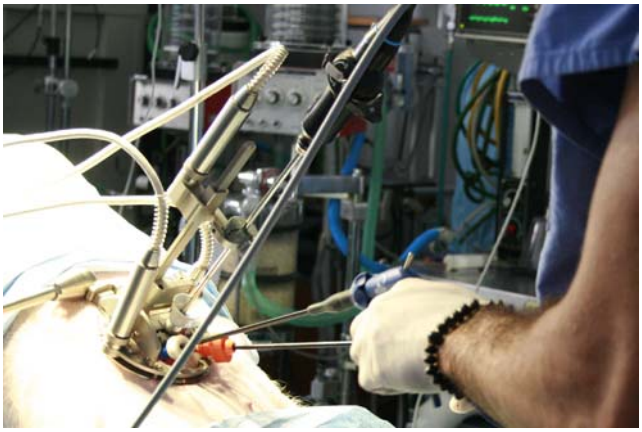

Figure 1 Image of robotically assisted single incision surgery. The robotically controlled camera holder, ViKY (Vision Kontrol for endoscopY; ViKY Ste Endocontrol-Medical SAS 38000, Grenoble, France) is holding a 5-mm deflecting scope (LTF-VP Deflectable Tip Video Laparoscope, Olympus Surgical America, Orangeburg, NY, USA). Two articulating 5-mm laparoscopic instruments (Realhand, Novare Surgical Systems, Cupertino, CA, USA) are being used.

Results

At our institution, two patients have been enrolled in an Institutional Review Board (IRB)-approved study to evaluate the safety and efficacy of this technique. Both procedures took less than 60 minutes and both patients were discharged home in less than 20 hours. To date, no wound infections or hernias have developed. We have recently begun performing totally transumbilical procedures with a robotically controlled camera holder in an animal model (Fig. 1) (Vision Kontrol for endoscopY; ViKY Ste Endocontrol-Medical SAS 38000, Grenoble, France).[8] To date, we have successfully performed a partial hepatectomy, distal pancreatectomy, and sleeve gastrectomy with robotic assistance in animals.

Conclusion

Totally transumbilical minimally invasive surgery (TTMIS) is feasible. Although single ports are coming on the market, enabling so-called SPA surgery, the TT technique obviates the need for this device and may help reduce costs. The use of a deflecting scope and an articulating instrument greatly reduces the "learning curve" of this procedure. More complex procedures may require two articulating instruments. Robotic assistance may further reduce operating room times and allow for the successful performance of more complex procedures with TT minimally invasive techniques in humans.

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CASE REPORT

Pancreatic Adenocarcinoma in the Pregnant Patient: A Case Report and Literature Review

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Abstract Pancreatic cancer is the fifth most common cause of cancer-related death in the USA. However, the antepartum diagnosis of pancreatic adenocarcinoma in the pregnant patient is exceedingly rare, with only six cases previously reported in the literature. Optimizing both maternal and fetal health outcomes is particularly challenging when surgical procedures are necessary for staging and/or therapeutic purposes—as these interventions often pose significant risks to both the mother and the developing fetus. In this article, we report a case of pancreatic adenocarcinoma diagnosed during pregnancy and review the literature on the management issues confronted in this unique clinical situation.

Keywords Pancreatic cancer · Pregnancy · Pancreaticoduodenectomy · Adenocarcinoma

Case

A 40-year-old G2P1 Caucasian female with no significant past medical history was transferred from an outside hospital at 24 weeks gestation with a 2-week history of epigastric pain, nausea and vomiting, early satiety, anorexia, reflux, and a 9-lb weight loss. She had been started on ranitidine 2 weeks earlier by her obstetrician without relief of symptoms. One week later, she was hospitalized for nausea, vomiting, and dehydration. An abdominal ultrasound revealed biliary sludge. She was discharged on a low fat diet and aluminum hydroxide/magnesium hydroxide with mild symptomatic improvement but was readmitted 3 days later due to persistent failure to thrive. At that time, laboratory studies revealed amylase 1,032 IU/L, alanine aminotransferase (ALT) 87 IU/L, and aspartate aminotransferase (AST) 37 IU/L. Abdominal ultrasound again showed biliary sludge with common bile duct dilation (1.7 cm) and no evidence of cholelithiasis or choledocholithiasis. Her condition was ascribed to cholecystitis and "gallstone pancreatitis". After developing soft, light colored stools and dark colored urine, the patient was ultimately transferred to our hospital for endoscopic retrograde cholangiopancreatography (ERCP) and further evaluation.

On admission, the patient was afebrile with normal vital signs. Physical exam revealed a gravid uterus, active bowel sounds, and mild epigastric tenderness to deep palpation. No scleral icterus or peritoneal signs were noted. There was no Murphy's sign. No fetal abnormalities were noted on pelvic ultrasound. Repeat laboratory evaluation revealed white blood cell 9.0 K/μL, hematocrit 30.4%, platelets 268 K/μL, international normalized ratio 1.1, total bilirubin 3.6 mg/dL, direct bilirubin 2.6 mg/dL, AST 42 IU/L, ALT

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106 IU/L, alkaline phosphatase 137 IU/L, amylase 850 IU/L, and lipase 709 IU/L.

Relief of the biliary obstruction by ERCP was unsuccessful due to a large duodenal ulcer with edema, local compression, and evidence of gastric outlet obstruction. Magnetic resonance cholangiopancreatography, chosen in deference to computed tomography for the safety of the fetus, revealed a "double-duct" sign—marked dilatation of the intrahepatic and extrahepatic biliary system, with the common bile duct measuring 2 cm distally and dilatation of the pancreatic duct measuring up to 9 mm in diameter (Fig. 1). Sludge in the gallbladder and distal common bile duct was again recognized. An area of increased signal was also noted within the posterior wall of the duodenum 2 cm caudal to the ampulla. Endoscopic ultrasound demonstrated duodenal wall thickening.

One week later, an ERCP was again attempted but was limited by postbulbar ulcer and stricture of the duodenum. Duodenal mucosal biopsy revealed invasive adenocarcinoma with lymphovascular involvement (Fig. 2). Because of the diagnosis of malignancy, a computed tomography angiogram was necessary to adequately stage the lesion in preparation for potentially curative resection. This revealed a 3.5×2.5-cm mass located in the groove between the head of the pancreas and the second portion of the duodenum (Fig. 3). A percutaneous cholecystostomy tube was placed and liver function tests improved. She did not take any food or liquid by mouth and was placed on total parenteral nutrition (TPN) until surgical resection. Amylase and lipase normalized after this period of prolonged bowel rest. Serum CA 19–9 drawn at admission returned elevated at 4,309 U/mL. In order to optimize maternal and fetal outcomes, a multidisciplinary approach involving the family, the neonatologist, perinatologists, surgeons, and oncologists ensued. A collaborative decision was made to proceed with delivery at 28 weeks. A cesarean was chosen for delivery due to concern for a long induction of labor despite her history of a successful home birth. At 28 weeks, after betamethasone

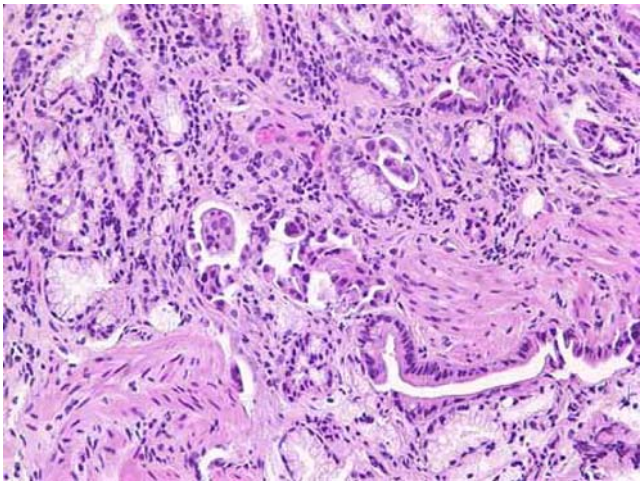

Figure 2 Duodenal biopsy showing invasive adenocarcinoma with lymphovascular involvement. ×20 magnification. Hematoxylin and eosin.

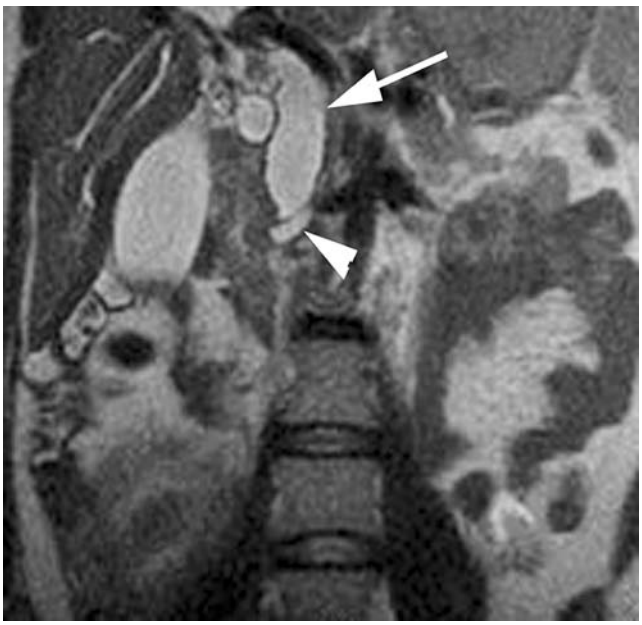

Figure 1 Coronal section from T2 weighted magnetic resonance image depicts marked dilatation of the common bile duct (*arrow*) and pancreatic duct (*arrowhead*).

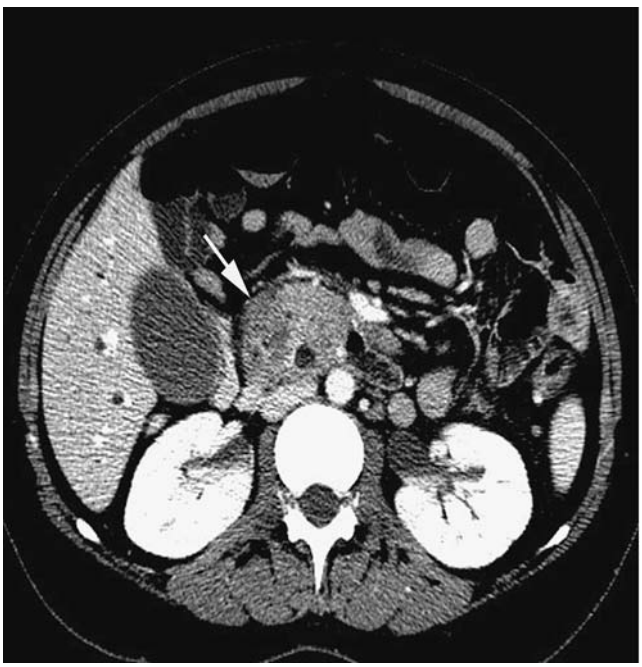

Figure 3 Axial contrast-enhanced computed tomographic image reveals a 3.5×2.5-cm hypoechoic mass (*arrow*) located between the head of the pancreas and the second portion of the duodenum.

was given for fetal benefit, the patient underwent a low transverse cesarean section via Pfannenstiel incision. She delivered a 2-lb 10-oz female with Apgar scores of 8 and 8 at 1 and 5 min, respectively. Her daughter was discharged home 10 weeks after delivery in good health.

Approximately 2 weeks later, magnetic resonance imaging (MRI) of the abdomen did not reveal any vascular invasion, peritoneal metastases, or abnormal lymph nodes. The patient and her husband were informed of the risks and benefits of surgical resection and chose to pursue aggressive therapy because of the possibility of cure. The patient also desired more immediate relief of her persistent biliary tract and gastric outlet obstruction, requiring cholecystostomy tube drainage and intermittent nasogastric tube drainage and TPN, respectively. Fifteen days following caesarean section, the patient underwent an uncomplicated pancreaticoduodenectomy (Whipple procedure). Surgical pathology revealed a 5-cm moderately differentiated stage III pancreatic adenocarcinoma with lymphatic and vascular invasion. Three out of eight lymph nodes obtained were positive for adenocarcinoma. Surgical margins were clear. She was discharged home uneventfully 9 days postoperatively. Despite aggressive chemotherapy, the patient developed metastatic liver disease 2 months after surgery and died of metastatic pancreatic adenocarcinoma 6 months after the Whipple procedure.

Discussion

Pancreatic Cancer: Epidemiology and Risk Factors

Pancreatic cancer continues to be one of the most lethal cancers worldwide. Although pancreatic cancer comprises only 2% of all new cancers diagnosed in the USA, it is the fifth leading cause of cancer death in this country.[1] While survival rates for other cancers have improved with new advances in treatment, those for pancreatic cancer have remained essentially unchanged over the past 25 years. This is likely attributable to the aggressive nature of this disease, limited screening and treatment options, and the relatively limited resources—both human and fiscal—afforded to research. Today, patients with pancreatic cancer have an overall 5-year survival rate of 3–5%.[2] This improves to 20% for the select subset of patients afforded potentially curative surgical resection.

Although the exact causes of pancreatic cancer have yet to be elucidated, several risk factors have been identified. These include advanced age (disease is rare before age 45); male gender (male-to-female ratio 1.3:1); African-American ethnicity; comorbidities such as diabetes, obesity, and chronic pancreatitis; and smoking, which increases the risk of pancreatic cancer approximately twofold.[3,4] Two percent of all pancreatic cancer is inherited. One means of inheritance is through familial cancer kindreds, with first-degree relatives affected by the disease. Several genetic syndromes and germline mutations, including familial breast–ovarian syndrome (BRCA2 gene mutation), familial atypical multiple mole melanoma (p16 gene mutation), Peutz–Jeghers syndrome, familial pancreatitis, and hereditary nonpolyposis colorectal cancer syndrome, have also been linked to pancreatic cancer, but these gene mutations are estimated to account for less than 20% of the inherited cases.[4,5]

Pancreatic cancer is unusual in women of childbearing age and extremely rare among pregnant women, with only six previously reported cases of pancreatic adenocarcinoma diagnosed antepartum.[6–11] While pancreatic cancer is unusual in pregnancy, malignancy—of any form—in pregnancy is not rare. It has been estimated that one in 1,000 pregnancies will be complicated by a diagnosis of cancer.[12] In addition, 0.2% to 1.0% of all pregnant women require nonobstetrical general surgery, independent of underlying cause.[13] Optimizing both maternal and fetal health outcomes is particularly challenging in the case of malignancy, when surgical intervention is necessary for staging or therapeutic purposes, and little data exist to guide management in such cases. Similarly, little is known about the relative maternal consequences of delaying surgical intervention to safeguard fetal maturation. These issues are particularly important for patients with aggressive malignancies like pancreatic adenocarcinoma, where early surgical intervention for those with resectable disease is the only potential for cure.

Surgical Management: Options for the Pregnant Patient

Pancreatic cancers are typically categorized as resectable, locally advanced/unresectable, or metastatic. Most cases of pancreatic adenocarcinoma are diagnosed when the disease is in the advanced stages. Only 15–20% of patients have resectable disease at the time of diagnosis,[1] and recent data suggest that only a fifth of these patients are appropriately referred to a surgeon for assessment.[14] Resectable disease is characterized by an absence of metastatic disease or distant lymphatic involvement outside the boundaries of resection (i.e., celiac, aortocaval, iliac basins), patent superior mesenteric–portal venous confluence, and a lack of involvement of the superior mesenteric artery or celiac axis.[4] Locally advanced disease pertains to those cases in which the pancreatic tumor encases a vascular structure. While both locally advanced disease and metastatic disease call for palliative chemoradiation therapy or supportive care, only those patients with resectable disease have an opportunity for cure, albeit slim.

In this case, initial work-up and diagnostic imaging appeared to be consistent with resectable disease. The pregnancy was at 24 weeks gestation, posing three treatment options: (1) risk pregnancy termination or poor fetal outcome and proceed with immediate surgical resection intrapartum, (2) delay surgery to term to maximize fetal outcome and risk maternal disease progression, or (3) perform surgical resection at the earliest gestational age associated with good fetal viability (delivery at 28 weeks associated with a 90–95% survival rate at most tertiary care centers)[15] and risk fetal complications of premature birth and potential maternal disease progression. The timing of illness is crucial to the decision-making process. In this case, the diagnosis was before the time of fetal viability. The patient's health care team felt that the risk for significant disease progression was relatively low over a 4-week period and that delaying delivery until 28 weeks gestation followed by a Whipple procedure was a reasonable approach to balance and maximize both maternal and fetal outcomes, based on the patient's wishes. But because of the aggressive biologic behavior of pancreatic adenocarcinoma, it is unlikely that this short, but deliberate, delay had either a positive or negative effect upon the mother's ultimate survival. However, given the extremely small number of reported pancreatic cancers diagnosed during pregnancy, there are no randomized controlled trials to guide decision making in an evidence-based manner, and even anecdotal experience with this population is extremely limited.

We reviewed the six cases of pancreatic adenocarcinoma diagnosed antepartum previously published in the English literature (Table 1). Gamberdella reported a 37-year-old patient who presented at 24 weeks gestation with right chondral burning, epigastric discomfort, weight loss, insomnia, and anxiety.[6] An exploratory laparotomy revealed a 4-cm lesion in the head of the pancreas. The patient opted to delay surgical resection until delivery and had healthy twins at 32 weeks by cesarean section. An "advanced pancreatic tumor" was discovered at delivery. She underwent palliative therapy and died of metastatic disease 3 months following delivery. Simchuk et al. described a 39-year-old woman who presented at 16 weeks gestation with right upper quadrant pain and anorexia.[7] An unresectable tumor in the head of the pancreas was found during a planned Whipple procedure at 20 weeks gestation and palliative bypass procedures were performed instead with concurrent tocolytic infusion. The patient delivered a healthy baby at 28 weeks by cesarean section. She died a few weeks after delivery. Blackbourne et al. reported a 32-year-old patient who presented at 17 weeks gestation with back pain, nausea, emesis, dark urine, scleral icterus, and hyperemesis.[8] While receiving continuous tocolytic infusion, a pylorus-preserving pancreaticoduodenectomy was performed around the time of diagnosis. Three months following surgery, the fetus was developing normally. Further information regarding maternal outcome was not discussed. Gojnic et al. described a 37-year old woman who presented in the second trimester of pregnancy (specific gestational age not provided) with abdominal pain and frequent fatty stools alternating with constipation.[9] The patient initially underwent a caesarean section and hysterectomy. She subsequently had a pancreatic resection. At the time of publication, the patient and infant were alive and well. Marinoni et al. reported a 38-year-old woman who presented at 27 weeks with obstructive jaundice and secondary pancreatitis.[10] Biopsy showed intraductal carcinoma of the pancreas. MRI revealed a 4-cm mass in the head of the pancreas as well as liver and lung metastases. A female infant was delivered at 30 weeks gestation by caesarean section. The patient died 50 days after delivery. Finally, Su et al. reported a 37-year-old who presented at 22 weeks gestation with epigastric pain.[11] An abdominal ultrasound revealed a mass in the head of the pancreas. Biopsy confirmed poorly differentiated metastatic adenocarcinoma. The patient decided to terminate the pregnancy at 24 weeks and proceed with chemotherapy. She died 4 weeks after diagnosis.

There are three additional reported cases of pancreatic adenocarcinoma in pregnancy.[16–18] However, in these cases, the diagnosis was made postpartum, and they are therefore not within the scope of this discussion. Two additional cases of pancreatic mucinous cystadenocarcinoma diagnosed antepartum have also been reported[19,20]; these cases have been excluded from this review due to the different biology and prognosis of cystadenocarcinoma.

The two most salient factors in determining a treatment strategy for pancreatic cancer diagnosed antepartum are the stage of disease and the gestational age. Clinical decision making must simultaneously address the risk for maternal disease progression while maximizing fetal development and survival for those patients who wish to continue the pregnancy. The decision to continue the pregnancy should be made by the patient and her family in consultation with an interdisciplinary team including a high-risk obstetrician, a neonatologist, an oncologist, and a pancreatic surgeon. In patients diagnosed with resectable disease in the first trimester, delaying surgical intervention by an additional 3–6 months could move the patient from resectable to locally advanced/unresectable disease, with an attendant decrease in median survival—18–26 months following surgical resection as compared to approximately 7 months with palliative therapy alone.[21] Delay at any stage could also pose additional risks to the pregnancy, including metastases to the placenta.[18]

Other fetal and technical factors also affect timing decisions. Surgical intervention during the first trimester

Table 1 Pancreatic Adenocarcinoma Diagnosed During Pregnancy: A Review of the Literature[6–11]

Author, Date of publication	Age of patient (years)	Gestational age at diagnosis (weeks)	Gestational age at surgery (weeks)	Intraoperative findings	Tumor type	Type of surgery performed (intent)	Maternal outcome	Fetal outcome
Gamberdella[6]	37	24	32	Nonresectable disease	Pancreatic adenocarcinoma	Cholecystostomy (palliative)	Patient died 3 months after delivery	Healthy twins delivered at 32 weeks gestation
Simchuk et al.[7]	39	16	Approximately 20	Nonresectable disease	Low-grade, well-differentiated adenocarcinoma	Choledochoduodenostomy and feeding jejunostomy (palliative)	Patient died a few weeks after delivery	Healthy male delivered at 28 weeks
Blackbourne et al.[8]	32	17	Approximately 17	Resectable disease	Partially cystic, mucinous adenocarcinoma	Pylorus-preserving pancreaticoduodenectomy (curative)	Patient data not discussed beyond the first 3 months after surgery	Fetus developing normally 3 months following surgery (pregnancy outcome not reported)
Gojnic et al.[9]	37	Second trimester (exact date not reported)	N/a (delivery of the fetus occurred during the second trimester, before tumor resection)	Resectable disease	Pancreatic adenocarcinoma	Pancreatic resection (details unspecified; curative)	Patient alive as of date of publication (unknown interval)	Live newborn female
Marinoni et al.[10]	38	28	Approximately 28	Nonresectable disease	Intraductal carcinoma of the pancreas	Transabdominal cholecystostomy (palliative)	Patient died 50 days after delivery	Healthy female delivered at 30 weeks
Su et al.[11]	37	22	N/a (no surgical intervention; disseminated disease at diagnosis)	N/a	Stage IV pancreatic adenocarcinoma	N/a	Patient died 4 weeks after diagnosis	Termination of pregnancy with vaginal misoprostol occurred at 24 weeks

portends an increased risk for spontaneous abortion.[22] During the third trimester, the size of the uterus may prohibit successful surgical intervention, given compromised access to the pancreas. Therefore, many feel that the second trimester is the most ideal time for surgical intervention. The risk of general anesthesia is also believed to be lowest then.[13] For patients with unresectable or metastatic disease, palliative surgical intervention can be considered.

Pancreaticoduodenectomy for adenocarcinoma, and other indications, has been performed during pregnancy.[8,23–26] Notably, most of these cases were performed in the second trimester and none resulted in preterm labor or maternal complications. Most infants fared well. One, delivered at 27 weeks, died secondary to intraventricular hemorrhage, although the relationship of this outcome to maternal surgery at 20 weeks is not clear.[23]

Chemoradiation therapy is an additional management consideration for resectable pancreatic cancer, both in adjuvant and neoadjuvant formats,[27] but has obvious limitations during pregnancy. Most patients are not physically ready to begin adjuvant chemoradiation until 6 weeks after surgical resection, which further delays time to treatment, allowing more time for disease progression if surgery is delayed. Further studies are needed to determine the relative efficacy of delayed adjuvant therapy if surgical resection is performed prenatally. Finally, it is important to contextualize decisions regarding the timing of surgical intervention with the overall risk and benefit of the surgery itself. While the mortality risk associated with pancreaticoduodenectomy is less than 2% in the hands of a specialist, morbidity rates are still high (around 50%) and the 5-year survival rate after pancreaticoduodenectomy for pancreatic cancer is only about 15%.[4,28] Furthermore, as evidenced from this review, the expected maternal survival in this specific scenario is even more modest. This fact may considerably impact the patient's choice of treatment.

Pancreatic cancer in pregnancy is a rare and devastating diagnosis. Challenges to early diagnosis include the frequency of nausea, vomiting, and/or biliary disease in pregnant women. Clues to the diagnosis in this case included weight loss and refractory symptoms associated with marked enzyme abnormalities. While early diagnosis may not alter long-term outcome, it may provide the patient with an earlier opportunity to evaluate decisions related to the pregnancy. In these rare cases, the treatment plan needs to cater to the individual needs of the patient, the stage of disease, the patient's desire to continue the pregnancy, and the risks and benefits of delaying surgery. Here, initially resectable disease ultimately led to death from metastatic cancer with only a 4-week delay in surgical resection. Whether earlier intervention could have altered this outcome is doubtful. It is notable that in four of five previously reported cases with known longer-term outcome, the patient died weeks to months following surgery and/or delivery, irrespective of whether surgery was delayed or performed (all four had unresectable disease at the time of surgery). The fifth case, distinguished by its favorable maternal outcome, is notable for resectable disease at the time of surgery and the delivery of a healthy newborn. However, although both patient and infant were alive at the time of publication, the time interval between delivery and publication is not specified. The remaining (sixth) case of antepartum diagnosis of pancreatic adenocarcinoma involves a patient who also had resectable disease at the time of surgery but does not provide any survival data beyond 3 months postsurgical resection, at which time the patient was still pregnant and the fetus was developing normally. Taken together, these data suggest an important role for earliest possible surgical intervention in cases where resection is possible and maternal outcome is prioritized. Additional data describing maternal survival as a function of disease stage and time to surgery would contribute to the challenging risk/benefit analysis of optimal management strategies in this extremely vulnerable population.

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HOW I DO IT

Laparoscopic Esophagomyotomy for Achalasia: How I Do It

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Abstract
Introduction The pathophysiology, diagnosis, and treatment options for achalasia are briefly discussed, followed by a description of the minimally invasive surgical approaches to this disease, as practiced by the authors.
Summary Laparoscopic myotomy is performed routinely at our institution in the lithotomy position under endoscopic control. The techniques for performing the myotomy, the use of fundoplication, and the adaptation of this approach to use the surgical robot are described. Laparoscopic esophagomyotomy has been highly effective, durable, safe, and widely accepted by patients. There is less data about the robotic approach, but increased degrees of freedom afforded by articulation in the instruments promises finer control and possibly lower perforation rates.

Keywords Esophagus · Esophageal · Achalasia · Laparoscopy · Robotics · Fundoplication

Introduction

Achalasia is a functional esophageal disorder manifest by aperistalsis of the esophageal body, failure of lower esophageal sphincter (LES) relaxation, and, in most cases, abnormally elevated LES pressure. The disease is characterized pathologically by the disappearance of ganglionic cells in the esophageal myenteric plexus, likely triggered by an immune or autoimmune disorder. Patients initially complain of non-specific symptoms such as heartburn, which may be mistaken early for gastroesophageal reflux disease. Later, dysphagia and chest pain are the more prominent and specific symptoms for this problem. Unlike strictures of the esophagus, solids and liquids equally induce dysphagia. Over time, increased intraluminal pressure causes laxity of the esophageal wall and marked esophageal dilatation so that it assumes a sigmoid appearance. The risk of esophageal cancer is increased in patients with long-standing achalasia.[1–3]

A diagnosis of achalasia is established with several studies. Chest X-ray is normal early in the disease, but barium swallow usually reveals esophageal dilatation, poor emptying of barium into the stomach, and an area of apparent narrowing in the esophagus at the LES. This classic bird beak appearance (Fig. 1) is characteristic of this disease. Manometry is the most useful test to establish the diagnosis, because it directly confirms aperistalsis of the esophageal body, failure of LES relaxation with swallowing, and elevated LES pressure. Upper gastrointestinal endoscopy excludes benign and malignant esophageal strictures. The endoscope distinguishes fixed strictures (scar or tumor) from physiological stricture caused by elevated LES pressure when, with gentle pressure, it passes into the stomach. Esophageal biopsies are performed to exclude tumor.

Treatment

No treatment addresses the lack of ganglion cells. Rather, successful treatments are aimed at lowering LES pressure so that food passes more easily into the stomach with

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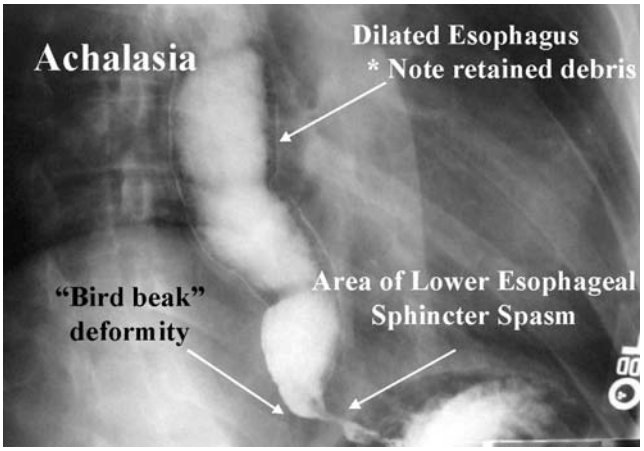

Figure 1 A barium swallow in a patient with achalasia is shown illustrating the classic features of this disease. The esophagus is dilated and contains retained and undigested food (debris). A segment of physiological narrowing caused by the high-pressure zone across the lower esophageal sphincter and failure of the sphincter to relax with swallowing is apparent. The classic bird beak deformity is characteristic of the achalasia.

gravity. Four modalities have efficacy. Drugs such as amyl nitrate, sublingual nitroglycerin, theophylline, and calcium channel blockers reduce LES pressure, but do not maintain a sustained response. They are used as a bridge to more definitive treatment, but otherwise have little utility in the management of this disease. Injection of botulinum toxin into the LES reduces resting pressure, but only improves about 1/3 of patients, and only by about 30%. Responses are transient (6–12 months) and repeat treatments are even less effective. Some surgeons believe the inflammation that occurs after botulinum injection increases the risk of intraoperative perforation if surgical myotomy is performed later. Moreover, there have been recent reports of pediatric deaths with off label use of Botox, making the use of Botox for this purpose even more controversial. We do not, therefore, recommend Botox for treatment of most patients with achalasia, although we continue to see patients who have been treated before referral to us. If used at all, this modality is best reserved for high-risk patients with limited life expectancy. Forced pneumatic esophageal balloon dilatation and surgically performed esophagomyotomy are the most useful treatments because they disrupt muscle fibers destroying the function of the LES.[1,2,4–6]

Balloon dilatation is performed with specially designed balloons ranging in diameter from 30 to 40 mm. Treatment effectiveness increases with balloon diameter, but so does the perforation rate. Patients are initially treated with a 30 mm balloon and may be retreated with a 35 mm balloon, if results are not satisfactory. Perforation rate (less than 3%) is acceptable with this strategy. Perforation rate rises when treatment is performed with the 40 mm balloon, but success rate does not. Good clinical results are obtained in 80–85% of patients using 1–2 dilatations. Many patients are evaluated, counseled and treated by a gastroenterologist before being referred to us. If treated by pneumatic dilatation, a single dilatation suffices in most patients. Failures of dilatation are candidates for surgery but some gastroenterologists choose a second treatment. We believe that, if two treatments do not yield good results, it is unlikely that further dilatations will be effective. Therefore, patients who fail two dilatations are considered to have failed non-operative therapy and are clear candidates for operation. Failures of balloon dilatation can be salvaged by performing esophagomyotomy. Likewise, we have had some success salvaging patients sent to us with failed myotomies using balloon dilatation.

Perforation after balloon dilatation can be successfully treated by immediate operative closure of the perforation and a myotomy on the opposite side of the esophagus if the esophageal perforation is recognized early. Patients with pain and/or tachycardia should be studied promptly to exclude esophageal perforation. A Gastrografin swallow is performed but if negative should be followed by a barium study. If a perforation is documented, the patient is taken to the operating room for either laparotomy or thoracotomy, depending on the location of the perforation. When diagnosed early, before inflammation is established in the surrounding tissues, the perforation can be closed in two layers (mucosal and muscular layers). The esophagus is then rolled to expose the side opposite the perforation and a myotomy is performed to relieve the symptoms of achalasia. The myotomy also facilitates healing of the perforation by decreasing the distal lower esophageal pressure and physiological distal obstruction. The site of repair of the perforation is then buttressed using a partial fundoplication or a pleural flap. It is reported that esophageal perforations after balloon dilatation have been successfully accomplished laparoscopically.

Patients who present with a massively dilated esophagus, a so-called sigmoid esophagus, do poorly with both balloon dilatation and esophagomyotomy. At this point, the esophagus is so flaccid and tortuous that destroying the LES no longer affords benefit. These patients are likely best treated with esophagectomy and esophageal replacement using a gastric tube or colon. Patients with markedly dilated esophagus, who do not yet have a sigmoid esophagus, may benefit from balloon dilatation or esophagomyotomy. However, success rates with these procedures are much lower than the reported overall results. Even if successful initially, the response may not be durable in these patients. They should be counseled about expectations for success specific for their situation.

Esophagomyotomy

Increasingly, patients present to us for consideration for surgery as an initial treatment. Surgical disruption of muscle fibers across the high-pressure zone was first described in the early 20th century by Heller. Heller performed both anterior and posterior myotomies using a thoracic approach. Subsequent modifications of Heller's procedure shortened the myotomy, eliminated the posterior myotomy, and approached the esophagus through the abdomen. The morbidity of and recovery from open thoracic and abdominal approaches favor balloon dilatation. Operative intervention was usually reserved for patients who failed pneumatic dilatation. Development of highly effective minimally invasive approaches for esophagomyotomy has more recently resulted in increasing popularity for primary operative treatment of achalasia.[1,7–19]

Patients are counseled about various methods of treatment, success and failure rates for operation, peri-operative expectations, and operative risks, especially the risk of conversion to open operation and esophageal perforation. It is also important for patients to understand that the operation, if successful, will markedly improve swallowing but will not restore normal swallowing since peristalsis remains abnormal. In addition, we review and discuss risks, benefits, and outcomes of open thoracic or abdominal approaches, video-assisted thoroscopic methods, and laparoscopic esophagomyotomy as well as the alternate medical treatments described above. All surgical approaches and patients undergoing pneumatic dilatation complicated by perforation of the esophagus require a general anesthesia. Each patient is then carefully evaluated for co-morbidities. Operative and anesthetic risks are estimated. If operation is not contraindicated, we recommend laparoscopic surgery to most patients, based on the outcomes reported in the literature. Success rates in relieving symptoms with laparoscopic esophagomyotomy exceed 90%, and complication rates, such as perforation with surgery, are acceptable. Most perforations are recognized at the time of surgery and repaired successfully without sequelae.[1,7–19]

Laparoscopic Esophagomyotomy

Patients are prepared for operation with several days of liquid diet to minimize retained material in the esophagus. A single dose of antibiotics is given within an hour of surgery to cover bacterial flora proliferating in the static esophagus in case perforation of the esophagus occurs. A patient with a dilated esophagus, which may contain secretions and debris despite preoperative liquid diet, is at risk for aspiration during induction of anesthesia and intubation. Therefore, strict attention to aspiration precautions, such as keeping the head of the bed elevated, cricoid pressure, and rapid sequence induction, should be followed.

We perform laparoscopic esophagomyotomy in a modified lithotomy or split-leg position and stand between the patient's legs (Fig. 2). Placement of monitors is important. The primary monitor is placed at the patient's head at eye level so that it can be viewed without turning or tilting the head. Surgeon comfort is important during precise dissection of the esophageal muscle. By necessity, the anesthesiologist is positioned above and to the right of the patient to allow positioning of the monitor.

Five ports are used to gain access to the upper abdomen and are positioned in a manner similar to laparoscopic fundoplication (Fig. 2). A camera port is placed in the midline above the umbilicus, but can also be placed to the left of the midline through the rectus muscle. A 30° or 45° scope is used. Retraction of the left lobe of the liver is accomplished with a Nathanson retractor placed through a 5-mm incision in the midline just below the xiphoid process of the sternum. A left lateral port is placed in the midaxillary line below the costal margin for retraction of the stomach. Two additional ports in the right and left midaxillary lines below the costal margins are required for dissection and suturing.

We begin the operation by dividing the upper short gastric vessels with ultrasonically activated scissors until the left crus of the diaphragm is identified. The dissection is carried posterior to the esophagus, freeing attachments of the stomach and esophagus to the posterior abdominal cavity. We then direct attention to the right side of the stomach. An opening is created in the gastrohepatic ligament, and the right crus of the diaphragm are identified. Dissection is begun in the right posterior mediastinum, the right posterior vagus nerve is identified and preserved; posterior attachments are freed to create a window behind the esophagus so that a Penrose drain can be placed for further retraction. Dissection is continued until at least 6 cm of esophagus is mobilized into the abdomen. The left anterior vagus nerve is identified and protected so that it is not injured during the myotomy.

We perform the myotomy with upper endoscopic control. It is important that this is performed by a skilled endoscopist. Careful manipulation of the scope as the myotomy is performed and while examining the completed myotomy is essential for minimizing mucosal damage and perforation. First, the extent of the zone of increased LES pressure is marked by the surgeon, as the upper and lower borders are transluminated by the endoscope. Others advocate use of intraoperative manometry, but this technique

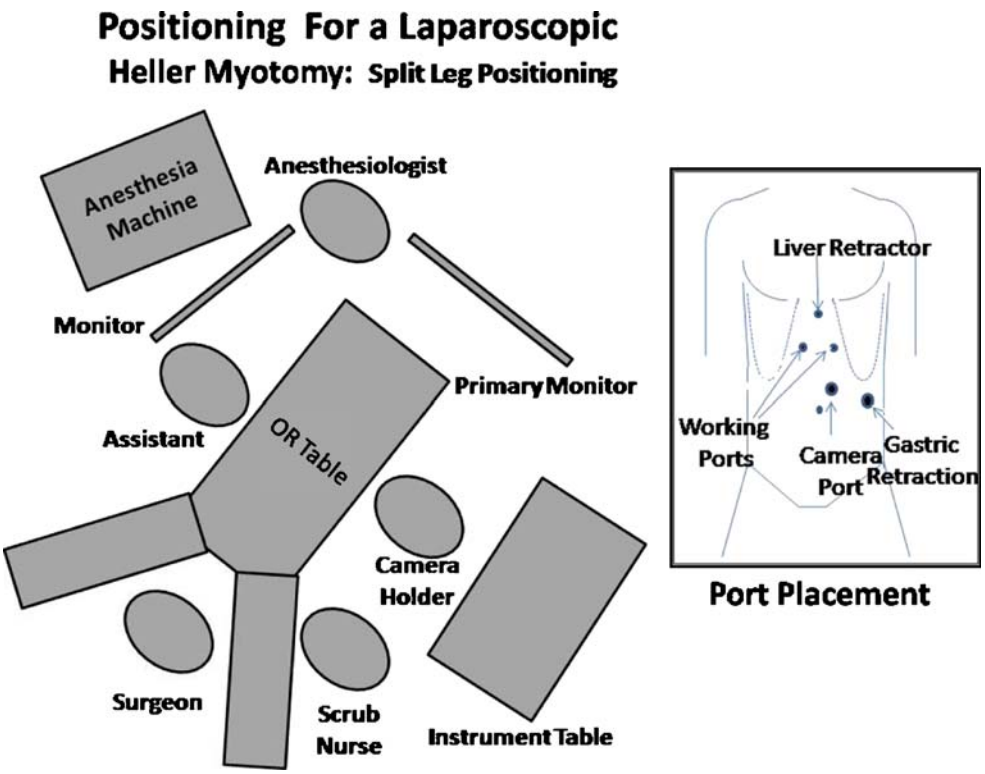

Figure 2 Positioning of the patient in the operating room is illustrated. The patient is placed in a modified lithotomy, split-leg position, with the surgeon between the patient's legs. This allows in-line viewing of the primary monitor for surgeon comfort. Trocars are placed in a manner similar to fundoplication.

requires a high degree of expertise with both the use and interpretation of intraoperative manometry.[16,19] The position of the myotomy depends on the type of fundoplication to be performed. The myotomy is begun by separating esophageal longitudinal fibers with sharp and blunt dissection. The defect is enlarged using bipolar scissors, a hook dissector with electrocautery, or the harmonic scalpel. Care is taken to limit application of electrocautery adjacent to the mucosa. Circular fibers are noted and divided sharply, although dissection is facilitated by bluntly using Maryland graspers and/or a Kitner dissector. This maneuver is very useful in disrupting small muscle fibers and undermining muscle to allow bulging of the mucus. The scope is advanced as the myotomy is performed to monitor progress. Esophageal translumination facilitates identification of circular muscle fibers which need to be cut (Fig. 3). The myotomy is extended from at least the distal 6 cm of esophagus onto the proximal 2 cm gastric cardia (Fig. 4). The exact length of the myotomy on the stomach is determined by insufflating air through the endoscope to visualize relaxation of the esophagogastric junction. This ensures completeness of the myotomy without extending the myotomy too far onto the stomach, since overly aggressive myotomy increases the incidence of reflux. At the completion of the myotomy, the upper abdominal cavity is filled with saline and the mucosa is checked for leaks by insufflating the esophagus with air. Small perforations manifest as bubbles (Fig. 5). Avoidance of injury to the mucosa is optimal, but if perforation occurs, the mucosa is closed with 4-0 absorbable sutures. Repaired perforations should be bolstered with a partial wrap that covers the myotomy.

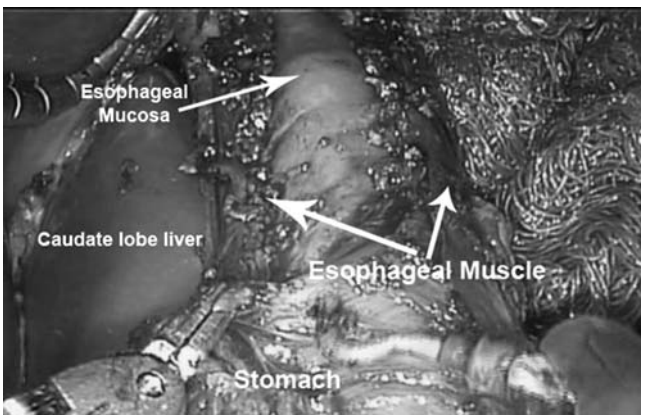

Figure 3 The illustration is taken from an esophageal myotomy performed using the robotic technique. However, the illustration is applicable to laparoscopic myotomy. Only the instrumentation differs. The esophageal portion of the myotomy has been completed and the esophageal mucosa (*arrow*) is bulging between the divided esophageal muscle (right and left edges labeled with *arrows*). The myotomy is now being carried onto the stomach. This is a critical portion of the procedure and perforation is common in this location since the esophageal and gastric muscle fibers interdigitate. The stomach fibers are being carefully dissected using a grasper (left instrument) and hook cautery (right instrument).

Figure 4 Dissection of fibers at the esophageal–gastric junction is further illustrated. Dissection over the stomach can be somewhat awkward with rigid, non-articulating laparoscopic instruments. The precision with which the fibers can be bluntly dissected, held, and, when necessary, cauterized with the robotic instruments is demonstrated.

Antireflux Procedures with Laparoscopic Esophagomyotomy

The need for fundoplication after myotomy is controversial. Fifteen to 30% of patients develop symptoms of GI reflux postoperatively, although most of the symptoms in these individuals can be controlled with medications.[1,7,12–14,20,21] However, the incidence of reflux is decreased by minimizing mobilization of the esophagus (so-called minimal dissection myotomy) or with a partial fundoplication. Richards and co-workers randomized 43 patients in a prospective manner to Heller myotomy or Heller myotomy plus a Dor procedure.[23] Gastroesophageal reflux, assessed using 24-h pH data, occurred in ten of 21 patients who had a Heller alone, while only two of 22 patients were found to have pathologic reflux when a Dor procedure was added. Relief of LES spasm and dysphagia was similar in both groups. In general, two types of fundoplication are employed: a Dor procedure (partial anterior wrap) or a Toupet fundoplication (270° posterior wrap—Figs. 6 and 7).[1,2,7,12–14,20,21] Both types provide antireflux protection and can be fashioned to cover the myotomy site protecting against perforation. A full wrap (Nissen fundoplication) is usually avoided because of poor esophageal motility in patients with achalasia.

When a Dor anterior fundoplication is performed, the left anterior vagus nerve is dissected free from the esophagus and moved to the right. The myotomy is performed in the left anterior esophagus. When completed, the anterior fundus of the stomach is advanced superiorly to cover the myotomy. This is accomplished by suturing the superior cardia of the stomach to the left crura. The anterior cardia is then advanced upward and to the right and is sutured to the right to cover the myotomy anchoring it to the right side of the myotomy and right crura with two sutures. The upper of these sutures incorporates the right crura while the lower is to the right side of the myotomy alone.

If a Toupet posterior fundoplication is to be performed, the posterior window behind the esophagus must be developed to easily accommodate the posterior fundus of the stomach. The myotomy is performed on the right anterior esophagus, to the right of the anterior vagus. The distal myotomy may have to be carried beneath the vagus without injuring the nerve. Once the myotomy is complete, the fundus is brought through the posterior esophageal window, ensuring that the fundus remains in position without holding it in place. We anchor the fundus to the right crus, ensuring that it rests in position without tension

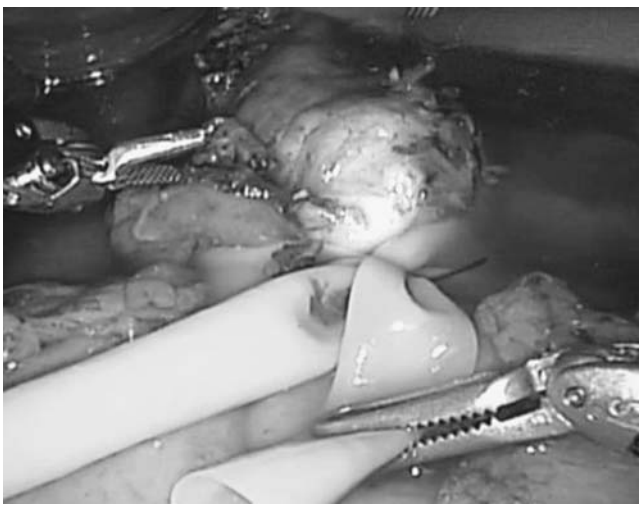

Figure 5 The completed myotomy is shown and the esophagus is being tested for small leaks. The esophagus is being insufflated with air through the endoscope with the upper abdomen filled with saline. The endoscope is also used to verify that the myotomy is complete and the esophagus and esophageal–gastric junction is widely patent. Note that the light from the endoscope can easily be seen as it transluminates through the esophageal mucosa.

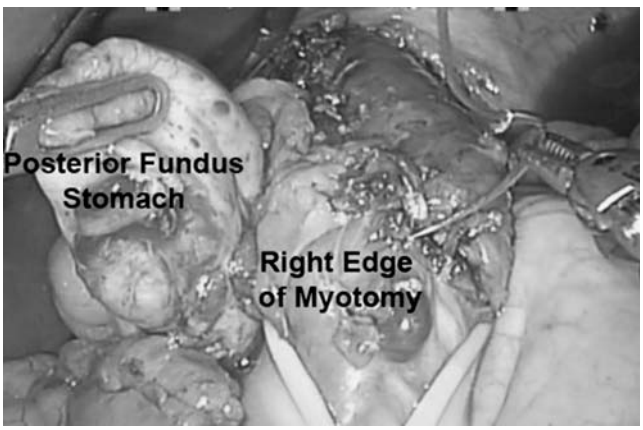

Figure 6 A Toupet fundoplication was constructed by creating a window behind the stomach and sewing the posterior fundus, which is brought through the window, to the right edge of the myotomy.

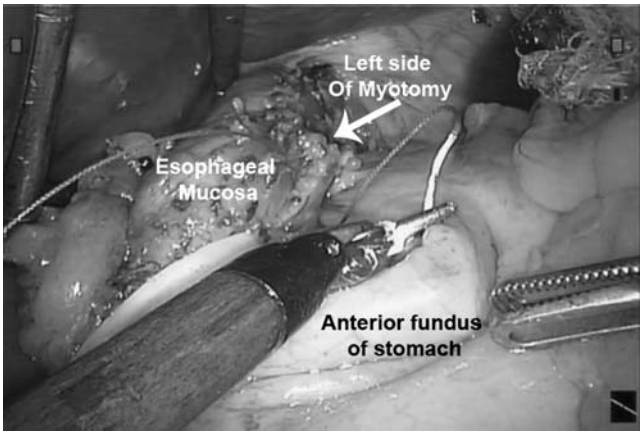

Figure 7 The procedure is competed by sewing the anterior fundus to the left edge of the myotomy.

(Figs. 5 and 6). The partial wrap is then completed by suturing the anterior fundus to the left side of the esophagus, so that 270° of the esophagus is wrapped in the fundoplication. The stomach is then sewn to the right side of the myotomy with non-absorbable sutures. If the myotomy is to be covered, a sufficient portion of fundus must remain so that it can be pulled over the defect and sutured without tension to the left side of the myotomy, or it may close the myotomy.

Robotic Esophagomyotomy

Robotically assisted myotomy is performed in a manner similar to the open and laparoscopic approaches. The advantages lie in its ability to provide superior visualization and more degrees of freedom of movement of the instruments during performance of the myotomy. The robotic Heller myotomy is an excellent example of how robotic technology may facilitate performance of a delicate procedure, translating into safer operations and improved outcomes. The disadvantage lies in the size and bulk of the instrument which changes several approaches to the patient and the time it takes to set up the device. Most groups, including ours, have robotic set-up times that approximate 15 min. On the other hand, some series have reported initial times as long as 1 h. Set-up of the robotic arms is associated with a learning curve, which will be variable, but certainly lessens as the operative team consistently works in the robotic operating room and if the robot is routinely used for other procedures.

Some surgeons believe that the added dexterity greatly decreases intraoperative perforation rate. Melvin et al.[21], reported a series of 104 patients from three institutions who underwent robotic esophagomyotomy without a perforation. In a randomized study by Horgan et al.[22], there were no intraoperative perforations in a group of 59 patients

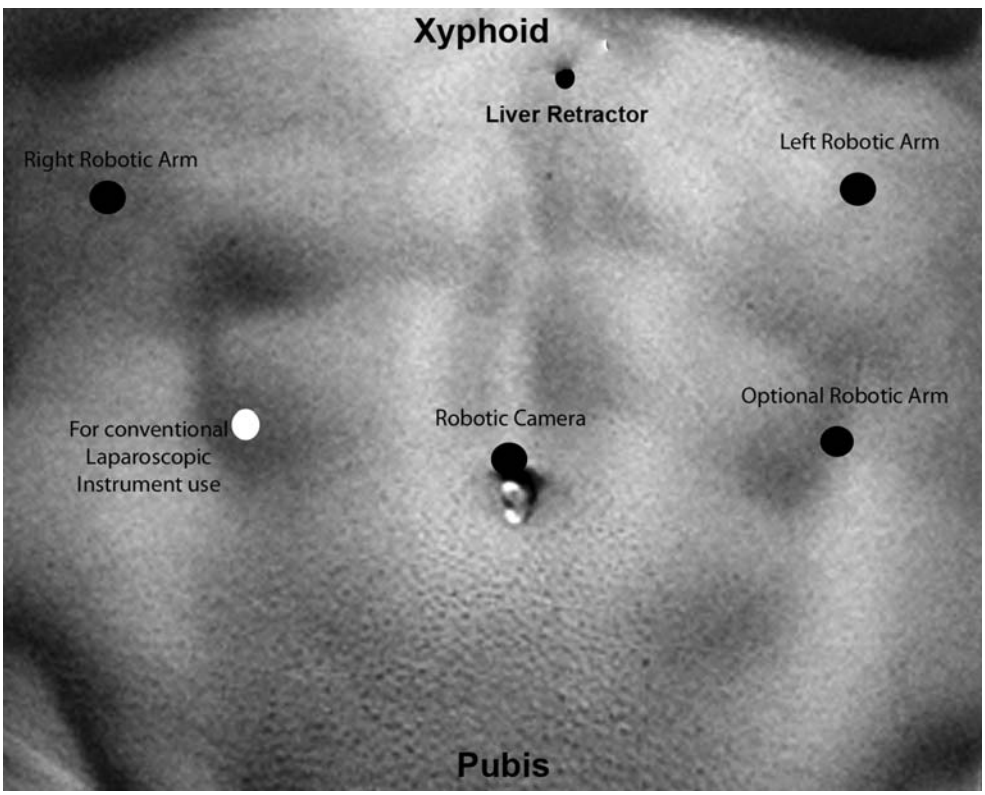

Figure 8 The placement of ports for the robotic myotomy. Note that the placement of ports is similar to laparoscopic myotomy but the robotic arms are placed more laterally, at or lateral to the rectus muscle. This is necessary to keep the robotic arms from interfering with each other.

undergoing robotic Heller myotomy, while perforation occurred in 16% of 63 patients undergoing a laparoscopic procedure. Robotic myotomy required about 20 min more to perform, although the authors report that operative time equalized in their last 30 patients.

Attention to specific details in setting up the robot is crucial. With the patient in the supine position, the arms must be tucked at the side, and anesthesia equipment and the airway must be well protected from the moving parts of the robotic system. The robot is placed at the patient's head and is brought over the patient's left shoulder. The equipment necessitates placement of the anesthesiologist at the foot of the patient, but the anesthesiologist must have ready access to the airway. Placement of a Nathanson liver retractor can also be problematic. Although placed in the same location as in the laparoscopic approach, the stationary mechanical arm that holds it can get in the way of the robotic device, if not placed correctly (Fig. 8).

Use of intraoperative endoscopy to guide the myotomy is impeded by the lack of space for the surgical endoscopist, due to the size of the robot. Several strategies may be used to accomplish the goals of endoscopy. For example, the robotic system can be disengaged and re-engaged to allow the endoscopy to be performed. Obviously, this does not allow simultaneous endoscopy during performance of the myotomy and may require two interruptions of the robotic procedure—initially, and then after the myotomy is performed, to ensure completeness and lack of mucosal perforation. On the other hand, three-dimension visualization allows excellent identification of circular muscle fibers and underlying mucosa during this surgery. Such stereoscopic detail could not be obtained from either open or laparoscopic approaches.

We move the patient into a reverse Trendelenburg position, before docking the arms of the robot to the ports. Four or five trocars are used, depending on the body habitus of the patient and the robotic system. Only three robotic arms are utilized for most of the surgery. Traditional laparoscopic instruments are used for retraction, suction, or to introduce sutures in the other ports. If necessary, a robotic arm can be moved to an alternate port to improve the approach to the esophagus. The robotic instrument ports are 5–7 mm and the camera port is 10–12 mm in diameter. Although trocar placement mimics that used for the laparoscopic approach, robotic ports must be further away from the target to allow full range of motion of the robotic arms and instruments. It is crucial to set all trocars and robotic arms in a way that minimizes conflict during movement of the instrument. An important part of any robotic procedure is learning the proper way to align the robotic arms.

The myotomy is performed as described for the laparoscopic procedure, again using a combination of sharp and blunt dissection. All of the instruments used in laparoscopic myotomy have been modified to use with the robot. Besides the added degrees of freedom with robotic instruments, the robot provides an excellent three dimensional, magnified view which greatly assists the surgeon's ability to perform the delicate dissection (Figs. 3, 4, and 5). Fundoplication may be performed using either robotic or laparoscopic techniques (Figs. 6 and 7).

Postoperative Care

Postoperatively, patients are given nothing by mouth initially. Routine barium swallows are not performed, but are used liberally if there is suspicion of perforation/leak. Liquids are begun the next day and diet is advanced as tolerated. Most patients note an immediate improvement in swallowing and diet can be advanced rapidly to soft or normal food. Patients may be discharged by the second postoperative day and require minimum care as outpatients.

Summary

Balloon dilatation and surgical myotomy are both effective treatments for achalasia. The development of minimally invasive approaches for performance of the myotomy were introduced more than 15 years ago and resulted in a resurgence of surgical treatment since patients are more willing to accept surgical options. Laparoscopic myotomy is an excellent and durable procedure. Success rates in relieving symptoms exceed 90%, making this approach attractive for patients who are good anesthetic risks. Perforation rates with surgery are acceptable; most perforations are recognized and repaired successfully at the time of surgery. Although not extensively studied, the degrees of freedom available with robotic instruments appear to facilitate the performance of the myotomy and show promise for decreasing intraoperative perforation rates. Minimally invasive esophageal myotomy is a safe, highly effective approach to relieve the symptoms of achalasia.

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HOW I DO IT

Transnasal Fine Gastrointestinal Fiberscope-guided Long Tube Insertion for Patients with Small Bowel Obstruction

Mitsuru Ishizuka · Hitoshi Nagata · Kazutoshi Takagi · Keiichi Kubota

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Abstract
Background The use of a transnasal fine gastrointestinal fiberscope (TNF-GIF) has been rapidly disseminating in Japan. However, there has been no trial of long tube insertion (LTI) using the TNF-GIF for patients with small bowel obstruction (SBO).
Purpose To examine whether TNF-GIF-guided LTI is superior to conventional LTI for patients with clinically diagnosed SBO.
Methods The time required for LTI was determined prospectively in each group of patients who underwent the conventional method (group 1, $n=10$) and the TNF-GIF-guided method (group 2, $n=10$) between March 2007 and November 2007. Insertion time was compared between groups 1 and 2.
Results Insertion time in group 2 was significantly shorter than that in group 1 (group 1, 22±16 min versus group 2, 9.2±5.4 min; $P=0.03$).
Conclusions Novel TNF-GIF-guided LTI is useful and superior to the conventional method.

Keywords Long tube insertion · Small bowel obstruction · Transnasal fine gastrointestinal fiberscope

Abbreviations

BFS	bronchofiberscope
LTI	long tube insertion
NG tube	nasogastric tube
STI	short tube insertion
TNF-GIF	transnasal fine gastrointestinal fiberscope
SBO	small bowel obstruction

Introduction

Small bowel obstruction (SBO) is one of the main complications after gastroenterological surgery.[1,2] When patients are clinically diagnosed as having SBO, in most cases, long tube insertion (LTI) is first attempted to relieve the intraluminal pressure of the bowel, instead of emergency laparotomy.[3,4]

Although LTI, instead of nasogastric tube (NG tube, short tube) insertion, is still a controversial method for treatment of patients with SBO,[5–7] recent reports revealed that LTI is recommended for treatment of SBO.[7–11] Moreover, a prospective randomized study comparing long tube decompression with short tube suction demonstrated that the long tube results were successful in 18 of 24 patients (75%) versus 16 of 31 patients (51%) for short tube suction for resolution of SBO.[5] Therefore, LTI is considerably advantageous for patient care. Firstly, a long tube can be automatically passed into the deeper portion of the intestine by balloon transport. Secondly, a long tube readily facilitates contrast studies[12] closer to the obstruction than a NG tube. Thirdly, a long tube can effectively reduce the intraluminal pressure closer to an obstruction than a NG tube.

Nevertheless, it is commonly believed that LTI is more difficult than short tube insertion (STI) because conventional LTI deeper in the intestine is sometimes associated with difficulty in passage through the pyloric ring to the

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duodenum in the case of blind insertion,[13] or with coil-up phenomenon in the fornix or antrum of the stomach. Moreover, most conventional LTI methods depend on sequential fluorographic observation until the tube passes the Treiz ligament, because of blind insertion.

On the other hand, LTI can theoretically be performed more easily than the conventional method by using a transnasal fine gastrointestinal fiberscope (TNF-GIF) with direct observation of the pyloric ring, similar to broncho-fiberscope (BFS)-guided intubation for direct observation of the vocal cords.[14,15]

However, there have been no reports comparing the conventional LTI method with the novel TNF-GIF-guided LTI method.

In the present prospective study, we investigated for the first time the utility of the TNF-GIF-guided LTI method in comparison with the conventional method.

Patients and Methods

Patients

We prospectively collected data for 20 patients who underwent LTI for treatment of SBO at the Department of Gastroenterological Surgery, Dokkyo University Hospital, between March 2007 and November 2007. Informed consent was obtained from all patients who underwent LTI, and the study was approved by our institutional review board.

Of the 20 patients enrolled, 10 were assigned to the conventional method (group 1=control group), while the remaining 10 were assigned to the TNF-GIF-guided method (group 2). These two methods were performed alternately. During the study period, there were no unevaluated patients.

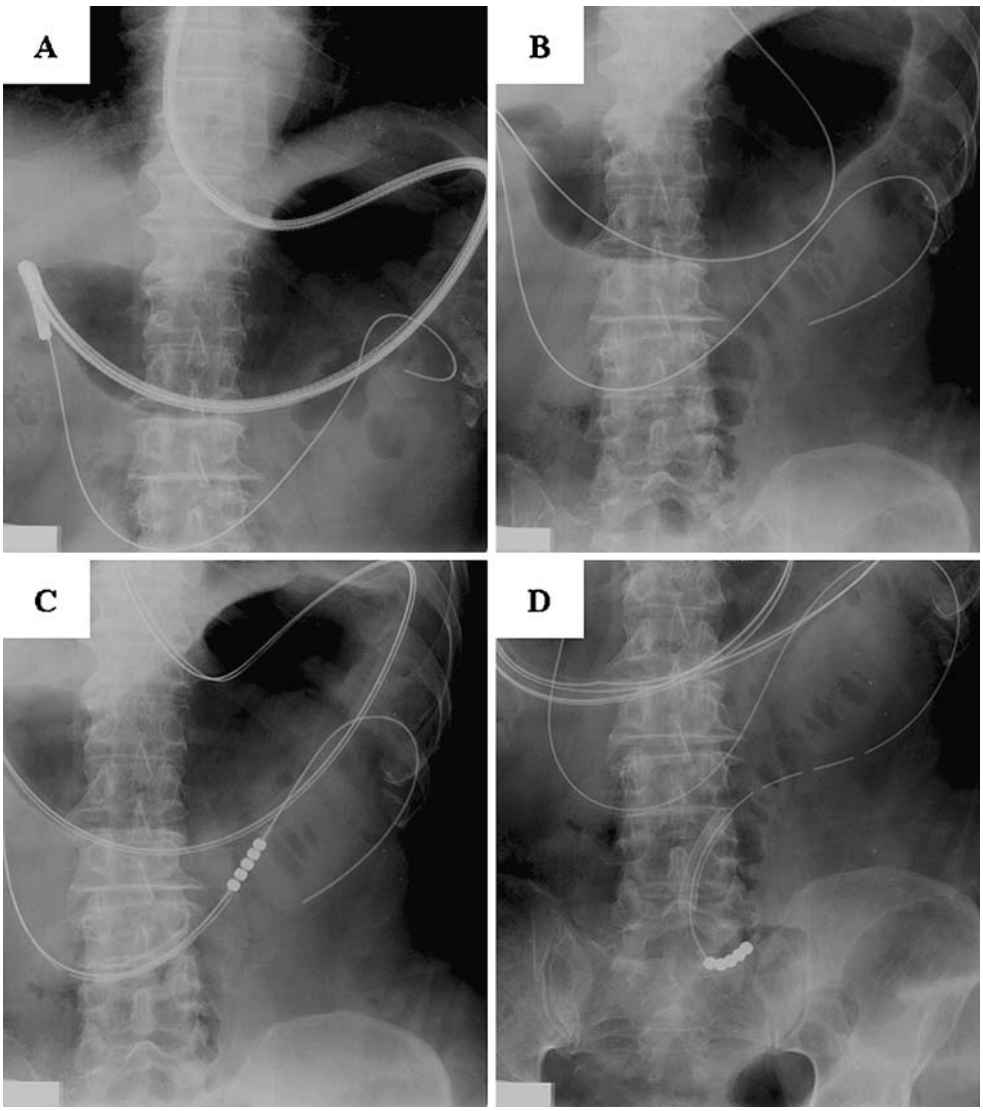

Figure 1 **a** GIF was inserted carefully from the pyloric ring into the first portion of the duodenum. Under direct observation of the duodenal lumen, guide wire insertion was performed carefully. **b** GIF was carefully removed without releasing the guide wire from its located position. **c** After positioning the guide wire, LTI was performed under guide wire guidance. **d** Once the LTI had been correctly inserted, the guide wire was removed.

Insertion time, defined as the time taken for the tip of the long tube to pass from the nose to the Treiz ligament, was compared between the groups.

Methods

Transnasal Fine Gastrointestinal Fiberscope-guided Long Tube Insertion

Under local anesthesia by injection of Xylocaine jelly into the nasal cavity, TNF-GIF (Slim SIGHT™; Olympus GIF type XP260N, Olympus Medical Systems Corp., Tokyo, Japan) insertion from nose to esophagus was performed carefully by direct observation of the nasal cavity or vocal cords. After GIF insertion into the stomach, suction was sufficiently performed to reduce residual fluid or air in the stomach to obtain a good field of observation. The GIF was then carefully inserted from the pyloric ring to the first portion of the duodenum (Fig 1a). If deeper insertion was possible, the guide wire was advanced further. Then, under direct observation of the duodenal lumen, guide wire insertion was performed carefully to prevent mucosal injury (Fig 1a). Once the tip of the guide wire had been confirmed to have passed through the Treiz ligament by using fluoroscopic observation, the TNF-GIF was carefully removed without releasing the guide wire from its located position (Fig 1b).

After positioning the guide wire, long tube (Super Dennis® Tube, single balloon type, 300 cm, 16Fr. Nippon Sherwood, Tokyo, Japan) insertion was performed using guide wire guidance (Fig 1c). Once the LTI had been correctly inserted, the guide wire was removed (Fig 1d) and a contrast study was performed to evaluate the dilatation of the small bowel or to confirm passage to the deeper portion of the small bowel. After inflating the balloon at the tip, the long tube was fixed at the patients' face. Then, an abdominal X-ray film was taken after LTI to confirm the proper position of the tube tip.

After LTI, intermittent continuous suction was performed to relieve the intraluminal pressure in the small bowel. Moreover, an abdominal X-ray film was obtained daily to evaluate the SBO status. The long tube was removed when SBO disappeared. If LTI continued for more than 1 week or if acute abdominal pain occurred, surgery was performed.

Results

Group 1 comprised seven males and three females, and group 2 comprised five males and five females (see Table 1). Group 1 included seven urgent insertions and group 2 included six urgent insertions. There was no significant difference in pre- or postoperative status between the two groups. Groups 1 and 2 had five and three patients who had previously undergone colorectal surgery, respectively. However, there was no significant inter-group difference in the type of surgery. On the other hand, a significant difference in patient age was observed between group 1 (67.4±14.2) and group 2 (50.4±16.4) (years, mean±SD, P=0.0234). Notably, there was a significant difference in insertion time between group 1 (22±16) and group 2 (9.2±5.4) (min, mean±SD, P=0.03).

Table 1 Background of Patients and Relationships between Groups

Variable	Group 1 n=10	Group 2 n=10	P
Sex (male/female)	7/3	5/5	0.3613
Nasal oozing or bleeding (yes/no)	6 /4	0/10	**0.0034**
Vomiting (yes/no)	5/5	0/10	**0.0098**
Success rate	10/13	10/10	0.6689
Initiation (elective/urgent)	3/7	4/6	0.6392
Status (postoperative/preoperative)	9/1	9/1	[a]
Previous surgery (colorectal/others)	5/5	3/7	0.3613
Operation (performed/not performed)	2/8	2/8	[a]
Term of hospital stay (days)	20.2±17.1	33.4±27.7	0.0864[b]
Age (years)	67.4±14.2	50.4±16.4	**0.0234**[b]
Time required for insertion (min)	22.0±16.3	9.2±5.4	**0.0300**[b]

Group 1, conventional method; group 2, TNF-GIF-guided method chi-squared test

[a] Unproved

[b] Mann–Whitney U-test (mean±SD)

Because comparison of patients' tolerance between groups 1 and 2 was difficult, we estimated the frequency of nasal oozing or bleeding or vomiting during LTI as patients' tolerance. In fact, six patients had nasal oozing or bleeding (P=0.0034) and five patients had vomiting in group 1 (P=0.0098). While there were no patients who had these complications in group 2, because conventional method required not only longer insertion time but also much more time of stroke to repair coil-up formation or to pass through pylorus ring than TNF-GIF-guided method, conventional method required much more patient's tolerance than TNF-GIF-guided method to insert the long tube.

Our definition of long tube insertion failure is the case which takes more than 30 min. There were three failure cases in group 1. Success rate of conventional method was 76.9% (10/13). This success rate was almost the same as our previous data (data not shown) and almost the same result of a recent report.[3] On the other hand, there were no failure cases in group 2 (P=0.6689).

There were two patients who underwent operation for SBO in the both groups. One ileo-cecal resection and one stoma formation were performed in group 1, while two ileo-cecal resections were performed in group 2. Surgical findings revealed that there were rigid adhesions in abdominal cavity. The other patients received successful resolutions of SBO by the conservative treatment of intermittent suction using LTI. In addition, there was no significant difference in the hospital stay between these two groups (group 1, 20.2±17.13; group 2, 33.44±27.7; days, mean±SD, P=0.0864).

Although we did not estimate the amount of radiation in the duration of each method, in most cases, conventional method required fluoroscopic observation for almost all the time of LTI. On the other hand, TNF-GIF-guided method required only spot time of fluoroscopic observation to confirm positioning of guide wire to prevent from removing or to advance the long tube through the guide wire. Therefore, about three quarters of time of LTI was required for TNF-GIF observation.

The average costs were as follows: for the conventional method, the average cost was $418 and for the TNF-GIF-guided method, the average cost was $533 (418+115); $418 is the cost for LTI; $115 is the cost for using TNF-GIF observation.

Discussion

Although it is still controversial whether LTI or STI is better for decompression in patients with SBO,[5–7] the multi-luminal construction of a long tube is advantageous for treatment and diagnosis. However, with conventional methods of LTI, such as blind insertion, the procedure may take a long time or may be impossible. Moreover, LTI may be uncomfortable or painful to the patient and may involve unnecessary exposure to X-ray examination. If a blind insertion is performed, the tip of a long tube sometimes cannot pass through the pyloric ring to the duodenum.[13]

On the other hand, it is well known that BFS-guided intubation allows easy intubation for patients in whom this is difficult. Because BFS allows easy insertion into the trachea, intubation can be performed easily using BFS guidance.[14,15] Therefore, our method merely adapts this method to LTI.

LTI depends mainly on the time taken to pass through the pyloric ring to the duodenum, because of the difficulty in performing this under fluorographic observation alone. On the other hand, passage through the pyloric ring is easy using GIF under direct observation. Therefore, TNF-GIF-guided LTI is considered useful for reducing the time needed for this limiting step. Moreover, recent reports demonstrated that placement of a nasoenteral feeding tube with a slim gastrointestinal fiber scope was feasible, safe, and more successful than the standard method.[16–18]

In fact, although this study was small-scale and preliminary, the results strongly indicated the usefulness of LTI. TNF-GIF-guided LTI uses equipment that will soon be standard in all hospitals, and can be performed by anyone experienced in endoscopy of the upper gastrointestinal tract.[19] The method is safe, easy to perform, and improves the efficacy of LTI, and therefore can be recommended for patients with SBO.

In conclusion, this report, to our knowledge, is the first to compare the time required for insertion between TNF-GIF-guided LIT and the conventional method for patients with SBO, revealing that TNF-GIF guidance is advantageous in this respect.

Conflict of interest No financial support or other potential conflicts of interest exist.

All authors have no conflicts to disclose.

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HOW I DO IT

Reconstruction of the Replaced Right Hepatic Artery at the Time of Pancreaticoduodenectomy

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Abstract
Background The arterial anatomy supplying the liver is highly variable. One of the most common variants is a completely replaced right hepatic artery which is seen in about 11% of the population. Interruption of arterial flow to the right hepatic artery at the time of pancreaticoduodenectomy has been associated with biliary fistula and the consequent complications, as well as stenosis of the biliary enteric anastomosis. Malignancies of the posterior aspect of the head of the pancreas can encase a replaced right hepatic artery without involvement of other vascular structures. In this situation, it is possible to resect and reconstruct the replaced right hepatic artery to maintain oxygen delivery to the biliary enteric anastomosis.
Summary Herein we describe a technique to reconstruct a replaced right hepatic artery following resection of the vessel en bloc with the tumor during a pancreaticoduodenectomy, using inflow from the gastroduodenal artery.

Keywords Replaced · Right hepatic artery · Vascular reconstruction · Pancreaticoduodenectomy · Surgery · Whipple

Background

The arterial anatomy supplying the liver is highly variable. No less than ten anatomic variants have been described.[1] In the configuration typically described as 'normal' in anatomy textbooks, the celiac truck gives rise to the common hepatic artery which then branches into the gastroduodenal and proper hepatic arteries. The right and left hepatic arteries are then branches of the proper hepatic artery. This anatomy is seen in about 55% of patients,[1] while the remainder will exhibit an anatomic variant. One of the most common variants is a completely replaced right hepatic artery which is seen in about 11% of the population.[1] A replaced right hepatic artery originates from the superior mesenteric artery, courses either within the pancreatic head or posterior to it, and then superiorly along the right posteriolateral border of the common bile duct before entering the right lobe of the liver (Figs. 1 and 2).

Ligation of the right hepatic artery can have grave consequences for the patients undergoing pancreaticoduodenectomy because most of the blood supply to the common bile duct remnant is derived from the right hepatic artery following ligation of the gastroduodenal artery at the time of resection. Interruption of arterial flow to the right hepatic artery at the time of pancreaticoduodenectomy has been associated with biliary fistula and the consequent complications, as well as stenosis of the biliary enteric anastomosis. These complications are presumed to be a function of ischemia of the distal end of the common bile duct remnant.[2,3]

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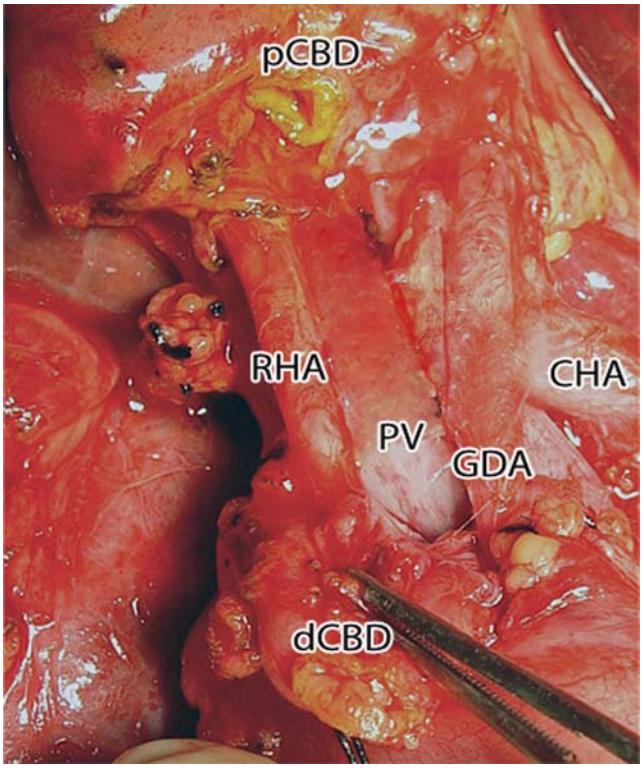

Figure 1 Operative photograph of the hepatoduodenal ligament demonstrating the aberrant anatomy of the replaced right hepatic artery. The bile duct has been transected and the distal portion has been reflected inferiorly. *pCBD* proximal common bile duct, *dCBD* distal common bile duct, *RHA* replaced right hepatic artery, *CHA* common hepatic artery, *GDA* gastroduodenal artery, *PV* portal vein.

Malignancies of the posterior aspect of the head of the pancreas can encase a replaced right hepatic artery without involvement of other vascular structures. In this situation, it is possible to resect and reconstruct the replaced right hepatic artery to maintain oxygen delivery to the biliary enteric anastomosis. Sarmiento et al. previously described using inflow from the gastroduodenal artery to reconstruct an injured proper hepatic artery.[4] Herein we describe a similar technique to reconstruct a replaced right hepatic artery following resection of the vessel en bloc with the tumor during a pancreaticoduodenectomy.

Technique

Once it has been determined that the tumor involves the replaced right hepatic artery, but is otherwise resectable, the hepatoduodenal ligament is dissected. The neck of the pancreas is divided. The patient is heparinized after obtaining vascular control of the common hepatic, proper hepatic artery, and replaced right hepatic arteries. The gastroduodenal artery is divided preserving as much length as possible. The uncinate dissection is completed, excising the segment of replaced right hepatic artery that is encased in tumor. The replaced right hepatic artery is ligated at its origin with the superior mesenteric artery. The remaining cut ends of the replaced right hepatic artery and gastroduodenal artery are then anastomosed to each other in an end-to-end fashion with interrupted sutures of 8-0 prolene. Vascular control is released and pulsitile flow is confirmed in the right hepatic artery (Figs. 3 and 4).

Comment

Several options are available for reconstruction of the replaced right hepatic artery after it has been resected with the specimen. Techniques involving venous or prosthetic interposition have been described.[5,6] Prosthetic material has the disadvantage of being placed in a field that is not sterile. Vein grafts require harvesting the vessel, often through a second incision. Any interposition graft will require two anastomoses. The gastroduodenal artery transposition technique described above eliminates the need for prosthetic

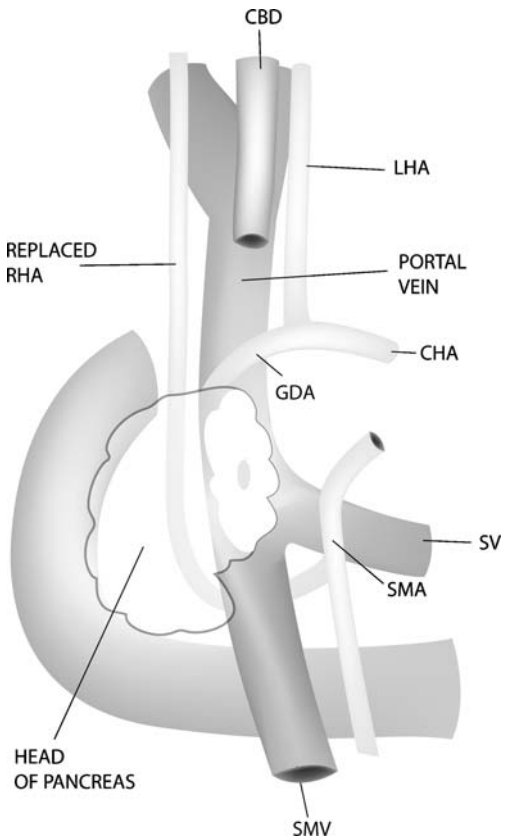

Figure 2 Line drawing depicting the anatomy of the replaced right hepatic artery. *CBD* common bile duct, *RHA* right hepatic artery, *LHA* left hepatic artery, *CHA* common hepatic artery, *GDA* gastroduodenal artery, *SMA* superior mesenteric artery, *SV* splenic vein, *SMV* superior mesenteric vein.

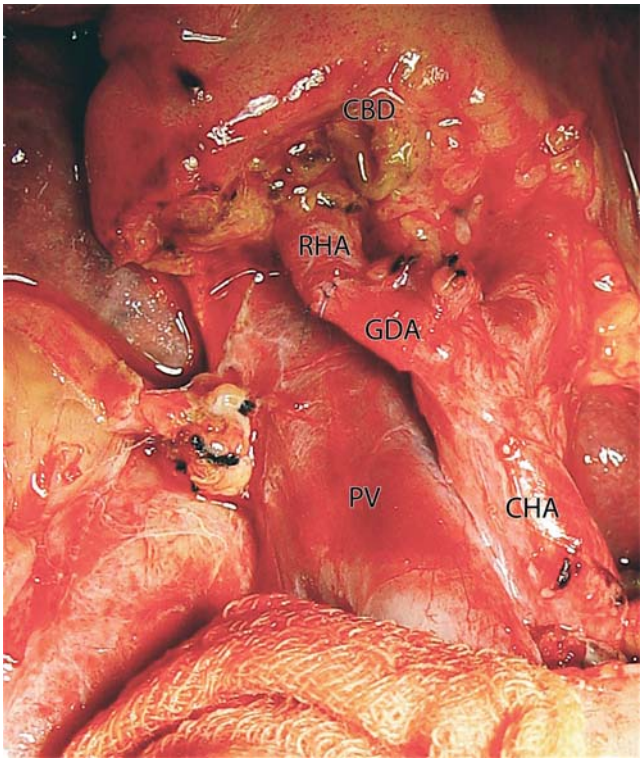

Figure 3 Operative photograph of the hepatoduodenal ligament following segmental resection and reconstruction of the replaced right hepatic artery demonstrating the end-to-end anastomosis between the right hepatic artery and the gastroduodenal artery. *RHA* replaced right hepatic artery, *GDA* gastroduodenal artery, *CHA* common hepatic artery, *PV* portal vein, *CBD* common bile duct.

material, provides arterial inflow with a size matched vessel, and requires a single anastomosis, enabling the surgeon to extend the safe limits of pancreatic resection to this unique patient population.

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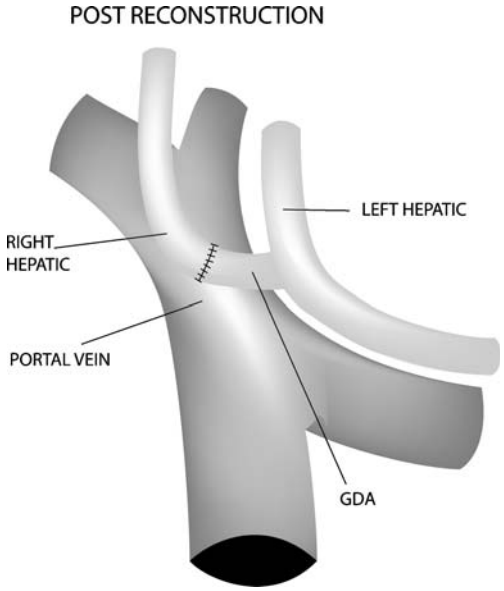

Figure 4 Line drawing depicting the vascular anatomy following the reconstruction of the replaced right hepatic artery. *GDA* gastroduodenal artery.

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REVIEW ARTICLE

Portal Triad Clamping Versus Vascular Exclusion for Vascular Control During Hepatic Resection: A Systematic Review and Meta-analysis

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Abstract
Objective To compare the clinical outcome of patients undergoing liver resection under portal triad clamping (PTC) versus hepatic vascular exclusion (HVE).
Methods A systematic literature search was performed following the guidelines of the Cochrane collaboration. Randomized controlled trials (RCT) comparing PTC to any technique of HVE were eligible for inclusion. Two authors independently assessed methodological quality of included trials and extracted data on overall morbidity, mortality, cardiopulmonary and hepatic morbidity, intraoperative blood loss, transfusion rates, postoperative transaminase and bilirubin levels, prothrombin time, and hospital stay. Meta-analyses were performed using a random-effects model.
Results Of the 1,383 identified references, four RCTs were finally included. These trials compared PTC to selective hepatic vascular exclusion (SHVE), total hepatic vascular exclusion (THVE), and a modified technique of HVE (MTHVE), respectively. Meta-analyses revealed no significant difference in morbidity and mortality between PTC and techniques of HVE. Further analyses showed significantly reduced overall morbidity for the PTC compared to the THVE group. There was a significantly lower transfusion rate for HVE compared to PTC.
Conclusion Hepatic vascular exclusion does not offer any benefit regarding outcome of patients undergoing hepatic resection compared to PTC alone. Further, well-designed RCTs evaluating adequate vascular control in major hepatectomy and in patients with underlying liver disease appear justified.

Keywords Liver resection · Portal triad clamping · Hepatic vascular exclusion · Clinical outcome

Abbreviations

PTC	portal triad clamping
HVE	hepatic vascular exclusion
RCT	randomized controlled trial
SHVE	selective hepatic vascular exclusion
THVE	total hepatic vascular exclusion
MHVE	modified technique of hepatic vascular exclusion
RR	relative risk
WMD	weighted mean difference
CI	confidence intervals

Nuh N. Rahbari and Moritz Koch contributed equally to this work

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Introduction

Excessive intraoperative blood loss and transfusion are known predictors for patients' outcome following hepatic resection.[1,2] Advances in knowledge of hepatic anatomy, surgical techniques, and equipment as well as perioperative care have significantly reduced intraoperative bleeding and improved the safety of hepatic resection within the last two

decades.[3] As a consequence, high-volume centers nowadays report morbidity and mortality rates equal to or below 30% and 5%, respectively.[4–6]

We recently demonstrated that portal triad clamping (PTC) does not offer any benefit regarding the outcome of patients undergoing elective hepatic resection.[7] We now intended to analyze the very strategy of hepatic vascular control, which, however, might still be required in certain cases. Besides liver inflow control by PTC, combined inflow and outflow control using hepatic vascular exclusion (HVE) has been proposed to decrease blood loss during hepatectomy. HVE can be performed in different ways with total and selective hepatic vascular exclusion representing the most commonly applied techniques. Total hepatic vascular exclusion (THVE) combines PTC with supra- and infrahepatic clamping of the inferior vena cava.[8,9] Selective hepatic vascular exclusion (SHVE) has been suggested as an alternative technique. SHVE, also known as hepatic vascular exclusion with the preservation of caval flow, consists of PTC plus transient occlusion of the hepatic veins.[10] There is disagreement if liver inflow or combined inflow and outflow control results in better outcome of patients undergoing elective hepatic resection and a meta-analysis including all available randomized controlled trials is still lacking.[11]

We conducted a systematic review and meta-analysis of RCTs to evaluate postoperative morbidity and mortality of patients undergoing hepatectomy with PTC compared to techniques of HVE.

Methods

Systematic Literature Search

The literature search followed validated methods of the Cochrane Collaboration.[12] We systematically searched the Medline (1950–11/2007), Embase (1974–11/2007), Science Citation Index (1945–11/2007), and the Cochrane Library database Clinical Trials (Register of Controlled Trials, 2007 Issue 4) using a highly sensitive filter for detection of RCTs and the following keywords: inflow occlusion, vascular occlusion, ischemic preconditioning, hepatic vascular exclusion, Pringle, portal triad clamping, portal triad occlusion, pedic* clamping, pedic* occlusion, hepatoduodenal ligament clamping, hepatoduodenal ligament occlusion, surgery, hepatectomy, hemihepatectomy, hepatic* resect*, hepatic* surgery, liver resect*, liver surgery. The detailed search strategy is available on request. The last search was carried out on November 13, 2007. Reference lists of retrieved relevant articles were screened for additional trials. Moreover, we contacted experts in the field of hepatic surgery in order to include all existing trials comparing PTC to HVE.

Study Selection and Data Extraction

Randomized controlled trials comparing PTC to any technique of HVE were eligible for inclusion. We excluded studies assessing laparoscopic techniques, studies on children, and on patients undergoing liver transplantation. Moreover, we excluded studies providing insufficient data on our predefined outcome variables. Search findings were screened for potentially relevant studies by two independent authors (NNR and KW) who separately evaluated these articles and extracted their data. Any disagreement during study selection and data extraction process was resolved by discussion with a third author (JW). In addition, we assessed methodological quality of included trials using a standardized extraction form following international recommendations.[13–15] Our critical appraisal comprised allocation sequence generation, randomization efficacy, allocation concealment, sample size calculation, description of outcomes, description of dropouts and withdrawals, and statistical analysis of individual trials.

We extracted data on baseline characteristics of included trials (i.e., indications for hepatectomy, performed procedures, transection technique) and study patients (i.e., age, sex, and underlying liver disease). The *primary outcome* measures were overall postoperative morbidity and mortality. We defined morbidity as the number of patients that developed at least one complication after surgery. Mortality was defined as in-hospital death due to any cause. *Secondary outcomes* were cardiopulmonary complications (i.e., cardiac failure, arrhythmia, myocardial infarction, pneumonia, pleural effusion, pulmonary edema, respiratory failure), hepatic morbidity (i.e., subphrenic collections, ascites, biliary fistula, bile leak, hepatic encephalopathy, liver failure), intraoperative blood loss, number of patients requiring blood transfusion, transaminase levels (aspartate aminotransferase) as measures of hepatic ischemic and reperfusion injury, postoperative bilirubin and prothrombin time, operation, and warm ischemic time as well as hospital stay.

Statistical Analysis

We pooled the synchronized extraction results as estimates of overall treatment effects in a meta-analysis using Review Manager, Version 4.2 for Windows (Cochrane Collaboration, Oxford) and a random effects model for more conservative estimates.[16,17] Odds ratio (OR) was chosen as estimated effect measure for dichotomous data and weighted mean difference (WMD) for continuous data. Both measures were reported with 95% confidence intervals (CI). Data that were presented as median (range) were not included in meta-analyses, as there are currently no methods available for meta-analyzing skewed data. Thus, it is discouraged to

calculate CI on the basis of ranges.[12] We checked all results for clinical and statistical heterogeneity and I^2 statistics was used for the evaluation of statistical heterogeneity (I^2 values of 50% or more indicating presence of heterogeneity.[18] Heterogeneity I^2 values of 25% or less was considered to indicate low and values of 75% or more to indicate high heterogeneity. Clinical heterogeneity was evaluated by assessing study populations and interventions, definition of outcome measures, concomitant treatment, and perioperative management, respectively. Furthermore, we performed analyses according to the different techniques of HVE being compared to PTC. For assessment of interobserver agreement on article selection for inclusion, we applied Cohen's (unweighted) κ statistic.[19]

In order to assess publication bias, we constructed a funnel plot for the primary outcome of overall morbidity, using relative risk (RR) as the measure of effect.[20] Forest plots were used to present meta-analyses. The vertical line represented the equivalence line between the methods being compared. Individual trials were displayed horizontally with the squares representing the point estimate for each trial. The area of the square was proportional to the amount of information (i.e., sample size), whereas the horizontal line represented the 95% CI. The diamonds represent the summary measures with the diamond width corresponding to the 95% CI.

Results

In accordance with the QUOROM statement,[21] Fig. 1 displays a flow diagram with the number of retrieved articles and the number of articles excluded at different steps of the study selection process. Interobserver agreement was good during the first step of the study selection, i.e., screening of titles and abstracts (Cohen's unweighted κ=0.66, 95% CI 0.48 to 0.84) and excellent (κ=1) during the second step (i.e., inclusion of relevant studies after detailed evaluation). Of the 12 studies selected for detailed evaluation, six studies were excluded due to inadequate study intervention[22–26] and two studies[27,28] due to their non-randomized study design. No study had to be excluded for providing insufficient data on our outcomes of interest. A total of four studies with a cumulative sample size of 320 patients were reviewed for quality and included in our meta-analysis. One trial compared PTC to THVE,[29] two trials PTC to SHVE,[30,31] and one trial PTC to a modified technique of hepatic vascular exclusion with PTC being combined with selective infrahepatic clamping of the inferior vena cava.[32] Two trials enrolled non-cirrhotic patients only,[29,30] whereas one trial also included those with Child A cirrhosis,[31] and one solely patients with Child A and B cirrhosis.[32] In all trials, major and minor hepatic

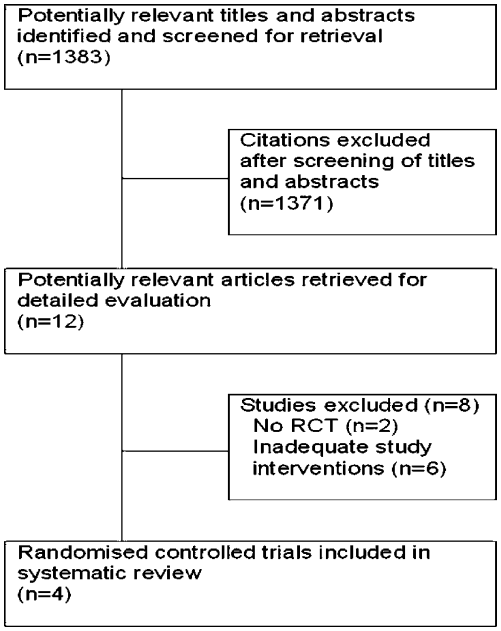

Figure 1 Modified flow chart according to QUOROM[21] showing number of abstracts and articles identified and evaluated during the review process.

resections were performed, but the trial by Belghiti et al. that exclusively included patients undergoing major hepatectomy. Methodological appraisal of included studies revealed rather moderate trial quality. While the study by Belghiti et al. was already published in 1996, none of the remaining three articles followed the CONSORT guidelines for reporting of RCTs published in 2001.[33] Table 1 summarizes information on baseline characteristics, relevant outcomes, and trial quality. Funnel plot to evaluate publication bias for outcome of overall morbidity did not demonstrate strong asymmetry, suggesting absence of severe publication bias (Fig. 2).

Morbidity and Mortality

Data on morbidity and mortality were available for all included studies. The overall morbidity and mortality rates were 43% and 1%, respectively. The trial by Belghiti et al. reported significantly less overall morbidity for the PTC compared to the THVE group (OR 0.27; 95% CI 0.08 to 0.94; P=0.04; I^2=n.a.).[29] With the exception of this finding, none of the further analyses showed superiority in overall morbidity and mortality for either group. In accordance with these results, meta-analyses of all trials comparing PTC to any technique of HVE demonstrated no statistically significant difference in overall morbidity (OR 0.76; 95% CI 0.47 to 1.22; P=0.25; I^2=3.6%) (Fig. 3) and mortality (OR 3.31; 95% CI 0.51 to 21.40; P=0.21; I^2=0%) (Fig. 4). There was no advantage of PTC or HVE in reducing hepatic morbidity (OR 1.28; 95% CI 0.69 to 2.39; P=0.44; I^2=0%). Analyses on cardiopulmonary morbidity

Table 1 Characteristics, Results, and Critical Appraisal of Randomized] Controlled Trials Comparing Portal Triad Clamping to Techniques of Hepatic Vascular Exclusion

Study	Baseline data, overall morbidity and mortality			Parameters of effectiveness			Study characteristics and critical appraisal
Smyrniotis (2003a)[30]		PTC	SHVE		PTC	SHVE	Population:
	Age [years]	61 (24–84)	59 (9–81)	Total blood loss [mL]	490±159	374±164	
	Male:Female	16:4	15:5	Packed red blood cells [units]	0	0	Patients undergoing surgery for resectable liver lesions
	N	20	20	Patients with blood transfusion[1]	0/20	0/20	Comparison:
	Cirrhosis	0/20	0/20	Operation time [min]	185±30	195±40	PTC vs. SHVE
	Benign/malignant disease	3/17	4/16	AST (POD 2) [U/L][a]	250±48	350±52	Transection technique:
	Major/minor hepatectomy	11/6	12/4	Bilirubin (POD 3) [mmol/L][a]	17±3	26±5	Clamp-crushing technique
	Overall morbidity	9/20	9/20	Prothrombin time [%]	n.a.	n.a.	Critical appraisal:
	Hepatic morbidity	3/20	0/20	Warm ischemic time [min]	42±12	39±14	• No description of allocation sequence generation
	Cardiopulmonary morbidity	6/20	9/20	Hospital stay [days]	11 (6–18)	10 (4–13)	• Adequate allocation concealment
	Overall mortality	0/20	0/20				• Efficient randomization
							• No description of sample size calculation
							• Adequate definition of outcome parameters
							• No description of withdrawals and drop-outs
							• Statistical analysis unclear
							• Article not following CONSORT guidelines
Smyrniotis (2003b)[31]		PTC	SHVE		PTC	SHVE	Population:
	Age [years]	62 (16–82)	61 (1–86)	Total blood loss [mL][a]	880 (350–2850)	420 (250–3100)	Patients undergoing major liver resection
	Male:Female	44/11	43/12	Packed red blood cells [units][a]	1 (0–14)	0 (0–12)	Comparison:
	N	55	55	Patients with blood transfusion	32/55	18/55	PTC vs. SHVE
	Chronic liver disease	n.a.	n.a.	Operation time [min]	189 (160–300)	198 (155–320)	Transection technique:
	Benign/malignant Disease	10/45	13/42	AST (POD 1) [U/L][a]	460(180–1110)	390 (160–880)	PTC group: Clamp-crushing technique
	Bisegmentectomy/(Extended) lobectomy	9/44	11/44	Bilirubin (POD 1) [mmol/L]	36 (20–80)	34 (24–160)	SHVE group: sharp parenchymal transection in 45 patients, clamp-crushing technique in 10 patients
	Overall morbidity	29/55	27/55	Prothrombin time (POD 1) [%]	48 (39–70)	44 (38–68)	Critical appraisal:
	Hepatic morbidity	14/55	10/55	Warm ischemic time [min]	32 (25–61)	34 (24–58)	• No description of allocation sequence generation
	Cardiopulmonary morbidity	18/55	15/55	Hospital stay [days][a]	15 (4–32)	11 (5–26)	• Adequate allocation concealment
	Mortality	1/55	0/55				• Efficient randomization
							• No description of sample size calculation
							• Adequate definition of outcome parameters
							• No description of withdrawals and drop-outs
							• Statistical analysis unclear
							• Article not following CONSORT guidelines
Chen (2006)[32]		PTC	MTHVE		PTC	MTHVE	
	Age [years]	41.5±4.1	39.7±3.6	Total blood loss [mL][a]	770±320	420±250	Population:
	Male:Female	51/7	53/7	Packed red blood cells [units]	n.a.	n.a.	Cirrhotic patients undergoing liver resection for HCC > 5 cm located in the central liver portion
	N	58	60	Patients with blood transfusion[a]	27/58	8/60	Comparison:
	Cirrhosis	58/58	60/60	Operation time [min]	124.5±10.7	133±11.8	PTC vs. PTC combined with occlusion of the inferior vena cava below the liver (MTHVE)
	Benign/ malignant disease	0/58	0/60	AST [U/L]	n.a.	n.a.	Transection technique:
	Major/minor hepatectomy	49/8	53/7	Bilirubin [mmol/L]	n.a.	n.a.	Clamp-crushing technique
	Overall morbidity	17/58	19/60	Prothrombin time [%]	n.a.	n.a.	• Critical appraisal:
	Hepatic morbidity	8/58	7/60	Hepatic ischemic time [min]	13.5±2.1	12.6±2.7	• No description of allocation sequence
	Cardiopulmonary morbidity	8/58	11/60	Hospital stay [days]	n.a.	n.a.	generation

Table 1 (continued)

Study	Baseline data, overall morbidity and mortality			Parameters of effectiveness			Study characteristics and critical appraisal
	Overall mortality	1/58	0/60				• Allocation concealment unclear • Efficient randomization • No description of sample size calculation • Inadequate definition of outcome parameters • No description of withdrawals and drop-outs • Article not following CONSORT guidelines
Belghiti (1996)[29]		PTC	THVE		PTC	THVE	Population:
	Age [years]	43±16	48±18	Total blood loss [mL]	989±1250	1195±1105	Non-cirrhotic Patients undergoing major liver resection
	Male:Female	8/16	13/15	Packed red blood cells [units]	2.9±3.9	2.5±3.4	Comparison:
	N	24	28	Patients with blood transfusion	10/20	8/24	PTC vs. THVE
	Cirrhosis	0/24	0/28	Operative time [min][a]	301±103	366±106	Transection technique:
	Benign/malignant disease	7/17	5/23	AST (POD 1) [U/L]	368±240	352±235	Parenchymal transection using Kelly forceps and ultrasonic dissector
	Major/minor hepatectomy	24/0	28/0	Bilirubin [mmol/L]	n.a.	n.a.	Critical appraisal:
	Overall morbidity	7/20	16/24	Prothrombin time (POD 1) [%]	47±14	42±12	• No description of allocation sequence generation
	Hepatic morbidity	3/20	9/24	Warm ischemic time [min][a]	35±9	42±12	• Allocation concealment unclear
	Cardiopulmonary morbidity	2/20	6/24	Hospital stay [days][a]	14±6	22±12	• Efficient randomization
	Overall mortality	1/20	0/24				• No description of sample size calculation • Adequate definition of outcome parameters • Adequate description of withdrawals and drop-outs • No intention-to-treat analysis

PTC portal triad clamping, *HVE* heptatic vascular exclusion, *THVE* total hepatic vascular exclusion, *SHVE* selective hepatic vascular exclusion, *MTHVE* modified technique of hepatic vascular exclusion, *AST* aspartate aminotransferase, *POD* postoperative day, *n.a.* not available,

[a] Significant values according to original publication; parametric values are reported as SD ± mean or median (range).

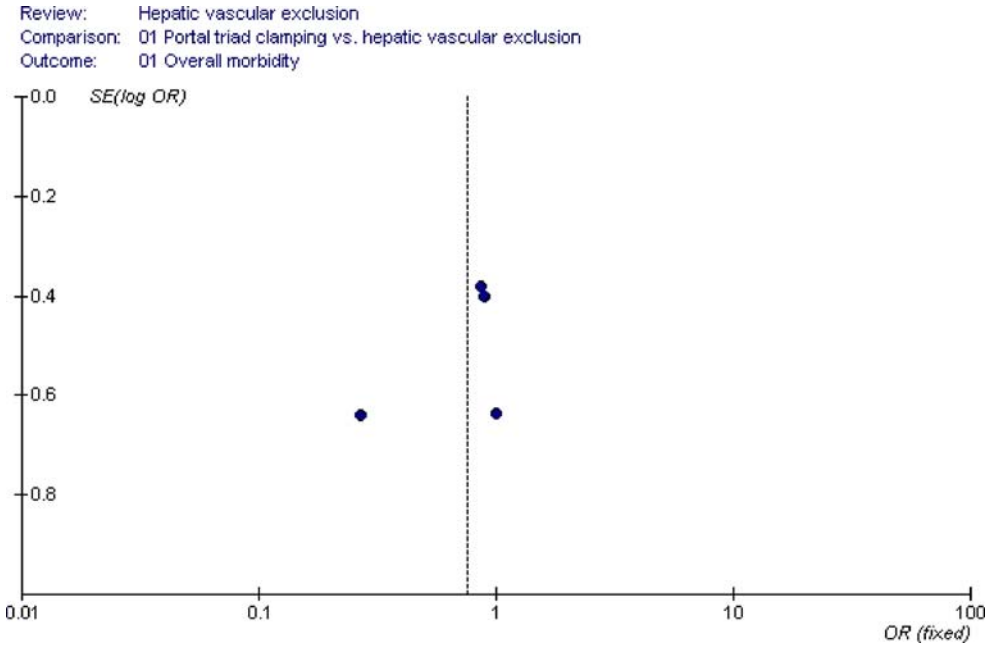

Figure 2 Funnel plot assessing publication bias for overall morbidity among RCT of portal triad clamping (PTC) versus hepatic vascular exclusion (HVE).

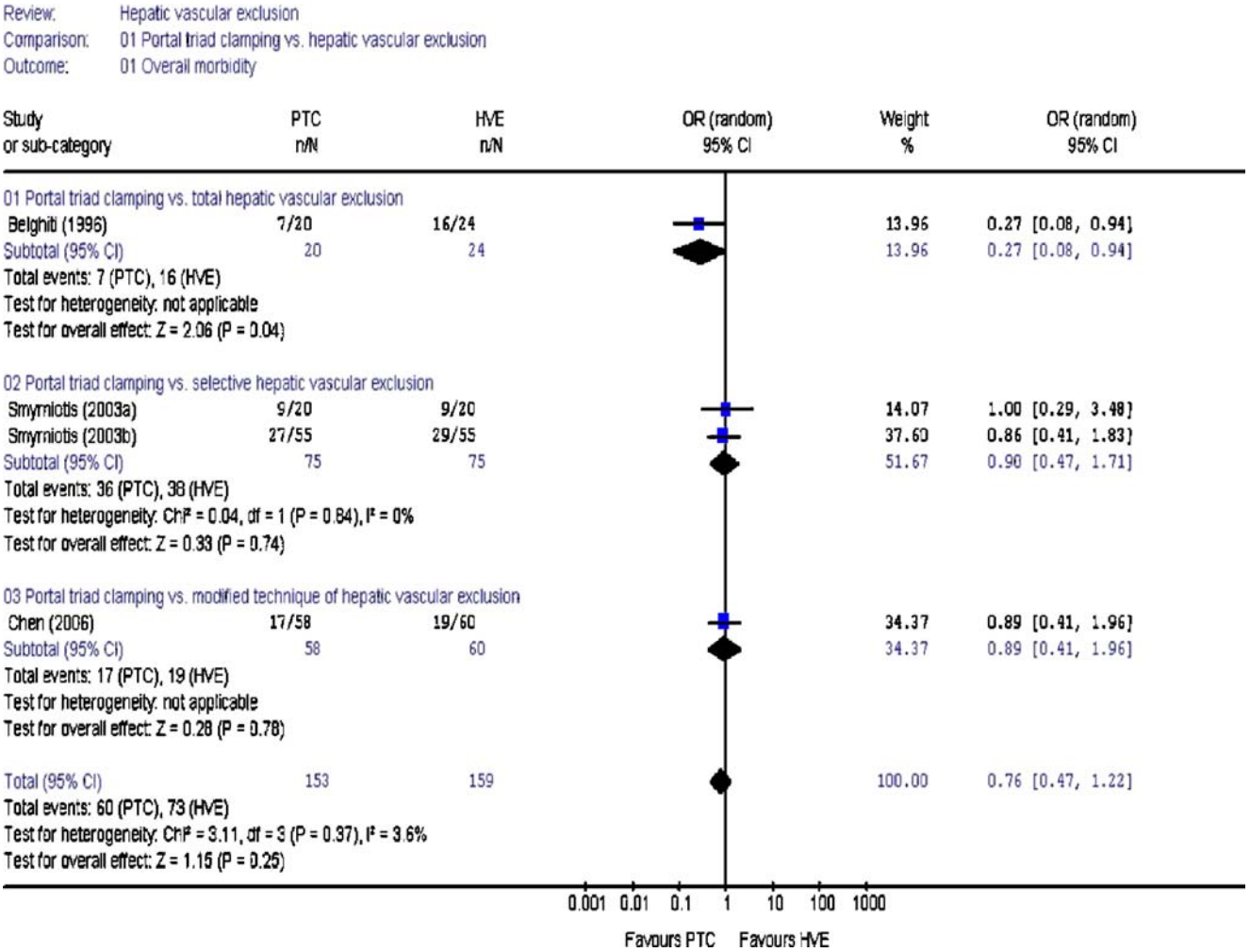

Figure 3 Meta-analysis of overall morbidity for RCT comparing portal triad clamping (PTC) to techniques of hepatic vascular exclusion (HVE).

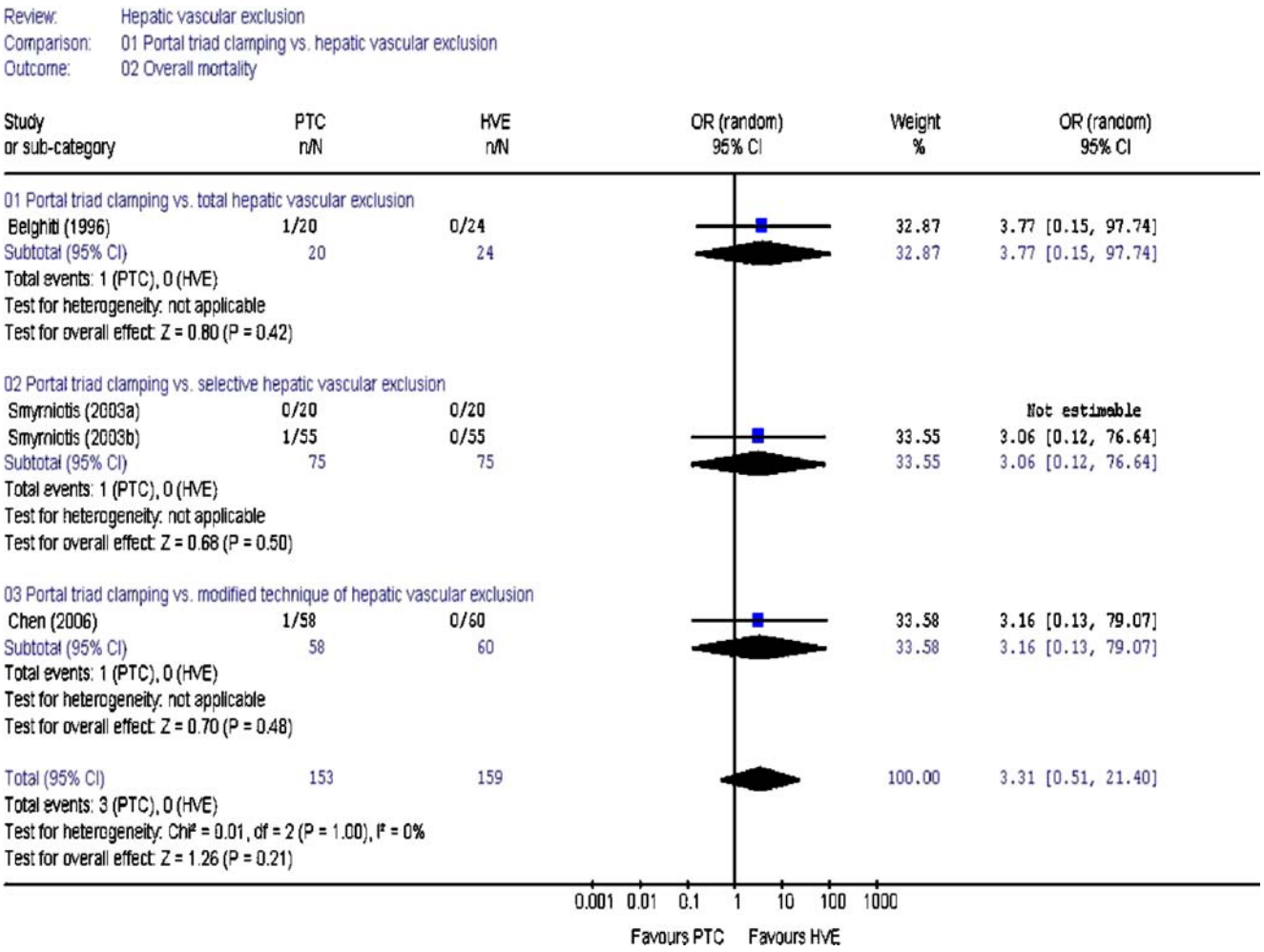

Figure 4 Meta-analysis of overall mortality for RCT comparing portal triad clamping (PTC) to techniques of hepatic vascular exclusion (HVE).

resulted in similar findings with no statistically significant difference between both strategies (OR 0.81; 95% CI 0.47 to 1.40; P=0.46; I^2=0%) (Table 2).

Perioperative Parameters

Information on intraoperative blood loss was available for all analyzed trials. Data from one of the trials by Smyrniotis et al. indicating significantly less blood loss in patients undergoing SHVE were reported as median (range) and could therefore not be included in meta-analysis.[30,31] Our analyses of the remaining studies revealed significantly higher blood loss for the PTC group compared to the SHVE group (WMD 116.00; 95% CI 4.33 to 227.67; P=0.04; I^2= n.a.) and the MTHVE group (WMD 350.00; 95% CI 246.16 to 453.84; P<0.00001; I^2=n.a.), whereas there was no significant difference between the THVE and PTC group (WMD −197.00; 95% CI −900.95 to 506.95; P= 0.58; I^2=n.a.). Meta-analysis of the three trials providing applicable data on intraoperative blood loss showed no significant difference between treatment groups either (WMD 198.06; 95% CI −23.75 to 419.87; P=0.08; I^2= 0%) (Table 2). Dichotomous data on patients requiring blood transfusion could be extracted for all four trials. While comparison of PTC to THVE found no difference, those of PTC to SHVE (OR 2.86; 95% CI 1.31 to 6.22; P= 0.008; I^2=n.a.) and MTHVE (OR 5.66; 95% CI 2.29 to 14.00; P=0.0002; I^2=n.a.) revealed significantly less patients requiring blood transfusion for the HVE groups. This advantage for the technique of HVE was also present in meta-analysis of all identified trials (OR 3.38; 95% CI 1.94 to 5.86; P<0.001; I^2=6.4%) (Table 2).

Usable data on operation time and warm ischemic time were available for three trials, whereas one of the trials by Smyrniotis et al. provided these measures as median (range).[31] The trial by Chen et al. reported significantly reduced operation time for the PTC compared to the MTHVE (WMD −8.50; 95% CI −12.56 to −4.44; P<0.0001; I^2=n.a.).[32] Meta-analyses of all three trials found no significant difference in operation time between PTC and HVE (WMD −11.56; 95% CI −25.49 to 2.36; P=0.10; I^2=37.4%) (Table 2). Besides the comparison of PTC and THVE with significantly reduced warm ischemic

Table 2 Results of Meta-Analyses Comparing Portal Triad Clamping to Techniques of Hepatic Vascular Exclusion for Secondary Outcome Parameters

OR/WMD (95% CI; P-value; I^2)	PTC vs. THVE	PTC vs. SHVE	PTC vs. MTHVE	PTC vs. HVE
Hepatic morbidity	0.53 (0.11–2.46; 0.42; n.a.)	1.88 (0.64–5.53; 0.25; 8.8%)	1.21 (0.41–3.59; 0.73; n.a.)	1.28; (0.69–2.39; 0.44; 0%)
Cardiopulmonary morbidity	0.33 (0.06–1.88; 0.21; n.a.)	0.95 (0.41–2.21; 0.91; 25.3%)	0.71 (0.26–1.92; 0.50; n.a.)	0.81 (0.47–1.40; 0.46; 0%)
Intraoperative blood loss [mL]	−197.00 (−900.95–506.95; 0.58; n.a.)	116.00 (4.33–227.67; 0.04; n.a.)	350.00 (246.16–453.84; 0.01; n.a.)	198.06 (−23.75–419.87; 0.08; 81%)
Patients with blood transfusions	2.00 (0.59–6.77; 0.27; n.a.)	2.86 (1.31–6.22; 0.01; n.a.)	5.66 (2.29–14.00; 0.01; n.a.)	3.38 (1.94–5.86; 0.01; 6.4%)
Operation time [min]	−65.00 (−126.94–−3.06; 0.04; n.a.)	−10.00 (−31.91–11.91; 0.37; n.a.)	−8.50 (−12.56–4.44; 0.01; n.a.)	−11.56 (−25.49–2.36; 0.10; 37.4%)
Warm ischemic time [min]	−7.00 (−13.21–−0.79; 0.03; n.a.)	3.00 (−5.08–−11.08; 0.47; n.a.)	0.90 (0.03–1.77; 0.04; n.a.)	−0.91 (−6.09–4.27; 0.73; 68.7%)
Aspartate aminotransferase level [U/L]	16 (−125.08–157.08; 0.82; n.a.)	−100.00 (−131.01–−68.99; 0.01; n.a.)	n.a.	−63.25 (−169.02–42.52; 0.24; 59.6%)

PTC = Portal triad clamping; HVE = Heptatic vascular exclusion; THVE = Total hepatic vascular exclusion; SHVE = Selective hepatic vascular exclusion; MTHVE = Modified technique of hepatic vascular exclusion; min = minutes; mL = milliliters; U/L = units per liter; OR = odds ratio; WMD = weighted mean difference; 95%CI = 95% confidence interval; I^2 indicates degree of statistical heterogeneity; P-values of 0.01 include all data of ≤0.01.

time in patients receiving PTC (WMD −7.00; 95% CI −13.21 to −0.79; P=0.03; I^2=n.a.),[29] there was no difference in this parameter in any other analysis, nor in meta-analysis of all three trials (WMD −0.91; 95% CI −6.09 to 4.27; P=0.73; I^2=68.7%) (Table 2).

Two trials provided usable data on postoperative transaminase (aspartate aminotransferase) levels. Postoperative aspartate aminotransferase (AST) values were significantly lower in the PTC vs. SHVE group (WMD −100.00; 95% CI −131.01 to −68.99; P<0.00001; I^2= n.a.), whereas there was no difference in meta-analysis of PTC vs. THVE and meta-analysis of both trials, respectively (WMD −63.25; 95% CI −169.02 to 42.52; P=0.24; I^2=59.6%) (Table 2). The second trial comparing PTC to SHVE reported data as median (range) and showed significantly lower AST values in the latter group.[31] Chen et al. provided figures on AST levels only. In their study, there was no difference in postoperative AST values between the PTC and MTHVE. Meta-analyses of postoperative bilirubin level and prothrombin time were not feasible, as data were mostly not reported, presented as median (range) or as figures.

Discussion

In most cases hepatic resection can nowadays be safely performed without any kind of vascular control.[7] Some conditions such as centrally located lesions or lesions adjacent to major liver vasculature may require hepatic blood flow control, particularly in case of unexpected hemorrhage. It has been controversial, if selective inflow control by PTC or combined inflow and outflow occlusion by HVE offers best benefit to patients' outcome. With the exception of lower morbidity for PTC compared to THVE, our systematic review and meta-analysis of RCTs comparing PTC to techniques of HVE revealed no advantage of either strategy regarding overall morbidity of patients undergoing hepatectomy. Further analyses revealed significantly lower transfusion rates for HVE, whereas there was no statistically significant difference in overall mortality, hepatic and cardiopulmonary morbidity, postoperative transaminase levels, operation and warm ischemic time.

In contrast to our pooled analysis of all available trials, further analysis revealed significantly less morbidity in patients treated with PTC as opposed to THVE. Our findings are in line with a case-matched study showing increased morbidity in patients who received THVE compared to patients with PTC during liver resection following prolonged neoadjuvant chemotherapy.[27] A RCT comparing SHVE to THVE in patients undergoing major liver resection confirmed these findings.[23] Despite comparable effectiveness in control of intraoperative bleeding

between THVE and SHVE, increased morbidity together with less hemodynamic tolerance of patients should reserve THVE technique for specific indications such as resections of the inferior vena cava. Introduction and application of vascular occlusion techniques is backed by data reporting intraoperative bleeding a strong predictor of patients' outcome.[1,2] Further studies suggest better tolerance of the liver to warm ischemia than massive hemorrhage and blood transfusion.[34–36] Our data suggest higher effectiveness of combined inflow and outflow control for blood loss reduction than selective inflow occlusion. Interestingly, higher transfusion rate in the PTC group did not result in inferior outcome as suggested by the above studies.

In theory, selective inflow control bears the two risks of massive hemorrhage and air embolism, particularly in case of resection for tumors involving the hepatic veins. A recent nonrandomized study on patients who underwent resection for tumors adjacent or adhering to the junction of one or more hepatic veins demonstrated SHVE of being more effective in preventing excessive hemorrhage and complications including pulmonary air embolism.[28] Patients of the studies enrolled in our analysis were, however, not limited to those with tumors of the above-mentioned location. Our results, therefore, do not generally favor either technique for patients requiring vascular control during hepatectomy. However, SHVE might be superior if lesions involve the hepatic veins.

Proportion of patients with underlying cirrhosis varied among included trials. None of the patients in the trial on THVE and only a minority of patients in both trials on SHVE had known cirrhosis, leaving the question of these techniques' safety in patients with cirrhosis unanswered. The trial by Chen et al. on cirrhotic patients reported PTC in combination with infrahepatic clamping of the inferior vena cava to be a safe and effective technique.[32] Due to lack of evidence, further trials assessing HVE in cirrhotic patients are required. Cirrhotic patients are, however, particularly susceptible to ischemia. No information could be obtained regarding proportion of patients with steatosis hepatis. Although studies on the effect of steatosis hepatis on outcome after hepatectomy are rare, they consistently report this abnormality as a risk factor for patients' outcome.[37–39] There is, moreover, mounting evidence from animal models that steatotic livers are more susceptible to ischemia and reperfusion injury, presumably due to impaired microcirculation and regeneration deficits.[40–42] Due to the fact that steatosis hepatis is probably not a rare phenomenon,[1,43] further trials should consider this factor with special regard to the different techniques of hepatic vascular control.

All identified trials in our meta-analysis used the technique of continuous vascular control during hepatic resection. While several studies recommended intermittent PTC or PTC with previous ischemic preconditioning in order to attenuate ischemic and reperfusion injury,[44,45] studies evaluating different clamping techniques and intervals for HVE are scarce. Azoulay et al. randomized patients to undergo major liver resection under SHVE with and without prior ischemic preconditioning and could not detect any positive effect on hepatocellular damage and patient's clinical outcome, respectively.[46] In the study by Smyrniotis et al., patients randomly underwent hepatic resection under SHVE with ischemic preconditioning or intermittent vascular occlusion.[25] This study did not show benefits of either technique for short ischemic times, but better cytoprotective effect of intermittent vascular occlusion in case of ischemia duration above 40 min. In analogy to PTC alone, these results suggest HVE to be performed in an intermittent fashion in case of prolonged liver transection phase until further trials provide further data on the benefit of intermittent HVE.

Systematic reviews might be influenced by potential sources of bias. Our comprehensive literature search followed the guidelines of the Cochrane collaboration and comprised the most relevant databases. Using a funnel plot, we formally tested for publication bias, which did not appear to be excessive. We cannot exclude that our literature search still might have failed to detect all relevant evidence. The limited number of RCTs that compared different techniques of HVE to PTC might form weak evidence for valid conclusions. Incomplete or missing reporting of important methodological issues such as sample size calculation, randomization process, and blinding impaired assessment of trial quality and might raise doubts on adequate power of these studies. The given clinical heterogeneity caused by varying study populations and applied techniques of HVE should be considered when interpreting our results. Particularly against the background of the limited number of studies, this heterogeneity requires very cautious interpretation of the data. We, however, consider the results of this systematic review and meta-analysis to be relevant and helpful for evidence-based decision-making regarding adequate technique of vascular control during hepatectomy. All trials were carried out at high-volume institutions by experienced surgeons, indicating comparable standards of surgical care among randomized patients. Using a random effects model, we addressed heterogeneity and therefore present more conservative estimates.[16,17]

In conclusion, besides higher morbidity in patients receiving THVE, the currently available highest level of evidence does not favor PTC or techniques of HVE regarding outcome of patients undergoing elective hepatic resection. In case of required vascular control, the preferred method should be chosen based on the surgeon's experience and the lesion's location. Total and selective hepatic

vascular exclusions appear favorable for tumors involving the inferior vena cava and the hepatic veins, respectively. Further trials are required assessing optimal technique of hepatic vascular control for patients with underlying liver abnormality.

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REVIEW ARTICLE

Early Enteral Nutrition Within 24 h of Intestinal Surgery Versus Later Commencement of Feeding: A Systematic review and Meta-analysis

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Abstract
Background We set out to evaluate early commencement of post-operative enteral nutrition versus traditional management in patients undergoing gastrointestinal surgery.
Methods Electronic databases were searched, references lists were scanned and authors contacted for additional information. We looked for randomised controlled trials comparing early commencement of feeding (within 24 h) with no feeding in patients undergoing gastrointestinal surgery. Primary endpoints were wound infections, intra-abdominal abscesses, pneumonia, anastomotic leakage, mortality, length of hospital stay and complications of feeding. Data were combined to estimate the common relative risk of post-operative complications and associated 95% confidence intervals.
Results Thirteen trials, with a total of 1,173 patients, fulfilled our inclusion criteria. Mortality was reduced with early post-operative feeding. Early post-operative feeding increased vomiting. The direction of effect is suggestive of a reduction of risk of post-surgical complications and reduced length of hospital stay.
Conclusion There is no obvious advantage in keeping patients 'nil by mouth' following gastrointestinal surgery. Early enteral nutrition is associated with reduced mortality, though the mechanism is not clear. This review supports the notion that early commencement of enteral feeding may be of benefit.

Keywords Early · Enteral · Nutrition · Post-operative

Introduction

Surgical patients are often malnourished,[1–3] which in severe cases is known to increase morbidity and mortality.[4] Prior to surgery, patients often feel nauseous or are starved for investigations. After gastrointestinal surgery, a period of 'nil by mouth' is common practice before fluids then solids are introduced. Within 24 h of starvation, changes in metabolism are evident including increased insulin resistance and reduced muscle function. Experimental data from both humans and animals shows evidence that providing nutrition in the immediate post-operative period improves wound healing (relevant to the integrity of the intestinal anastomosis), muscle function, insulin resistance and reduces sepsis.[5]

In a meta-analysis of studies comparing enteral versus parenteral nutrition, those patients receiving enteral nutrition had a lower incidence of septic complications.[6] In 1979, the first randomised study of jejunal feeding within 24 h of surgery reported tolerance of the feed and showed a reduced length of hospital stay in patients fed early.[7] Subsequent studies have given inconsistent results[8,9] and have not convincingly established a benefit for early post-operative enteral nutrition following colorectal surgery. The use of early post-operative enteral nutrition remains controversial.

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This systematic review of randomised controlled trials examines the evidence that early enteral nutrition following gastrointestinal surgery is of clinical benefit.

Materials and Methods

Eligibility Criteria and Literature Search

We defined early enteral nutrition as any oral caloric intake (i.e. normal diet or nutritional supplements) or any kind of tube feeding (gastric, duodenal or jejunal) commenced within 24 h of gastrointestinal surgery. The control arm is traditional management, defined as no caloric oral intake or tube feeding within 24 h post-operatively. Studies on parenteral nutrition were excluded from this review. Trials were considered even when blinding or use of a placebo were not described (Fig. 1).

Electronic bibliographic databases were searched from 1979 onward to identify relevant studies: Cochrane Central Register of Controlled Trials, Cochrane Colorectal Cancer Group Specialised Register, Pubmed, EMBASE and LILACS. The following search strategy was used (ENTERAL and NUTRITION) or ENTERAL NUTRITION, ((TUBE or SIP) or ORAL) FEED, (#2 and #3), DIET-THERAPY, DIETARY-SUPPLEMENTS (((#1 or #4) or #5) or #6), COLORECT, COLO, RECT, ABDOM, (((#8 or #9) or #10) or #11), (#7 and #12). Reference lists of identified articles, abstracts from conference proceedings and relevant scientific meetings were hand searched in order to identify additional trials. We contacted manufactures and authors to clarify published and unpublished data.

Data Extraction and Outcomes

A data extraction sheet was developed before identification of trials and was not deviated from during the review process. The authors (HKA, SJL, ST) independently abstracted data and quality assessed all identified primary studies, review articles or others and decided whether they should be included in the review.

Data were collected for each study on the site of surgery, formation of an intestinal anastomosis or not, if the pathology was benign or malignant, the type of feed used and the method of feed administration. Data on the following outcomes was collected: pneumonia, wound infections, intra-abdominal abscess, anastomotic leakage, length of hospital stay and mortality within 30 days post-operatively. Adverse events such as nausea and vomiting were recorded.

Assessment of Methodological Quality

We assessed the two dimensions of methodological quality that empirically have been shown to be associated with biased estimates of treatment effects[10,11]: adequacy of concealment of patients' allocation to treatment groups and double blinding. Heterogeneity was tested in a subgroup analysis comparing studies with a higher methodological score to those with lower scores.

Analysis

We combined data to estimate the common relative risk (RR) of post-operative complications and calculated the associated 95% confidence intervals (CI). For analysis, we used both random and fixed effects models. The treatment effect on length of stay was estimated using effect size (presented as mean±standard deviation). Where not stated standard deviations were estimated by dividing ranges by factor 4. Analysis was done using Revman Analyses 1.0.5 from the software Review Manager 4.2. Some outcomes were not analysed but presented in a descriptive way. We used a random effects model to estimate overall risk ratio and effect size.

Results

Descriptions of Studies

The searches revealed 38 potentially relevant trials of which 15 randomised controlled trials fitted our inclusion criteria. Two trials[12,13] were excluded because no relevant outcomes were reported and attempts to obtain unpublished data from the authors were unsuccessful. Thirteen trials fulfilled our inclusion criteria, with a total of 1,173 patients, and are presented in this review (Table 1).

Additional unpublished data was obtained for seven of the studies.[8,14–19] The earliest study was published in 1979[7]; the majority were published between 1995 and 1998.

In four of the included studies, enteral feeding was started within 6 h after surgery.[5,8,20,21] The 13 included studies all describe early enteral feeding after elective gastrointestinal surgery for a wide variety of gastrointestinal conditions. Eight trials reported patients undergoing lower gastrointestinal surgery solely.[5,14,16–19,22,23] Four studies included mixed site of surgery (upper and lower gastrointestinal). Three studies reported predominantly lower gastrointestinal surgery.[7,8,21] One study reported upper gastrointestinal or hepatobiliary as the predominant intervention.[15] One study did not report site of surgery but used the term 'intestinal resection' without specification.[20] Six studies did not state the underlying pathology of the study participants.[5,7,17,19,20,22] The seven remaining included both benign and malignant conditions.[8,14–16,18,21,23] Thirty-one patients from five trials underwent abdominoperineal

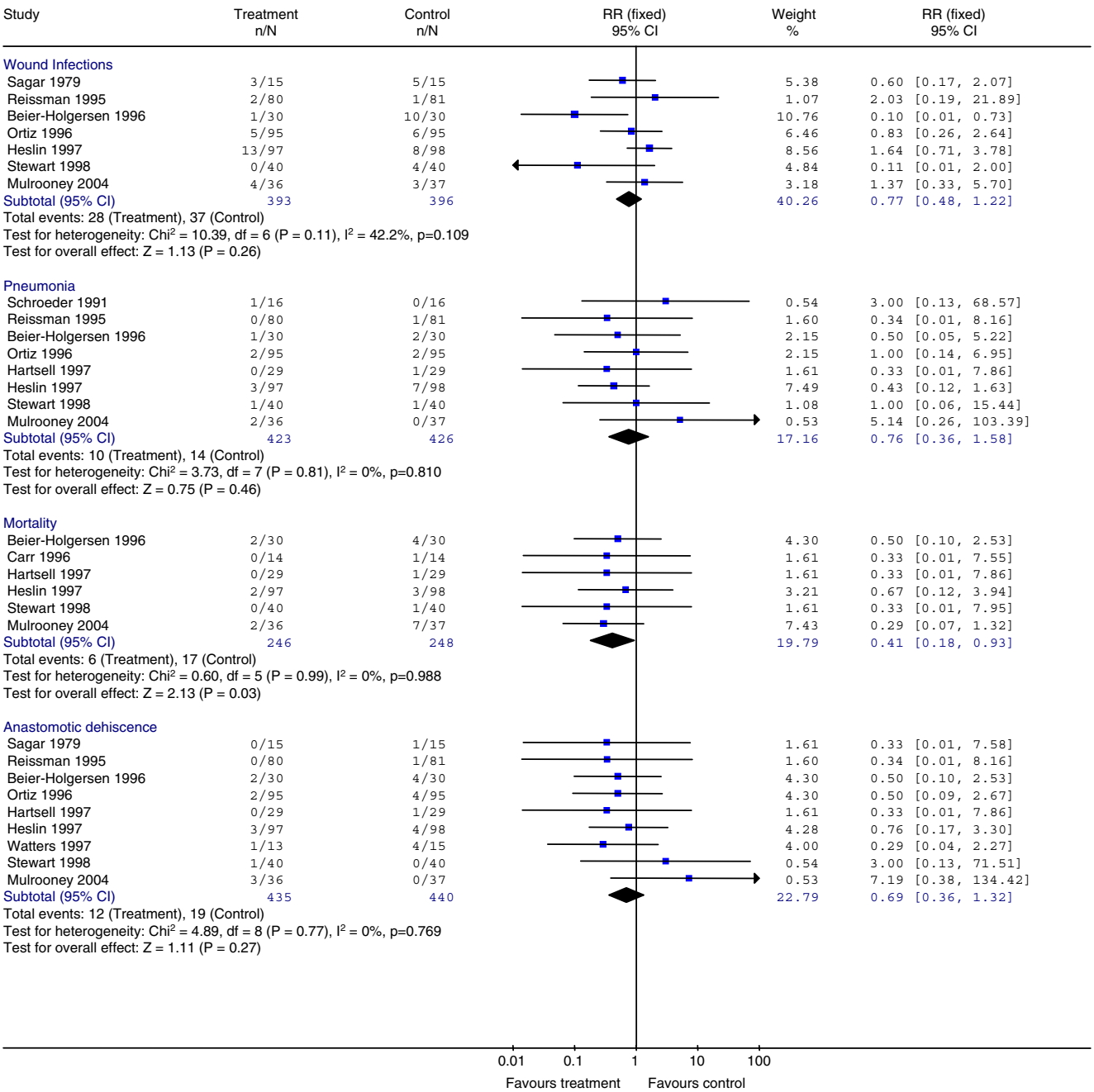

Figure 1 Early enteral nutrition within 24 h of colorectal surgery versus later commencement of feeding for post-operative complications.

resections or stoma creation and had no anastomosis. In seven studies, patients in the intervention group were fed directly into the small bowel[5,7,8,14,15,20,21] and in the remaining six studies, patients were fed orally.[16–19,22,23]

Methodological Quality of Included Studies

Six studies reported concealment of allocation of treatment (sealed envelopes) and blinding.[8,14,15,18,20,21] One trial used an open table with random numbers.[7] In the remaining six included studies, the exact method of randomisation was either unclear or not stated. Outcome assessment was only explicitly stated in the report by Heslin et al.[15]

Outcomes

Wound infection was an outcome in nine studies and was reported in seven studies. Absolute risks ranged from 0% (zero out of 40) to 13.4% (13/97) in the treatment groups and from 0% (zero out of 16) to 33.3% (ten out of 30) in

Table 1 Characteristics of 11 Trials of Early Enteral Feeding After Elective Gastrointestinal Surgery

Study	Year	Patient numbers		Feed type	Route of feeding	Pathology		Site of surgery			Primary outcome measures
		Active	Control			Malignant (%)	Benign (%)	Upper (%)	Lower (%)	HPB (%)	
Mulroony et al.[14]	2004	36	37	Standard	NJ	73	27	0	100	0	Infection, mortality, LHS, GI adverse effects
Smedley et al.[18]	2004	35	44	Standard	Oral	67	33	0	100	0	LHS; complications; costs
Stewart et al.[19]	1998	40	40	Standard	Oral	nr		0	100	0	Complications such as tube reinsertion
Heslin et al.[15]	1997	97	98	Imm En	Jej	93	7	51	0	49	Wound infection; anastomotic leakage; intraabdominal abscess; mortality
Hartsell et al.[23]	1997	29	29	Standard	Oral	64	28	0	100	0	Anastomotic leakage; mortality; adverse effects
Watters et al.[21]	1997	15	16	Standard	Jej	93	7	96	0	4	Anastomotic leakage; LHS
Beier-Holgersen et al.[8]	1996	30	30	Standard	ND	65	35	13	87	0	Wound infection; intra-abdominal abscess, anastomotic leakage; mortality
Ortiz et al.[16]	1996	95	95	Standard	Oral	87	23	0	100	0	Wound infection; anastomotic leakage; intra-abdominal abscess; intestinal obstruction
Carr et al.[20]	1996	14	14	Standard	NJ	nr		nr			Wound infection; mortality; LHS
Reissman et al.[17]	1995	80	81	Standard	Oral	nr		0	100	0	LHS; various complications e.g. tube reinsertion
Binderow et al.[22]	1994	32	32	Standard	Oral	nr		0	100	0	LHS; adverse events
Schroeder et al.[5]	1991	16	16	Standard	NJ	nr		0	100	0	Myocardial infarct; obstruction; various complications
Sagar et al.[7]	1979	15	15	Elemental	NJ	nr		27	73	0	Wound infection; anastomotic leakage; intra-abdominal abscess; LHS

Imm En Immune enhancing, *NJ* nasojejunal tube, *ND* nasoduodenal tube, *Jej* jejunostomy, *HPB* hepatobiliary, *nr* not reported, *LHS* length of post-operative hospital stay

the control groups. Combining results, the (RR) was 0.78, 95% CI 0.38, 1.62 (random effects model) and 0.77, 95% CI 0.48 to 1.22 (fixed effects model), with some heterogeneity between trials (χ^2=10.39, P=0.11). Beier-Holgersen et al.[8] differed from the other studies having a much higher proportion of patients with wound infection in the control group. A sub-group analysis without this study revealed less heterogeneity between trials (χ^2=5.70, P=0.46 and a RR 0.78, 95% CI 0.45 to 1.35).

Intra-abdominal abscess was reported in ten studies of which five studies reported events. Absolute risks ranged from 0% (zero out of 36) to 13% (two out of 15) in both the early feeding groups and the control groups. The combined RR for this outcome was 0.94, 95% CI 0.32, 2.77 (random effects model) and 0.87 95% CI 0.31, 2.42 (fixed effects model), with very little heterogeneity between trials (χ^2=1.45, P=0.84).

Anastomotic dehiscence was an outcome in ten studies and occurred in nine studies. The risk of dehiscence ranged from 0% (zero out of 80) to 8.3% (three out of 36) in early feeding groups and from 0%(zero out of 40) to 27% (four out of 15) in control groups. There was little evidence of benefit or harm related to the anastomosis with early feeding RR 0.62 95% CI 0.30, 1.28 (random effect model) and 0.69, 95% CI 0.36, 1.32 (fixed effect model) and heterogeneity between studies (χ^2=4.89, P=0.77).

Pneumonia was an outcome parameter in nine studies and reported in eight. Pneumonia events ranged from 0% to 6.3% (one out of 16) in the treatment group and from 0% to 7.1% (seven out of 98) in the control group. Combining results, there was some evidence of a reduced risk of pneumonia with early feeding, with a RR of 0.71, 95% CI 0.32, 1.59 (random effects model) and 0.76, 95% CI 0.36, 1.58 (fixed effects model) with heterogeneity (χ^2=3.73, P=0.81).

Mortality was reported in six of the ten studies where it was an endpoint. Apart from one study (30-day mortality

recorded[8]), all deaths occurred in hospital. Mortality reported ranged from none to 6.7% (two out of 30) in the early feeding groups and from none to 19% (seven out of 37) in the control groups. The combined RR was 0.42, 95% CI 0.18, 0.96 (random effects model) and 0.41, 95% CI 0.18, 0.93 (fixed effects model), with very little heterogeneity between trials (χ^2=0.6, P=0.99). The most commonly reported cause of death was anastomotic leakage, re-operation and acute myocardial infarction (Table 2).

Length of hospital stay was reported in 12 of the 13 studies. The mean length of stay ranged from 6.2 to 19.0 days in early feeding groups and from 6.8 to 16.0 days in control groups. Results show a reduction in duration of hospital stay for the treatment group weighted mean differences −0.89, 95% CI −1.58, −0.20 (random effects model) and −0.60, 95% CI −0.66, −0.54 (fixed effects model) with some evidence of heterogeneity between studies (χ^2=18.88, P=0.09).

Adverse Effects Reported

There was an increase in the risk of vomiting among patients fed early RR 1.23, 95% CI 0.97, 1.55 (random effects model) and 1.27, 95% CI 1.01, 1.61 (fixed effects model). Absolute risks ranged from 21% (17/80) to 50% (15/30) in the early feeding groups and from 14% (11/81) to 57% (17/30) in the control groups. When nasogastric tubes were not placed routinely at the time of surgery, the rate of placement because of nausea and vomiting was not higher in patients fed early RR 1.21, 95% CI 0.73 to 1.99, P=0.46.

Heslin et al.[15] reported that 9.3% of jejunostomies were associated with complications (clogging, local infection, fell out); one patient developed small bowel necrosis and another developed a prolonged fistula. A few trials reported other adverse events, such as acute myocardial infarction[5,8,19] and thrombosis,[16] but they were too infrequently reported to make meaningful comment.

Publication Bias

We examined publication bias (funnel plots) for all outcomes. There was no clear evidence of asymmetry and, thus, publication bias for the included trials or for any of the reported outcomes.

Discussion

The key message of this systematic review is that there is no obvious benefit for keeping patients ‘nil by mouth’ after gastrointestinal surgery. Mortality was reduced with early enteral feeding. Our findings are suggestive of a reduced risk of infectious complications and length of hospital stay with early enteral feeding.

This review includes two additional studies (n=152 patients)[14,18] which were published following our previous meta-analysis of early enteral feeding published in 2001.[24] Whilst much data on clinical complications could not be extracted from these two studies, our principle finding, which keeping patients ‘nil by mouth’ after gastrointestinal surgery is of no obvious benefit, is unaltered. There was little evidence that the nature of operative and peri-operative management had changed significantly within the two later studies[14,18] as lengths of hospital stay were not dissimilar to previous studies.

The reduction in mortality with early feeding is highly relevant though difficult to explain. In all six studies where mortality was reported, the direction effects were towards reduced mortality in early fed patients. The causes of death in control patients were predominantly due to cardiac dysfunction, anastomotic leak or sepsis all conditions that

Table 2 Causes of Mortality

Study	Deaths	Active	Control
Mulroony et al.14	2:7	Stroke “peri-operative complications”	Pneumonia 2× myocardial infarction Sepsis Cardiac failure 2× “medical complications”
Stewart et al.[19]	0:1	None	Myocardial infarction
Heslin et al.[15]	2:3	Not described	Not described
Hartsell et al.[23]	0:1	None	Anastomotic leak causing sepsis
Beier-Holgersen et al.[8]	2:4	Myocardial infarction Anastomotic leak (died after re-operation)	Pulmonary failure 2× anastomotic leak (died after re-operation) Septicaemia
Carr et al.[20]	0:1	None	Sepsis

benefit from nutrition. Unfortunately, there are no reliable surrogate markers of clinical benefit that would help determine any mechanism of benefit. Reduction of the mortality tended to be larger in the smaller studies, which may be due to chance, publication bias or a lower methodological quality of the smaller studies. Mortality was one out of nine outcome measures examined and small study bias was not evident for the other outcomes. It is possible that the association of decreased mortality is due to chance.

Individual clinical complications failed to reach conventional levels of statistical significance but the direction of effect indicates that earlier feeding may reduce the risk of dehiscence. Unfortunately, it was impossible to comment on many factors which may have influenced the clinical complication endpoints such as the fitness of the patient, experience of the surgeon, whether resections were on the small or large bowel, the operation time, post-operative pain analgesia, pain control, use of antibiotics and the success of the operation in removing the underlying pathology. Furthermore, the definition of dehiscence varied between the trials and in many trials, no explicit definitions were presented for other clinical complications such as pneumonia. A good example is in the study by Beier-Holgersen et al.[8] where wound infections occurred in a third of control subjects, whereas in other studies, minimal infection rates were noted. This would suggest that their definition of wound infection was too sensitive to be clinically relevant.

Length of hospital stay was reduced in nine out of 13 studies. Overall reduction corresponded to about a day, which is both clinically and economically important. Reduction in complication rates may explain this observation as might faster return of gastrointestinal function. Post-operative feeding after non-gastrointestinal surgery has also been shown to reduce post-operative inpatient stay. Few studies assessed the financial impact of early enteral feeding.

The 13 randomised trials identified were clinically heterogenous and most of them were small and of sub-optimal methodological quality. Combining trials that differ in terms of underlying condition, operation and intervention may not be appropriate. However, we were interested in the pragmatic comparison of early versus deferred feeding strategies after gastrointestinal surgery and not in differences between feed types or specific routes of feeding. It is noteworthy that the effect of early nutrition appears to be homogenous across a set of trials that were clearly heterogeneous in clinical terms. Our ability to detect heterogeneity between trials was, however, limited by the small number of patients in trials and inadequate reporting. Methods of randomisation and blinding of outcome assessments were not described in sufficient detail, which means that the uncertainty regarding the methodological quality of trails remains.

Surgical and anaesthetic practice has changed since publication of the first randomised controlled trial in 1979. Surgery has become less ‘stressful’ especially if undertaken laproscopically. Patients recover from anaesthetics faster and when combine with improved post-operative analgesia and attention to fluid balance, patients mobilise and recover more rapidly. Thus, patients today may be much more able to tolerate early enteral feeding than was seen in previous studies. It is also possible that the perceived benefits of early enteral feeding may not be so obvious.

This review has shown that keeping patients ‘nil by mouth’ is without benefit and early enteral feeding may reduce mortality. We believe that there is sufficient evidence to justify a large adequately powered clinical trial to show differences in endpoints and assess the positive benefits in patients undergoing gastrointestinal surgery, in particular, to examine if the amount of feed patients receive is relevant to outcome measures.

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Guarantor of the article Stephen J Lewis

Specific author contributions Search strategies were developed and primary trials were evaluated using a data extraction form developed by HKA and SJL. HKA, SJL and ST were all involved in data extracting, interpretation and drafting the review.

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GI IMAGE

CT Findings in Obturator Hernia with Meckel's Diverticulum—A Case Report

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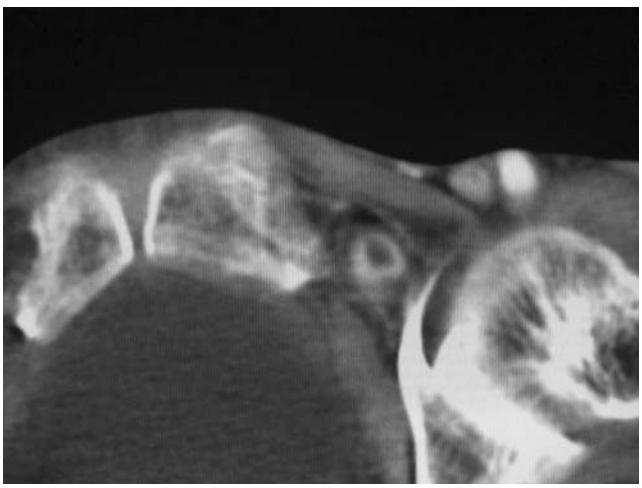
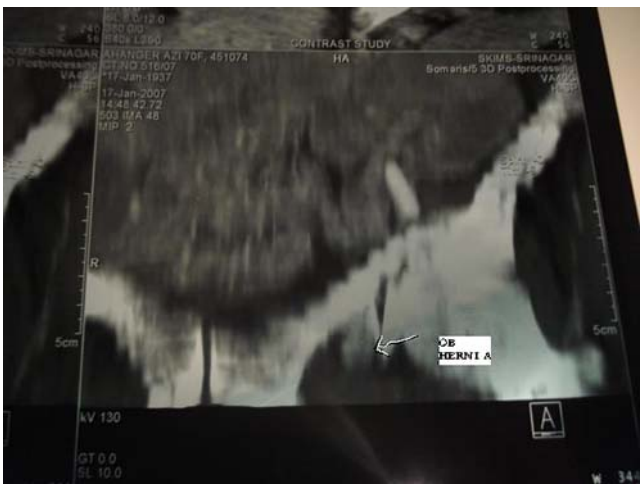
Abstract Obturator hernia is rare, constituting <2% of all abdominal hernias. Clinical diagnosis is rarely made due to vague signs and symptoms. Delayed diagnosis markedly increases postoperative morbidity and mortality especially because the affected patients are often old with other comorbid conditions. Pelvic CT is almost 100% accurate in the diagnosis of obturator hernia and should be the modality of choice in older patients presenting with intestinal obstruction of unknown etiology.

Keywords Obturator hernia · Meckel's diverticulum · Computed tomography

Case Report

A 75-year-old female presented to the gastroenterology department with a case of unexplained abdominal pain of 1 month duration. The pain was also referred to the left hip and medial thigh. X-ray of the abdomen showed evidence of small gut obstruction. Ultrasound of the abdomen did not reveal any significant information as to the cause of the abdominal pain. CT scan of the abdomen after oral and IV contrast revealed small bowel herniation through internal obturator foramen with distended small gut loops in the abdomen.





The patient was subjected to emergency abdominal surgery, which revealed small bowel herniation through obturator foramen.The hernial sac contained inflamed Meckel's diverticulum along with loop of adjacent small gut. The postoperative course in the hospital was uneventful.

Discussion

Obturator hernia is relatively rare, representing 0.07–1.4% of all hernias.[1] Elderly women with chronic disease are

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frequently affected. Most common presentation is intermittent mechanical small bowel obstruction, associated sometimes with pain in the groin or thigh area. Clinical findings are usually nonspecific and a correct preoperative diagnosis is rarely made on the basis of clinical findings alone.[2] Lack of accurate preoperative diagnosis leads to delayed intervention, resulting in high gut resection rate and a mortality of >25% in some series.[3] Clinically, specific signs, like Howship–Romberg sign or Hannington–Kiff sign, are rarely present or detected in the affected patients[4] and, in fact, were absent in all patients in one study.[3]

Pelvic computed tomography with oral and i.v. contrast is a very useful diagnostic tool to investigate cases of clinically indeterminate small bowel obstruction like obturator hernia. CT scan shows the classical signs of incarcerated bowel through the obturator foramen and was successful in all six cases of one study.[5] Other studies also revealed CT to be 100% accurate in the diagnosis of Obturator hernia.[6]

Most of the studies so far have revealed incarcerated small bowel, especially ileum, within the hernial sac. Our case is unique in that it contained incarcerated Meckel's diverticulum, which was successfully resected with uneventful postoperative recovery.

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GI IMAGE

Total Gastrointestinal Tract Necrosis After Ingesting a Considerable Amount of Hydrochloric Acid

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Abstract
Background It has not been reported that ingesting large amounts of strong acid resulted in total gastrointestinal tract necrosis. Here we describe a case of a man with total gastrointestinal tract necrosis after ingestion of a considerable amount of hydrochloric acid.
Discussion Computed tomography (CT) scan showed significant free air in the neck, lateral esophagus, and abdominal cavity, which indicated perforation of the esophagus and gastrointestinal tract. In addition, the abdominal CT image showed splenic subcapsular hematorna and swollen pancreatic head caused by strong acid causis. We found the entire gastrointestinal tract from stomach to rectum necrosis in the emergency exploratory laparotomy. Our case suggests that ingestion of a considerable amount (e.g., 500 mL) and concentration of strong acid could result in total gastrointestinal tract necrosis. Emergency laparotomy should be performed as early as possible to benefit this kind of patient.

Keywords Hydrochloric acid · Caustic ingestion · Gastrointestinal tract necrosis · Caustic injury

Case Report

A 45-year-old man was admitted to our hospital for ingesting about 500 mL 20% (6 mol/L) hydrochloric acid in a suicide attempt. He was previously healthy and had no history of digestive system disease. The patient was in a state of shock and showed change in consciousness. Before operation, blood test indicated severe metabolic acidosis (pH: 6.7, HCO_3^-: 4.1 mmol/L). The patient's white blood count was 20,300/μL, creatinine 198 μmol/L, and lactic acid 3.4 mmol/L (normal 0.7–2.1). Computed tomography (CT) scan showed significant free air in the neck, lateral esophagus, and abdominal cavity, which indicated perforation of the esophagus and gastrointestinal tract. In addition, the abdominal CT image showed splenic subcapsular hematorna (high density area around splenic subcapsule) and swollen pancreatic head (Fig. 1). Emergency exploratory laparotomy was performed with intensive medical treatment and life support. The time period from ingestion to operation was about 2 h. When the abdomen was opened, large amounts of strong acid fluid were found in the abdominal cavity. The entire gastrointestinal tract from stomach to rectum all showed diffuse blackish discoloration and had no enterocinesia, which indicated total gastrointestinal necrosis. Moreover, the peritoneum and omentum showed extented necrosis due to the strong acid causis (Fig. 2). The patient died during the operation.

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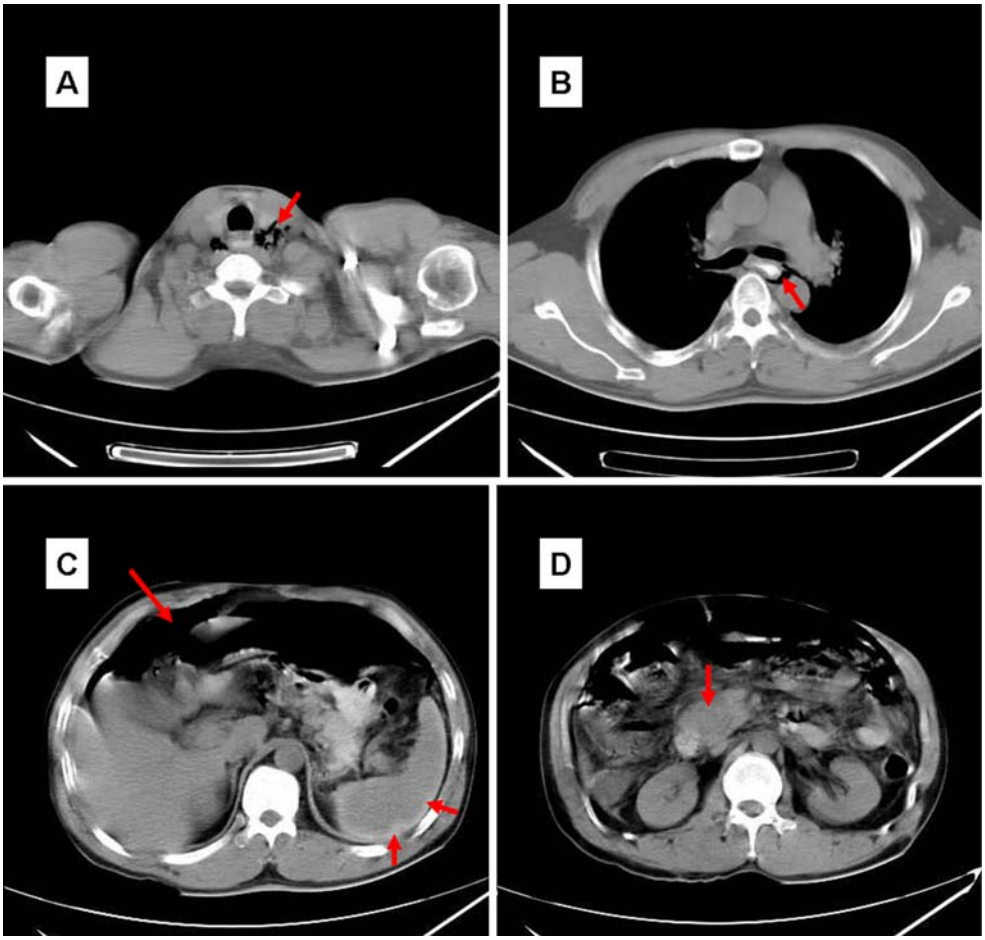

Figure 1 **a** Axial CT image showing free air in neck (*arrow*), **b** free air in lateral esophagus (*arrow*), **c** free air in abdominal cavity (*arrow*), **d** swollen pancreatic head (*arrow*).

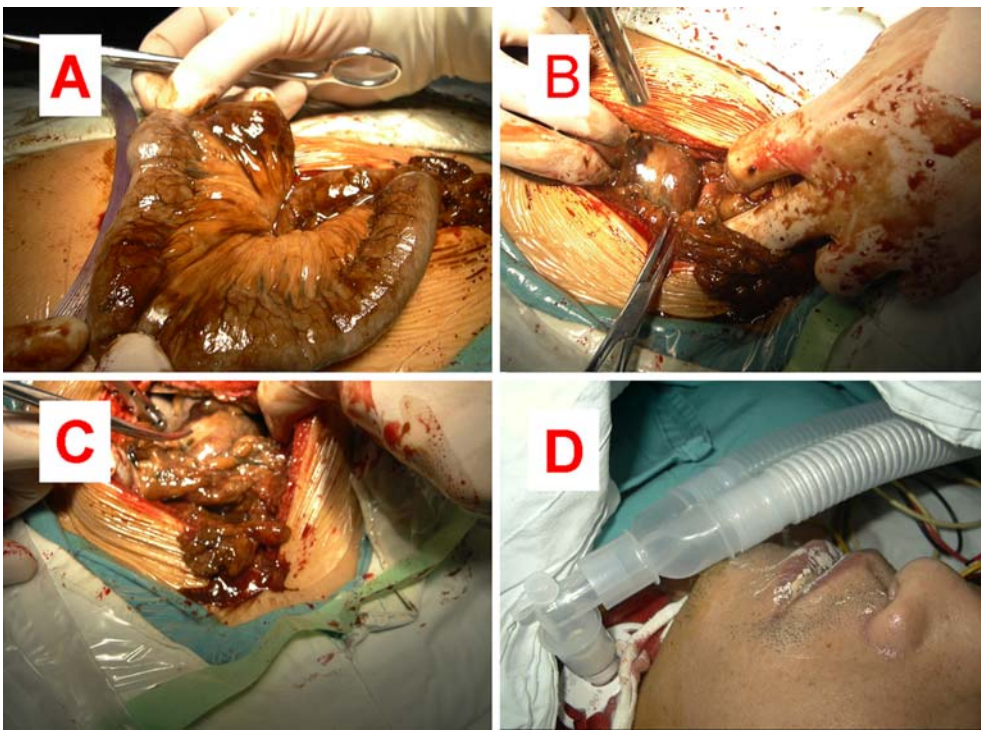

Figure 2 **a** Small intestine necrosis, **b** rectum necrosis, **c** stomach and omentum necrosis, **d** mechanical ventilation with tracheotomy and the causis caused by hydrochloric acid in the patient's mouth.

Discussion

There are only a few previous reports about extensive acid injury involving the GI tract beyond the pylorus.[1,2] It has not been reported that ingesting large amounts of strong acid resulted in total gastrointestinal tract necrosis. The reported volume of ingestion of strong acid ranged from 80 to 500 mL.[1,3,4] The amount of hydrochloric acid ingested by this patient was quite large, it would be reasonably to believe that it would lead to severe consequences. It is also scarce that the CT image show significant free air in the neck, lateral esophagus, and abdominal cavity simultaneously. The management of metabolic acidosis for the patient was not prompt enough, which could be another cause leading to such devastated clinic outcome. The immediate surgery is necessary when the amount of ingesting strong acid is large, especially when there are the signs of perforation. With regard to this patient, our operation may be late slightly. The surgical procedure should be performed as early as possible to benefit the patient, although the role of surgery in patients with severe corrosive burns is not clear.[5] The pyloric spasm induced by acid could prevent acid fluid from reaching the duodenum. However, such protection of pyloric spasm will be seriously diminished under such circumstance as a large volume of strong acid was ingested (e.g., 500 mL). During the operation, prompt clamping of the pylorus could stop the acid fluid from passing through the pylorus and improve prognosis.[3] The pancreatic head lesion should be noted in the patients with a considerable amount of strong acid ingestion. If there is any possibility of pancreatic head involvement by a strong acid, it is reasonable to resect the pancreatic head. Furthermore, immediate Whipple's operation can also be considered.[1,3] However, we believe that it does not accord with the principle of damage control surgery nowadays. In addition, splenic subcapsular hematorna caused by strong acid seen in this patient should also be noted.

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