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The Esophageal Anastomosis: Traditional Methods to Prevent Leak

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Despite significant advances in staging, preoperative selection, operative techniques, and post-operative care, esophagectomy remains a morbid procedure. Recent large multi-institution studies reveal a mortality rate of 8–11% with a morbidity rate of 40–50%.[1,2] Anastomotic complications remain a significant contributor to morbidity and mortality but vary widely. In the same large multicenter studies, anastomotic complications were reported in 15–37% of patients.[1,2] Although high volume centers can demonstrate significantly lower anastomotic complication rates, the contribution to post-operative morbidity and mortality cannot be understated. In a single center report on 393 consecutive esophagectomies, Briel and colleagues[3] from the University of Southern California documented a 10% rate of postoperative conduit ischemia or anastomotic leak with an overall mortality of 3.5%. Conduit ischemia and leak was associated with a threefold increase in mortality and accounted for 37% of all hospital deaths after esophagectomy. Moreover, anastomotic ischemia and leak predisposes patients to post-operative stricture formation,[3] increased length of stay,[4] increased risk of adverse medical events,[4] and poorer quality of life.[5]

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The factor unique to esophageal reconstruction that dramatically increases the rate of anastomotic complications is ischemia. In order to replace the intrathoracic length of the esophagus, the surgeon is forced to partially devascularize an abdominal organ, most commonly the stomach. The result is relative ischemia of the conduit at the anastomotic site which has been well documented. For example, Boyle and colleagues demonstrated up to a 72% reduction in flow in the proximal stomach following division of the left gastric artery.[6] Traditional methods to prevent leak basically involve an evolution of surgical techniques that help mitigate this factor. Unfortunately, the incredible variability in techniques prevent a definitive conclusion regarding the optimal technique to minimize technical complications. Several surgical variables, however, that have been reasonably well studied include anastomotic technique, conduit location, anastomotic location, and conduit selection.

Anastomotic Technique

The evolution of the anastomotic technique began with the hand-sewn anastomosis. The anastomosis can be performed with single vs. double layer and running vs. interrupted techniques with a variety of suture material. There has been no clear demonstration of a superior technique, surgeon experience is likely the most important factor. The introduction of mechanical stapling devices, however, has dramatically altered the landscape of esophageal surgery. Early stapling techniques utilized an end to end technique with a circular stapler. In a meta-analysis of four randomized controlled trials Beitler and colleagues[7] demonstrated no difference in anastomotic leak rates (stapled 9% vs. hand-sewn 8%; $P=0.67$) but did reveal a higher rate of

stricture formation in the stapled group (27% vs. 16%; $P<0.02$).

In the 1990s a hybrid stapled technique was subsequently introduced by Collard and colleagues[8] extrapolating from experience with transoral stapling of Zenker's diverticulum. Utilizing a side-to-side technique stapled posteriorly and hand-sewn anteriorly, they were able to demonstrate a 65% increase in the anastomotic cross-sectional area. Orringer and colleagues[9] subsequently published a series of 114 consecutive patients with a modified hybrid technique that revealed a reduction in anastomotic leak rate to 2.7% from 10–15% in 1,000 historical controls. Notably, this led to a reduction in overall length of stay and patient satisfaction. Additionally, Ercan and colleagues[10] at the Cleveland Clinic retrospectively compared the modified Collard technique with a standard hand-sewn anastomosis in 274 patients. Using a propensity-matched analysis, they revealed freedom from anastomotic leak was not statistically significant between groups (stapled 96% vs. sewn 89%; $P=0.09$) but freedom from cervical wound infection (stapled 92% vs. sewn 71%; $P=0.001$) and freedom from anastomotic dilatation (stapled 34% vs. sewn 10%; $P<0.0001$) was improved in the stapled group.

Conduit Location

Various routes may be utilized to bring the conduit up into the chest for anastomosis including posterior mediastinal, retrosternal, transpleural, and subcutaneous. The most common route utilized today is the posterior mediastinal route; however, the retrosternal route is also utilized, sometimes out of necessity (e.g. staged reconstruction after caustic ingestion or perforation) or due to concerns regarding local tumor recurrence affecting conduit function or conduit damage due to adjuvant radiation. A meta-analysis of six randomized controlled trials by Urschel and colleagues,[11] in fact, did not demonstrate a difference in outcomes for the two routes. More modern single-center series, however, have demonstrated a significantly higher leak rate utilizing the retrosternal route.[12,13] This is likely due to the longer route that is required[14] as well as compression and angulation at the thoracic inlet which often requires an additional manubrial resection thus adding to the morbidity of the procedure.

Conduit Selection

The stomach has evolved as the conduit of choice for gastrointestinal reconstruction following esophagectomy in most centers due to ease of preparation, robust blood supply, and adequate length. Alternative conduits including the colon and jejunum are utilized less frequently, most often when the stomach is not a suitable conduit. Proponents of colonic interposition, however, have suggested that the colon may be a superior conduit due to decreased rates of reflux esophagitis and better long-term functional outcomes.[15] When comparing conduits, anastomotic complications appear to be highly surgeon-dependent and likely related to experience as well as patient selection bias. For example, Briel and colleagues[3] report significantly lower anastomotic complication rates in patient undergoing colonic interposition when compared to gastric conduits. Others, however, have reported higher anastomotic complication rates associated with colonic interposition[12,13,16] yet these are also centers that tend to use the colon only when the gastric conduit is unsuitable.

Anastomotic Location

Debate persists regarding the optimal location for the esophageal anastomosis. Generally speaking, the cervical anastomosis is associated with a higher leak rate but the morbidity and mortality associated with the leak is lower when compared to the intrathoracic anastomosis.[17] Contemporary studies, however, have demonstrated mortality for intrathoracic leaks comparable to cervical leaks[18–20] thus supporting a renewed interest in the transthoracic approach.

Two large multicenter trials have compared the transthoracic to the transhiatal approach. Connors and colleagues[2] utilized the Nationwide Inpatient Sample database to evaluate 17,395 patients undergoing esophagectomy and demonstrated no difference in gastrointestinal complications (including anastomotic complications) when controlling for confounding variables such as age, comorbidities, and hospital volume. Similarly, utilizing the SEER database, Chang and colleagues[1] performed a retrospective cohort review comparing 225 transhiatal resections to 643 transthoracic resections. The unadjusted mortality rate for the transhiatal approach was significantly lower than the transthoracic approach (6.7% vs. 13.1%; $P=0.009$) but the anastomotic complication rate was higher (43.1% vs. 34.5%; $P=0.02$). The hazard ratio for mortality, however, when adjusted for confounding variables, was not significantly different. A similar analysis was not performed for anastomotic complications. Notably these studies were not clearly differentiating anastomotic location but rather the surgical approach, the transthoracic route included McKeown ("three hole") esophagectomies which place the anastomosis in the neck.

There are many other variables that likely contribute to anastomotic complications. Malnutrition, neoadjuvant therapy, smoking, diabetes mellitus, and other comorbidities

likely play a significant role. Technical variables such as conduit size, conduit compression/twisting, and utilization of gastric outlet procedures (e.g. pyloroplasty) are important considerations. Hemodynamic management and postoperative management including conduit decompression are additional important variables. Finally, surgeon experience and hospital volume are important contributors and emphasizes the importance of tracking outcomes in order to optimize care for patients requiring esophageal resection.

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The Esophageal Anastomosis: How Improving Blood Supply Affects Leak Rate

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Keywords Ischemic conditioning · Supercharge · Esophageal leak · Anastomosis · VEGF · Delay phenomenon

surgical preparation of the conduit in order to reduce morbidity and optimize patient outcomes.

Introduction

Esophagogastric resection and anastomosis have long served as a technically demanding task for gastrointestinal and thoracic surgeons. The location of the structures involved and the morbidity incurred from ischemia of the completed conduit have put into question the validity of the operation. Several techniques including preoperative embolization of specified vessels, vascular anastomoses at the time of esophagogastric anastomosis, and staged vascular ligation followed by delayed esophagogastric resection and anastomosis have been employed over the last 50 years to reduce leak rates from 25% to less than 6% in some series. Angiogenic gene therapy is now being investigated as a modality to further reduce morbidity of the anastomosis. The next advancement in esophagogastric resection and anastomosis will likely utilize a multidisciplinary approach with endoscopic delivery of conditioning agents, as well as

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Discussion

From the inception of surgical approaches to diseases of the human foregut, the resection and anastomosis of the esophagus has provided surgeons with a formidable challenge. Traversing the thoracic outlet into the posterior mediastinum, the esophagus courses between vital and fragile structures making the surgical approach to it (along with resection and replacement) a technically demanding and inherently risky endeavor.

From the 1670s through the initial portion of the twentieth century, surgeons sought to resect the esophagus and replace it either using non-autologous components such as eel skin or rubber hoses, or avoid the hazards of the posterior mediastinum for reconstruction via substernal or extracorporeal approaches. By the second half of the twentieth century, the stomach and colon became the standard conduits for use as the neoesophagus, most often placed in anatomic apposition to the transected end of the esophagus. The configuration of these reconstructions, which are predisposed to inadequate blood supply to the furthest portion of the conduits and the resultant ischemia, has played a role in the sequelae of esophagogastric and esophagocolonic anastomotic leaks in 3–25% of cases.

To combat ischemia of the neoesophagus, several approaches have been investigated with the common goals of improved blood flow to the at risk anastomosis and reduced rates of ischemia related anastomotic leaks. In the late 1990s, Akiyama et al. performed preoperative angiographic embolization of the left gastric, distal right gastric,

and splenic arteries in a study group of patients, followed a few days later by esophagogastrectomy with gastric tubularization and esophagogastrostomy. The same operation was performed in a single stage in a control group without preoperative embolization. The reduction in blood flow to the furthest end of the gastric conduit was 33% from baseline in the embolization group and 67% from baseline in the control group. Anastomotic leak rate was slightly higher in the control group. The majority of embolized patients suffered either epigastric pain and/or nausea following embolization, however splenic infarction was a rare event.[1]

A different approach to reducing the effects of ischemia to the end of the gastric conduit was also being investigated via vascular anastomoses and "supercharging" of the neoesophagus. Although descriptions of mesenteric vascular augmentation commenced from the 1940s, quantitative investigation of this principle was performed by Nagawa et al. in 1997 when nine patients underwent intraoperative anastomoses between the left gastroepiploic and transverse cervical arteries resulting in no anastomotic leaks, as compared to the 10–25% leak rate previously experienced by the group using unaugmented techniques.[2] Murikami et al. expanded this experience to a group of 15 patients who underwent vascular anastomoses involving the short gastric vessels and transverse cervical vessels. A 36% increase in blood flow was noted at the tip of the gastric conduit following venous anastomosis, due to decreased venous congestion and a 108% increase in blood flow was noted following venous and arterial anastomoses. No leaks were noted in the study patients, while 23% of the 26 control patients suffered anastomotic leaks.[3] The vascular anastomoses resulted in both decreased venous congestion and augmented arterial inflow at the level of the at risk anastomosis during the critical period of initial healing, and hence reduced the incidence of anastomotic leaks. This improved outcome however required multiple surgical teams with experience in microvascular anastomoses as well as esophageal surgery and increased operative time and logistic (microsurgical) arrangements. A simple approach which could be applied via a minimally invasive approach would streamline this process.

In 2004, Reavis et al. revisited the concept of preoperative ischemic conditioning in an opossum model. Fourteen animals underwent ligation of the left, distal right, and short gastric vascular pedicles 4 weeks prior to definitive esophagogastrectomy and esophagogastrostomy formation instituting the Delay phenomenon of conduit conditioning. Blood flow to the gastric fundus initially dropped by 73% following ligation; however, at the time of definitive resection blood flow to the newly formed gastric tube was three times higher in the Delay animals when compared to 15 control animals which underwent definitive resection without prior Delay. There were no leaks in the Delay group and two leaks leading to death in the control group. Upon histological evaluation, the anastomotic tissue showed significantly more atrophy of the muscularis mucosa in the control group than the Delay group and the Delay animals showed greater numbers of capillaries throughout the conditioned tissue when compared to the baseline control animals.[4] Clinical use of Delay in humans was initiated by Nguyen et al. who staged nine individuals with laparoscopic ligation of the left gastric vascular pedicle along with a staging laparoscopy and placement of jejunal feeding catheter, followed by definitive esophagogastrectomy and esophagogastrostomy several days later. The additional procedure took 45 min and none of the patients leaked.[5,6] Holscher et al. expanded this concept to 83 patients who underwent ligation of the left gastric vascular pedicle and gastric conduit formation followed by definitive resection and anastomosis 4 to 5 days later. Six percent of patients had minor leaks which were treated with stenting and there were no deaths at 3-months follow-up.[7] The advantages of this concept include the simplicity of application via a minimally invasive approach, the opportunity to recover from two smaller operations rather than one single larger operation, and the reduction of clinical severity of anastomotic leaks when they do occur. Improving on this requires a single stage application with the most minimal invasive approach possible and very specifically targeted tissues. This has been studied using plasmid delivery of vascular endothelial growth factor (VEGF) by Enesvedt et al. Five study opossums received VEGF 165 to the gastric fundus involved in the most at risk portion of the neoesophagus immediately following esophagogastrectomy and esophagogastrostomy. There were no leaks in the study group and one leak in the control group of six animals. Increased bursting strength, neovascularization, and VEGF mRNA were detected in study animal tissue compared to the control group.[8] This technology has the potential to be deployed laparoscopically, endoscopically, or even orally via cell receptor directed therapy and is applicable not only to esophageal anastomoses but to any hollow viscus anastomosis. At the present time this is probably best reserved for situations involving non-malignant disease states in order to avoid potentially augmenting blood flow to microscopic residual malignant disease following resection.

Conclusions

Overall, the use of various modalities to increase blood flow to the esophageal anastomosis following resection and reconstruction results in decreased leak rates from initially as high as 25% to now less than 6%. In order to improve on the previous advances, we will likely employ a multidisci-

plinary approach incorporating molecular and genetic engineers to develop targeted delivery systems and endoscopic as well as surgical delivery of those systems to the at risk tissue, in order to condition the new conduit and strive for optimal surgical outcomes.

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Dilating the Stenotic Gastrojejunostomy After Laparoscopic Roux-en-Y Gastric Bypass for Morbid Obesity: When Things Go Wrong

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Keywords Stenotic gastrojejunostomy · Laparoscopic Roux-en-Y gastric bypass · Dilation

Introduction

The number of bariatric surgeries performed worldwide every year continues to grow because of the increased number of morbidly obese individuals that fail medical treatment and the increased awareness of the safety and success rate of bariatric surgery. However, as expected—and as a result of the above mentioned—the number of complications of bariatric surgery continues to grow as well. Stricture formation at the gastrojejunal anastomosis (GJA) is a relatively common complication after laparoscopic Roux-en-Y gastric bypass (LRYGB) that is reported in 3% to 27% of patients. Treatment options of this complication can vary from observation, endoscopic dilatation, or surgical revision depending on the time of onset and nature of the stricture.[1–3]

Etiology

The etiology of this complication is multifactorial. Chemical agents, such as nonsteroidal anti-inflammatory drugs and tobacco abuse; technique (circular stapler, linear stapler, or hand sewn); tension followed by ischemia and scarring; suture granulomas (nonabsorbable sutures and staples); or foreign bodies such as nonabsorbable preanastomotic rings that result in erosions, ulceration, and stricture formation are the most common causes of GJA stricture. A relatively unusual complication of LRYGB, such as a gastrogastric fistula, can also result in recurrent anastomotic stricture due to the large amount of acid that flows from the gastric remnant into the pouch, which results in marginal ulceration followed by stenosis.[4,5]

A very important factor to take into consideration when analyzing the etiology of this complication is the anatomy and mechanism of LRYGB as a weight-loss procedure. A GJA during gastric bypass is fashioned in such a way that it creates restriction (allowing a small amount of food to create satiety) and prevents dumping syndrome (slowing down the passage of food and carbohydrates into the small bowel). A large anastomosis, on the other hand, will result in failure of weight loss, and in weight regain and severe dumping syndrome. Because of the above mentioned, the GJA is the only anastomosis in gastrointestinal and general surgery that is purposely fashioned as small as possible. As a result of this, errors in judgment performing a too small anastomosis are a common cause of stricture formation. In Dr. Mason's original description of a RYGBP, the size of the anastomosis was 12 mm. Until today, there has been no consensus on the ideal GJA size. Most surgeons will agree that 15 mm is a reasonable diameter that will prevent early stricture formation and dumping syndrome while creating restriction.

Classification

Anastomotic strictures can be classified based on mechanism of formation as the following: membranous strictures that

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result from prolonged fasting; cicatricial strictures that are a direct consequence of foreign body erosion, ulceration, and anastomotic leaks; and granular strictures that follow tissue necrosis, as seen in anastomosis with tissue ischemia due to tension.[6] Another form of anastomotic stricture classification is based on time of onset. The acute stricture type is seen, on extremely rare occasions, in patients that cannot tolerate liquids in the immediate postoperative period. It is associated with extreme belching and sialorrhea. The reason for this type of acute stricture formation is a technical error in judgment. If, after 4 to 5 days of observation, a patient does not show signs of improvement, the patient should undergo endoscopic examination, dilatation, and possible redo anastomosis. The reason for this aggressive approach is to avoid the risk of aspiration pneumonia. The late or chronic stricture type is the most common form and is seen, on average, 52 days postoperatively when patients transition from soft to solid food.[3,6,7]

Diagnosis

It is expected for postbariatric surgery patients to develop nausea and vomiting as they will develop high blood levels of ketone bodies and will need to learn to eat more slowly. Not every patient with nausea and vomiting after bariatric surgery should undergo a diagnostic workup to rule out a GJA stricture. Understanding the type of operation performed and the potential for signs and symptoms of obstruction, such as belching, sialorrhea, nausea, and vomiting, are crucial in having a clinical suspicion of anastomotic stricture.

A large majority of patients that visit the emergency room complain of nausea and vomiting, and among the differential diagnoses of GJA stricture, we should also list dehydration and thiamine deficiency. All patients will require intravenous fluids regardless of the final diagnosis since dehydration has to be ruled out as a potential cause of nausea and vomiting. If GJA stricture is suspected, the patient should undergo a gastrografin upper gastrointestinal (UGI) series with the patient in supine and left lateral decubitus to rule out a gastrogastric fistula. Endoscopic examination and possible dilatation should be performed if the UGI series shows that the anastomosis is narrow and there is prolonged holdup of contrast material in the esophagus and pouch.[2,8]

Treatment Options

Observation, endoscopic dilatation, and surgical revision are the three treatment alternatives for patients with anastomotic strictures.

Observation The natural history of a GJA is that it will dilate over time since food is a natural dilator. As a result, it is not advantageous to dilate a GJA since it will result in loss of restriction, failure of weight loss, and weight regain. In what situations should we consider dilatation? Dilatation should be considered when the patient cannot tolerate liquids or consume enough of the daily protein requirements. In our experience, symptoms of anastomotic stricture can develop between 20 and 154 days after the original procedure. In two cases out of 2,600 LRYGBs (0.07%), patients developed an acute anastomotic stricture in the immediate postoperative period that had to be managed surgically. When can we consider endoscopic dilatation after LRYGB? In our experience, 7 days postoperatively should be a safe option, although there is no literature that supports this statement.

Dilatation There are multiple options to dilate a stenotic GJA, including fluoroscopic guided balloon, bougie dilatation, and endoscopic guided through-the-scope (TTS) or outside-the-scope balloon dilatation. It is our preference to use the TTS endoscopic dilatation as the main treatment option.[3]

In a retrospective study of 1,012 patients who underwent LRYGB from January 2001 to May 2004 at the Cleveland Clinic Florida's Bariatric and Metabolic Institute, 61 patients were found to have anastomotic strictures, corresponding to an incidence of 6%. In total, 134 upper endoscopies were performed, with 128 dilatations. The number of dilations per patient was as follows: a single dilation in 28% of patients, two dilations in 33%, three dilations in 26%, four dilations in 11.5%, and five dilations in 1.5% of patients. All the patients responded to dilation without need for formal surgical revision. However, after balloon dilatation, three patients (4.9%), which corresponds to 2.2% of all dilatations, had a bowel perforation that required surgical exploration. There was no mortality in this series.[9]

Surgical exploration The need for surgical revision of a GJA stricture is extremely rare. In a series of 154 patients that required anastomotic dilatation due to a stricture, 10 patients (0.4%) required a surgical revision. All patients had at least four consecutive dilatations with no improvement in solid food intake. All revisions were performed laparoscopically.

Conclusions

GJA stricture is a frequent complication of LRYGB that can be successfully treated with endoscopic dilatation when indicated. Endoscopic dilatation should be performed only in patients that cannot tolerate liquid diet and/or are not able

to maintain their daily protein requirements. Our series have shown that TTS endoscopic dilatation is a highly effective and safe treatment for GJA strictures and should be considered as a primary intervention prior to proceeding with a surgical revision.

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SSAT/SAGES JOINT SYMPOSIUM

Management of Leak in the Bariatric Gastric Bypass Patient: Reoperate, Drain and Feed Distally

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Obesity is recognized as an epidemic in industrialized nations including the USA. It is well known that up to 30% of the adult population in the USA is obese.[1] Roux-en-Y gastric bypass has proven to be a reliable and durable treatment for obesity, with medical management being mostly ineffective.[2] Roux-en-Y gastric bypass has gained popularity since its inception in the 1960s. Laparoscopic gastric bypass (LRYGB) is a safe procedure in comparison to open gastric bypass (ORYGB) and has been shown by multiple authors to reduce major wound complications including wound infection and incisional hernia.[3] Of the complications of gastric bypass, leak may be the most devastating. Leak after gastric bypass is associated with a high morbidity and mortality. The overall incidence of leak after gastric bypass ranges between 2% and 5%, with the gastrojejunal (GJ) anastomosis being the most common site.[1] Management strategy of leak after gastric bypass is a topic of much discussion in the bariatric literature. For surgeons performing this procedure, it is important to understand how to manage this complication.

The leak rate varies depending upon the type of procedure performed. Lee et al.[1] reported leak after ORYGB to be 2.6%, after LRYGB to be 5.2%, and after revisional gastric bypass to be 8.0%. The experience of the surgeon impacts the incidence of leak. DeMaria et al.[3] reported an overall leak rate of 6.8% in their first 102 LRYGB, followed by a reduction to 1.8% over the next 164 patients. This group also performed a multivariate analysis of over 3,000 GBP and defined age, male gender, sleep apnea, and procedure type as independent risk factors for leak.[2] The leak-associated mortality rate was 1.5%, with defined risk factors being weight, hypertension, procedure type, and presence of leak. Livingston et al.[4] confirmed male gender to be a predictor of leak and age to be a risk factor for mortality.

The most common site of leak after gastric bypass is at the GJ anastomosis, followed by the jejunojejunostomy (JJ) and excluded stomach. Leaks can occur at any staple line or site of serosal injury. The leak rate after LRYGB has been shown to be higher than ORYGB as indicated earlier, but the post-leak mortality rate appears to be lower in LRYGB versus ORYGB (2.3% vs. 18.4%, $p=0.015$). This is thought to be at least partially due to earlier detection in LRYGB versus ORYGB (1 vs. 3 days, $p<0.001$).[1] A leak occurring at the JJ anastomosis is more ominous than the GJ anastomosis with an associated mortality of 40%, again thought to be related to a longer time to detection reported by Lee to be 4 days versus 2 days for a leak at the GJ anastamosis.[1]

We have developed a strategy to reduce the occurrence of anastomotic leak including adhering to the principles of excellent exposure, access and "reach," trying to make the creation of the anastomosis as easy as possible. Relieving the tension on the GJ is accomplished by cutting back into the mesentery, selective use of a retrocolic/retrogastric roux limb path, complete mobilization of the pouch down to the limb, and lengthening of the lesser curve tubular pouch to a minor degree in selected cases. The practice of placing a juxta-anastamotic drain may allow non-operative management of leaks in stable patients, but this is only done

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currently in cases in which there is an intraoperative concern about the anastomosis. Further leak prevention measures include: over-sewing the pouch and remnant staple lines and assessing the anastomosis with both visual inspection and an underwater air leak test. Finally, never leave the operating room with persistent air bubbles seen during gastroscopic insufflation of the anastomosis.

Even for the most vigilant surgeons, leaks will occur and the most important risk reduction strategy is early detection. Symptoms of leak can include back or shoulder pain, anxiety, or the feeling of impending doom. Signs that may indicate leak include tachycardia ($p \geq 125$), tachypnea, hypoxia, hypotension, and oliguria. In any patient with persistent signs/symptoms, the choice of a Gastrografin® upper gastrointestinal (UGI) series versus re-laparoscopy should be entertained. Even with a negative UGI, continued suspicion of leak, non-improvement of signs/symptoms, or instability should prompt reexploration. We have increasingly relied upon repeat laparoscopy rather than UGI during the laparoscopic bariatric surgery era, including patients with minimal signs of possible leak, preferably within 24 h of the primary procedure. A negative repeat laparoscopy in such patients appears to minimally impact their course, while such early leak detection and repair appears to attenuate the septic response in this population.

The practice of a routine postoperative UGI study has not been shown to have benefit over its use in selective cases. In fact, it may be detrimental, giving the clinician a false sense of security. Lee et al.[5] retrospectively reviewed their patient population before and after the elimination of routine UGI. In their first group undergoing routine UGI study (267 patients between 2003 and 2004), 18 (6.7%) GJ leaks were detected; in the second group receiving selective UGI determined by patient signs/symptoms or elevation in GJ drain amylase (151 patients between 2005 and 2006), six (4.0%) GJ leaks were detected. Of the detected leaks, 14 patients in the first group and three patients in the second group underwent reoperation with no difference in the mortality rate. Although it was not statistically significant, the second group also showed a shorter length of stay.

Once a leak is identified, management proceeds according to the status of the patient. In the clinically stable patient with a contained leak, management with closed suction drainage, broad-spectrum antibiotics, nil per os, and total parenteral nutrition have been shown to be safe, particularly in those patients presenting with symptoms days after surgery.[1] We believe that the stable, early postoperative patient with a leak is better served by laparoscopy, as reexploration gives the advantage of diagnosis and treatment with a high level of accuracy. The use of computed tomography (CT) or UGI may be of more use in the patient with delayed presentation. In an unstable patient with suspicion for leak, immediate return to the operating room should not be delayed for UGI or CT.

The process of repeat laparoscopy should be regimented. Difficulties are commonly encountered during the reoperation. Visualization may be limited secondary to dilated loops of small bowel, adhesions, and the presence of intra-abdominal fluid/pus/blood. Helpful practices to ease the process include: use of steep reverse Trendelenburg, placement of blunt trocar ports under direct vision, and strict control of leaking CO_2 pneumoperitoneum, which can often be minimized by the placement of purse string sutures around port sites and suturing the trocars to the abdominal wall. The small bowel should be inspected carefully bearing in mind that roux limb obstruction can cause GJ leak. JJ leaks are lethal, and serosal injuries can be the site of leak. Liver retraction is necessary to gain exposure of the GJ anastomosis.

Four important steps exist for exploration and treatment of leaks. First and most important is detection, exposure, and drainage of abscess. This is followed by characterization of the leak through careful blunt dissection to define structures and intraoperative testing to delineate the extent of injury. Once the leak is fully elucidated, including rotation of the anastomosis to inspect the posterior aspect of the connection if necessary, suture repair is executed. Finally, indwelling drains are left near the anastomosis and beneath the diaphragm. Decompressing/feeding gastrostomy tubes are not considered mandatory in our practice and are placed on a case by case basis.

In order to positively impact the patient's outcome in the face of sepsis after a repaired leak, an aggressive approach is necessary. We advocate reoperation if signs of sepsis worsen or fail to improve within 24–48 h with a low threshold for conversion to an open procedure. Further, the use of bedside washout/exploration in the critically ill population is effective. The limitation of initial injury associated with the laparoscopic approach in experienced hands and the reduction of resistance to early reoperation has continued to reduce major morbidity and mortality. Maher et al.[6] recently reported continued reduction in adverse outcomes associated with LRYGB in a series of 450 consecutive laparoscopic procedures, with no leak or mortality over the final year of their study.

The most common life-threatening complication after gastric bypass is a leak. This issue must be addressed early and appropriately. The application of a low-threshold to reoperation in borderline cases has proven to be effective in reducing morbidity and mortality. LRYGB has surfaced as an effective approach to weigh reduction surgery. Typically, patients do quite well even early after LRYGB; if they do not, the clinician should consider intervention.

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Treatment of Leaks and Other Bariatric Complications with Endoluminal Stents

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Keywords Leaks · Bariatric complications · Endoluminal stents

Introduction

Weight loss surgery is the most effective treatment for morbid obesity we have today. However, gastric bypass surgery is associated with an anastomotic complication rate up to 6% including leaks, fistula formation, and strictures.[1] These complications can be potentially severe, accounting for sepsis and death. Traditional treatment of anastomotic leaks has been surgical with source control and drainage at the leak site.[1] Patients are without oral intake for a variable length of time, and nutrition is provided by either distal enteral feeding if tolerated or by parenteral nutrition that carry their own intrinsic co-morbidities. Strictures often times require multiple dilations and sometimes even surgical revision of the anastomosis which can be very challenging.

Revisional surgery for anastomotic leaks or fistulas is time consuming and associated with considerable morbidity. Gonzalez et al. reported a striking overall morbidity of 53% and mortality of 10% including recurrent strictures (13%) and gastrogastric fistulas (10%).[2]

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With that background in mind, there is the need for a less invasive treatment modality of these potentially disastrous complications.

Endoscopic Stents to Treat Gastrointestinal Leaks

For some time, endoscopic stents have been used in the gastrointestinal tract to treat malignant strictures with success. Recently, applications for stents were extended to treat esophageal and gastrointestinal leaks or benign strictures. The purpose of the stent is to seal the leak and exclude it from the enteric stream while healing progresses; at the same time, the patient can resume oral nutrition. For strictures, the stent would keep the intestinal lumen open long enough after dilation to support healing while minimizing fibrosis and recurrence. Current available stents that potentially meet the characteristics required are either made of metal or polyester with an inner coverage of silicon and are removable (contrary to single metal-based stents that are permanent and used for malignant strictures).

Early Results

In small case series, excellent healing rates of esophageal and gastrointestinal leaks were reported after bariatric surgery using these types of stents.[3]

We have recently proven the concept of intralumenal placement of a covered stent over a leaking gastrojejunal anastomosis in a porcine model. Acute leaks were created in the anterior anastomosis, and stents could be placed without disrupture of the anastomosis, while sealing the defect which was confirmed by fluoroscopy.

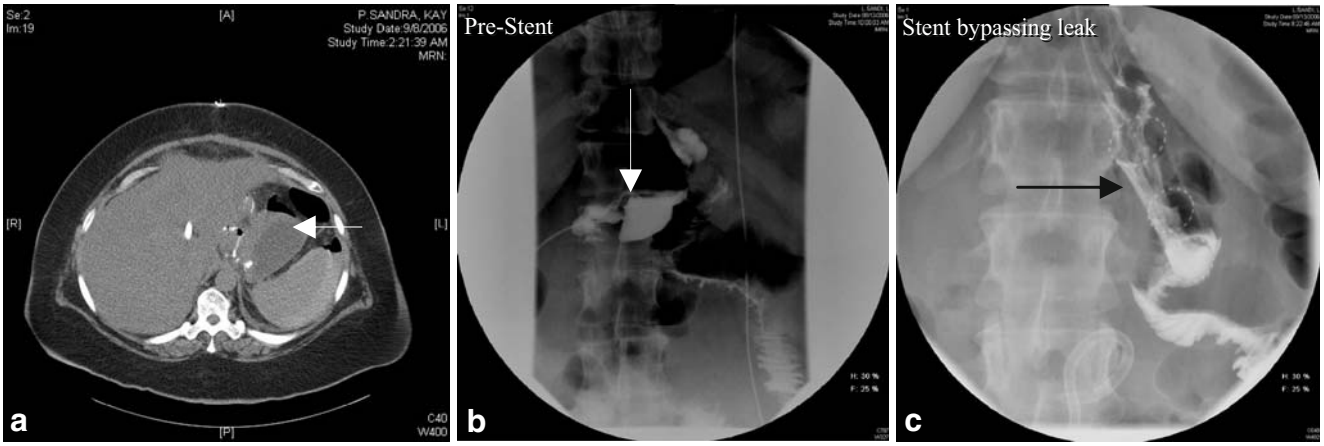

Figure 1 **a**, **b**, **c** CT showing abscess after gastrojejunal anastomosis (**a**) with leak on contrast study (**b**) and sealing after stent placement (**c**).

In a first case series, we used polyester stents (Polyflex, Boston Scientific) in six patients after gastric bypass surgery with leak closure in 70% over a mean period of 41 days.[4] These patients were all on oral nutrition.

Based on the early results, we subsequently treated 19 patients with removable covered stents, either polyester stents (Polyflex, Boston Scientific) or metal stents (Alveolus), between January 2006 and June 2007.[5] We included patients with acute leaks (n=11), chronic fistulas (n=2), and strictures (n=6) either at the gastrojejunostomy (n=17) or at the staple line after gastric sleeve resection (n=2). Leaks were identified endoscopically, marked radiographically, and stents deployed under fluoroscopy. Source control of infected fluid collections was achieved by percutaneous or laparoscopic drainage as necessary. Strictures were first dilated to 18 mm followed by stent placement. Figure 1 show a gastrojejunal leak with abutting abscess (CT and radiograph) and stent treatment followed by confirmed sealing on postoperative imaging. Healing was confirmed by contrast study after stent removal (Fig. 2). Oral feeding could be started in 79% of the patients after stenting. At a follow up of 3.6 months, successful healing was achieved in 91% of acute leaks, 100% of gastrocutaneous fistulas and 81% of strictures, respectively, with a mean healing time of 30 days. Overall, 34 stents (23 polyester, 11 metal) were needed to be placed due to stent migration (migration rate 58%, 60% for polyester, and 54% for metal based stents). All patients treated for strictures required narcotic pain medications while their stents were in place. We saw three complications where stents migrated distally and required laparoscopic removal.

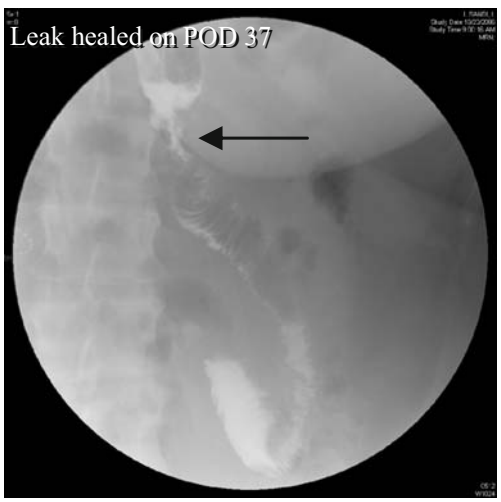

Figure 2 Healed anastomotic leak after stent removal.

Discussion

Preliminary data from the literature and our own data suggest that endoscopic treatment of gastrointestinal leaks and strictures with removable covered stents (polyester or metal based) seem to be effective. Stents seal the defect and/or keep the intestinal lumen patent and enable oral nutrition during the healing process. This treatment modality is far less invasive than traditional surgical management with lower morbidity and can potentially avoid complex surgical procedures. Most of the treatment failures and complications observed so far are related to stent migration, which is the biggest problem. Current available stents are not primarily made for this application. One possible way to decrease stent migration may be to overlap two stents, thereby increasing the surface area of attachment to the mucosa. There is also the need of collaboration with the industry to improve stent design for this novel treatment modality. Once these goals are achieved, stents can be a

powerful tool to treat these threading complications after gastrointestinal surgery in the future.

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ORIGINAL ARTICLE

Study of Swallowing Sound at the Esophagogastric Junction Before and After Fundoplication

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Abstract
Introduction Swallowing sounds can be heard in the lower esophagus by xiphoid auscultation. We hypothesize that the xiphoid sound analysis could provide information concerning the integrity of the esophagogastric junction (EGJ), i.e., superposition of the lower esophageal sphincter (LES) and the diaphragm to assess clinical diagnosis of gastroesophageal reflux disease (GERD) and results of Nissen fundoplication (NF). The aim was to evaluate the changes in sound parameters using our acoustic technique after reorganization of the EGJ after NF.
Methods For 21 patients with GERD and hiatus hernia, two microphones were placed below the cricoid and on the xiphoid cartilages. The frequency and duration of xiphoid sounds, esophageal transit time were calculated. We defined the xiphoid sound as composed of vibration groups separated by periods >100 ms. The number of vibration groups, number of vibrations per group, and interval between groups were also calculated.
Results The xiphoid sound frequency was increased after NF, and the esophageal transit time and xiphoid sound duration were significantly decreased. A significant correlation was found between xiphoid sound duration and LES–diaphragm displacement. The number of vibration groups and interval between groups were reduced after NF.
Conclusion The acoustic technique for swallowing revealed the effects of NF upon the dynamic profile of the EGJ. The organization of vibration groups at the EGJ suggested that the passage of the bolus was modified by hiatus hernia, i.e., dissociation between the LES and the diaphragm and regularized by NF. Concomitant acoustic and radiologic study should contribute to better understanding of sound related to EGJ structure and boli.

Keywords Gastroesophageal reflux · Hiatus hernia · Fundoplication · Acoustic technique · Swallowing sounds

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Introduction

Cervical auscultation has been applied to the study of pharyngeal swallowing.[1–4] Hamlet et al.[5] demonstrated that the sounds are generated by the flow across the cricopharyngeus, and Cichero et al.[6] suggested an analogy between heart sounds and swallowing sounds because of the valve and pump system in the pharynx as in the heart.

With our digital acoustic recording technique for swallowing, we have performed combined cricoid (cervical) and xiphoid (thoracic) auscultation to study bolus displacement through the esophagus and the lower esophageal sphincter (LES) during swallowing.[7] Using concurrent perfusion manometry and acoustic technique, we demonstrated that xiphoid sound occurs in the second half of the LES relaxation.[7] Swallowing sounds recorded by noninvasive acoustic techniques are thus produced in the

upper esophagus and also in the lower esophagus during the relaxation of these zones of constriction and during the passage of the bolus.

Incompetence of LES mechanisms leads to gastroesophageal reflux disease (GERD), i.e., when the LES has a low resting pressure[8,9] or when transient lower esophageal sphincter relaxation is too frequent and too long.[10,11] The presence of a hiatus hernia enhances reflux by inducing dissociation between intrinsic LES and extrinsic crural diaphragmatic high pressure zones and reducing esophagogastric junction pressure.[12,13] Fundoplication is currently used mainly to treat GERD patients and is performed under laparoscopic conditions.[14,15] The gastric wrap restores the high pressure zone of the distal esophagus and reduces the triggering of transient LES relaxation.[16,17] Fundoplication achieves closure of the esophageal hiatus and reduction of the hiatus hernia to create a new anti-reflux barrier.

The xiphoid sounds are thus produced in the esophagogastric junction (EGJ) where the hiatus hernia induces dissociation between the LES and the crural diaphragm, both EGJ components. We therefore hypothesize that the xiphoid sound analysis could provide information concerning the dynamic function and integrity of the EGJ to assess clinical diagnosis of GERD and results of Nissen fundoplication (NF). The aim of this study was to describe and evaluate the changes in swallowing sound parameters at the EGJ after its surgical reorganization. Patients were examined using acoustic technique before and after NF.

Material and Methods

Patients

Twenty-one patients with GERD (11 men, ten women, mean age 43.2±10.3 years) were enrolled. All patients were hospitalized in the Department of Visceral Surgery at the University Hospital of Tours. The study was approved by the Ethics Committee of the Hospital, and informed written consent was obtained in advance from each patient. None of the patients had a history of upper swallowing disorder. All patients had a hiatus hernia. The length of the intrathoracic displacement was 3.2± 0.7 cm, calculated during endoscopic examination before surgery. Esophageal manometry was performed with the slow pull-through technique to evaluate proximal (55.7± 16.9 mmHg) and distal (87.5±35.5 mmHg) esophageal peristaltic pressure and length (2.9±0.7 cm) and resting pressure (8.8±4.2 mmHg) of LES before surgery. Gastroesophageal reflux was treated by 360° laparoscopic NF by the same surgeon (NH) to reproduce the surgical technique precisely. After closure of the crura and reduction of hiatus hernia, the wrap (approximately 3 cm in length) was realized. Patients were excluded if they had had esophageal or gastric surgery before NF and if the laparoscopic intervention was switched to a laparotomy approach during surgery.

Acoustic Acquisition and Parameters

Acoustic data were obtained in an identical environment for each subject. Two omnidirectional microphones (Electret tie clip Sony® microphone, frequency range 50–18,000 Hz) were used. The cricoid microphone was placed in direct contact with the skin, on the anterolateral surface of the neck pressing just below the cricoid cartilage. The other microphone was inserted in a standard stethoscope and the flat diaphragm was placed on the xiphoid cartilage to obtain xiphoid sound. The microphones were kept in place by a fabric collar or belt. The microphones were connected to an amplifier linked to a computer audio acquisition card to obtain stereo signals under ".wave" form. The patients were instructed to fast for at least 6 h before the sound recordings. Each patient remained standing upright and was asked to perform a six-swallow sequence with 10 mL of 50% barium sulfate suspension (Micropaque® Laboratoire Guerlet, France) 1 day before and 2 days after surgery. The bolus volume was measured by syringe, placed in the mouth, and then swallowed. Each swallow was separated by 30 s.

All the recordings were analyzed using the Cool Edit Pro software program (Syntrillium Software Corporation, Phoenix, USA). Each recording was filtered with a band-pass filter (500–1,200 Hz) to extract xiphoid sounds. The stereo signal (cricoid and xiphoid sounds) obtained after filtering and zoom is illustrated in Fig. 1.

After all the acoustic signals had been heard, the frequencies of cricoid and xiphoid sounds were calculated before and after surgery in percent (%). For each sound recording, the esophageal transit time (the time between the start of the cricoid swallowing sound and the start of the xiphoid swallowing sound) and the duration of the xiphoid sound (the time elapsed between the start and the end of each sound) were measured in milliseconds (ms). We defined the xiphoid sound as composed of vibration groups separated by periods >100 ms. The zoom allows precise measurement of the sound components (Fig. 1). The number of vibration groups, number of vibrations per group, duration of each group (the time elapsed between the start and the end of each group), and intervals between groups (ms) were calculated for each xiphoid sound before and after surgery. The mean umbers and mean durations were calculated.

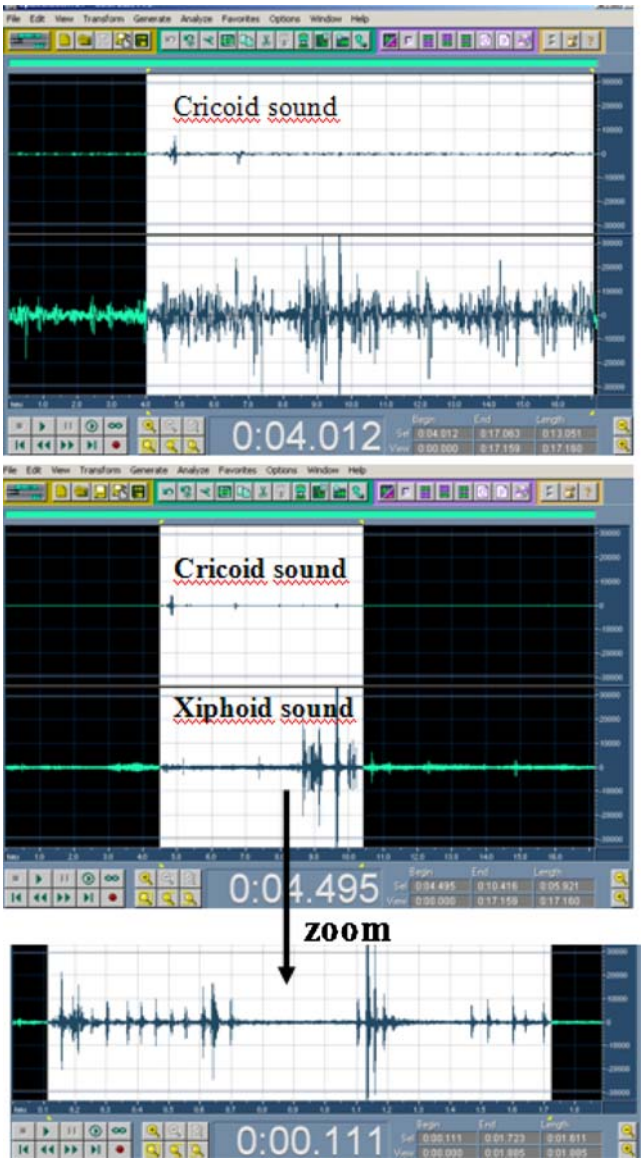

Figure 1 Stereo swallowing sounds recorded at the cricoid (*above*) and at the xiphoid (*below*) positions. Initial stereo swallowing sounds (*upper*). Stereo swallowing sounds after band-pass filtering, the xiphoid sound appears more clearly (*middle*). The zoom allows precise measurement of the xiphoid sound parameters (*lower*). The xiphoid sound (total duration, 2,060 s) was composed of three vibration groups. First group was composed of 13 sound vibrations (587 ms), second group was composed of five sound vibrations (122 ms), and third group was composed of five sound vibrations (229 ms). Intervals between bursts were 386 and 229 ms.

Statistic Analysis

Data were expressed as mean with their standard deviation (SD). A paired Student's *t* test was used to compare the sound parameters before and after NF. Pearson correlation test was applied to establish correlations between the sound parameters and the EGJ displacement, or the LES pressure, or the distal esophageal pressure before NF. A p value <0.05 was considered significant.

Results

We obtained a total of 252 recordings. Two hundred twenty-six of them (90%) were good enough to permit analysis.

The cricoid sound was always heard before and after NF (100%).

Frequency of xiphoid sound was significantly enhanced after NF: 54% vs 84.8% ($p<0.05$). For one man, no xiphoid sound was recorded before or after NF, and for one woman, no xiphoid sound was heard before NF. These two patients were excluded from the analysis because comparison between before and after NF was impossible (16 recordings).

Esophageal transit time was significantly higher before NF than after (6,865±809 vs 5,194±726 ms, $p<0.05$). Individual values are shown before and after NF in Fig. 2. A significant positive correlation between esophageal transit time and EGJ displacement was present ($r=0.78$, $p<0.001$) before NF (Fig. 3). No significant correlation was found between esophageal transit time and LES pressure or distal pressure of esophagus.

Duration of xiphoid sound was significantly reduced after NF (1,671±580 vs 758±261 ms, $p<0.05$). Individual values of xiphoid sound duration are shown before and after NF in Fig. 2. A significant positive correlation between xiphoid sound duration and EGJ displacement was present ($r=0.76$, $p<0.001$) before NF (Fig. 3). No significant correlation was found between this parameter and LES pressure or distal pressure of esophagus.

The xiphoid sound is composed of vibration groups separated by periods >100 ms (Fig. 1). Number of vibration groups and interval between groups were significantly reduced after NF (3.8±1.7 vs 2.05±0.8, $p<0.05$ and 228±98 vs 128±51 ms, $p<0.05$, respectively). In contrast, number of vibrations per group and duration of groups significantly increased after NF (3.7±2.0 vs 6.3±4.2, $p<0.05$ and 283±137 vs 360±97 ms, $p<0.05$). Significant positive correlations between number of groups or interval between groups and EGJ displacement were present ($r=0.68$, $p<0.001$ and $r=0.59$, $p<0.05$, respectively) before NF. Significant negative correlation between duration of groups and EGJ displacement was present ($r=-0.59$, $p<0.001$) before NF. Typical example of xiphoid sounds before and after NF for the same patient is shown in Fig. 4.

Discussion

By using the digital acoustic recording technique for swallowing, we demonstrated that the frequency of xiphoid sound enhanced after NF. Fundoplication significantly decreased the durations of esophageal transit time and

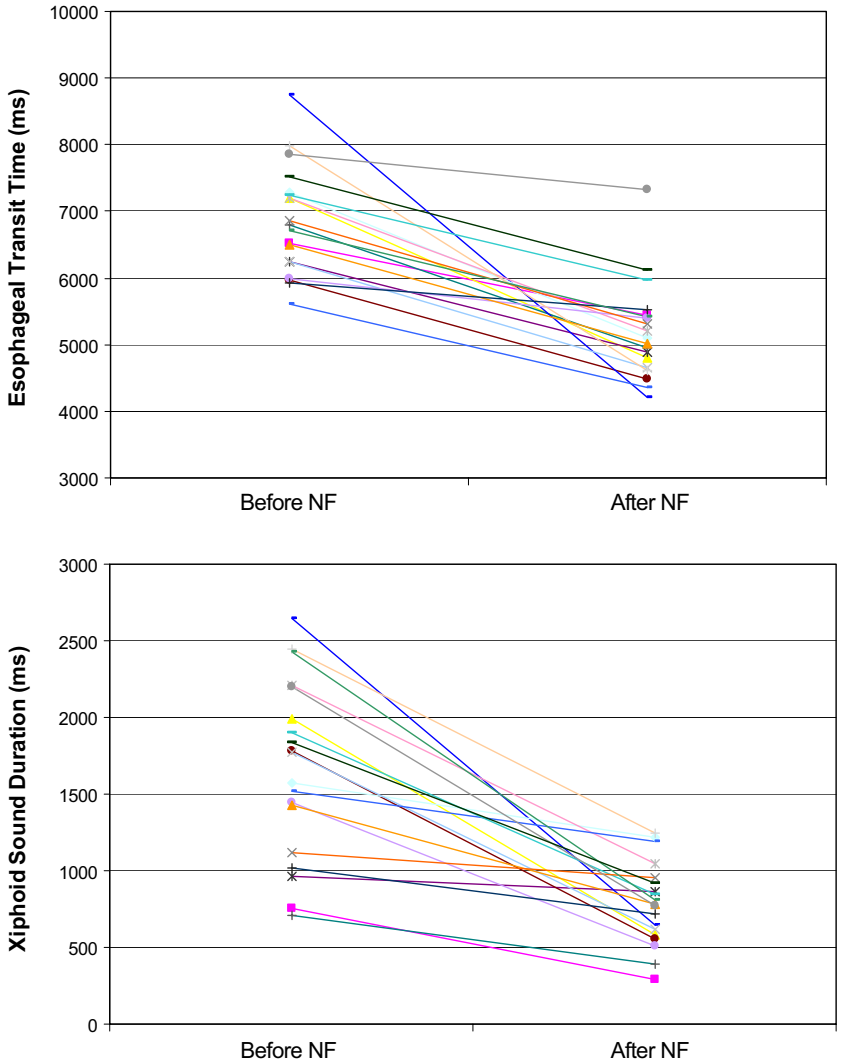

Figure 2 Evolution of individual esophageal transit time (*upper*) and duration of xiphoid sound (*lower*) before and after Nissen fundoplication (*NF*).

xiphoid sound. We also described the xiphoid sound, which is composed of vibration groups, and showed that the number of groups were significantly reduced after NF, separated by shorter intervals between groups. The number of vibrations per group and the durations of groups were significantly increased after NF.

In our study, the patients were placed in an upright position as in scintigraphy,[18] impedancemetry,[19] or high-resolution manometry.[20]

In the present study, the beginning of the cricoid sound was used to determine initiation of the swallowing reflex, as in the manometry technique where a displacement receptor was positioned on the neck near the cricoid cartilage.[21,22] Cricoid sounds were always heard because patients with dysfunction of the upper esophagus were excluded from this protocol. The frequency of the xiphoid sound was low before NF. Bolus displacement was perhaps affected because the hiatus hernia created esophageal shortening,[23] influenced the primary peristalsis by attenuation of shortening,[24] and decreased the distal amplitude of the esophagus.[22] These disorders of peristalsis might affect the speed of displacement of the bolus, which would then pass without making a sound. This is also the case when the LES pressure is low, the bolus met little resistance, and passed over the LES without sound. The frequency of xiphoid sound increased after NF, although without reaching normal values (i.e., 95%).[7] It was demonstrated that NF reestablished the anti-reflux function by creating pressure on the distal esophagus by means of the gastric wrap, suppressing the hiatus hernia and reducing the diameter of the diaphragmatic hiatus.[17,25,26] However, residual pressure was maintained with this restructuring during swallowing.[27]

We found that esophageal transit time was significantly longer before NF. With hiatus hernia, the LES and hiatus

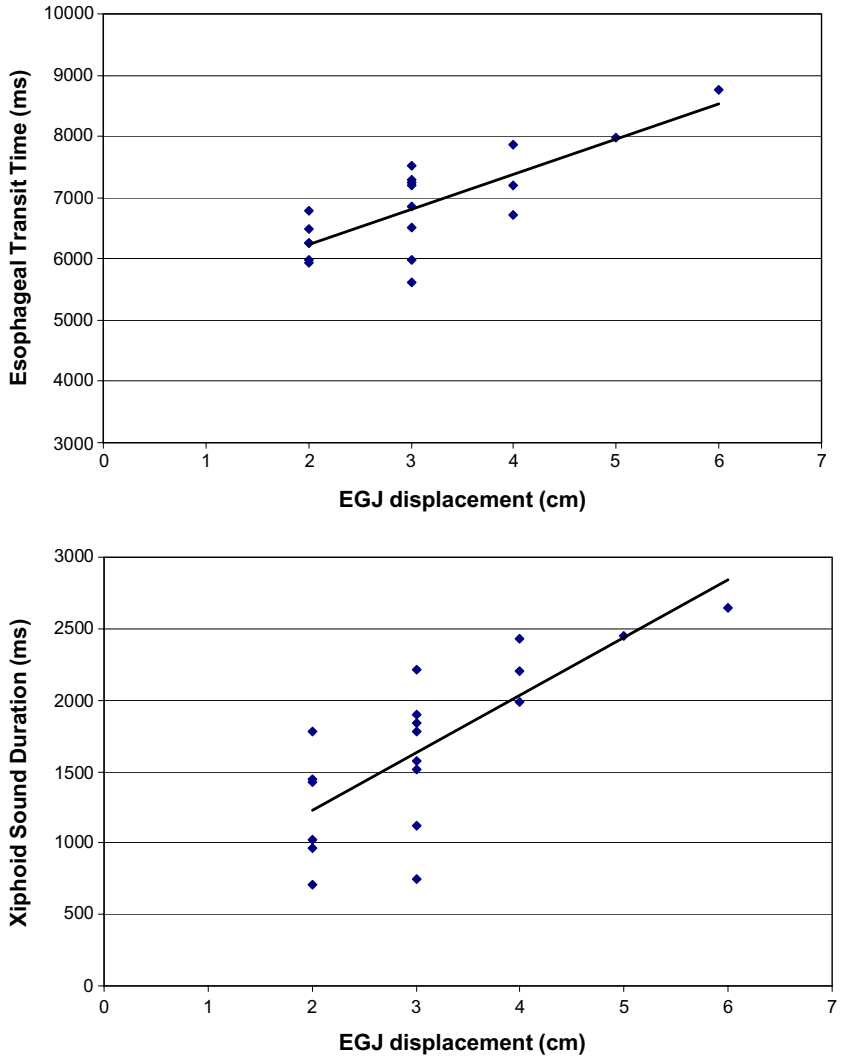

Figure 3 Relationship between EGJ displacement and esophageal transit time (r=0.78, p<0.0001; *upper*) and xiphoid sound duration (r=0.76, p <0.0001; *lower*).

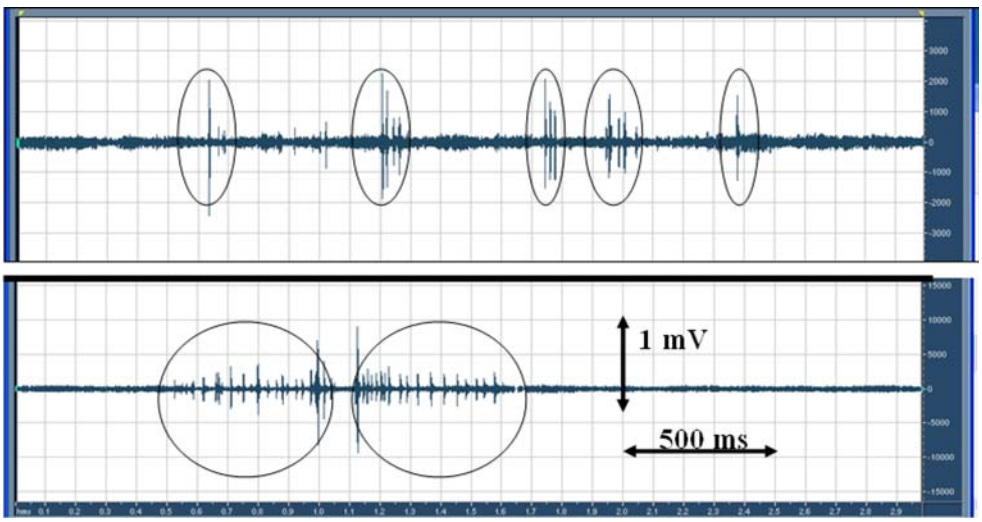

Figure 4 Xiphoid sound before and after Nissen fundoplication (*NF*) for the same patient. Before NF, duration of xiphoid sound was 1,885 ms with five vibration groups (*circle*, *upper*). After NF, duration of xiphoid sound was 1,152 ms with two vibration groups (*circle*, *lower*).

canal were dislocated and bolus transit was slowed down by the first passage across the LES and the second passage over the diaphragmatic hiatus.[28,29] Fifteen patients had impaired peristalsis in the distal esophagus, which helped to decrease the rate of bolus displacement.[30,31] Esophageal transit time decreased after NF because a single zone of high pressure was reconstructed at the EGJ. A significant positive correlation between esophageal transit time and EGJ displacement was found which would explain the effect of the hiatus hernia on the lengthening of bolus transit. Esophageal transit time was about 6–7 s after NF, the time required to pass through the entire esophagus, and was comparable to values reported by other authors[32] (i.e., 7.2 s for water).

On the window of the Cool Edit Pro software, the xiphoid sound is simultaneously heard and visualized to facilitate the sound analysis. Computer programs able to process the xiphoid signal are being developed by our team to provide more detailed analysis of such signals.

Xiphoid sound duration and the organization of the vibration groups seem to be linked. We showed that the xiphoid sound was composed of vibration groups and that these groups were more numerous and more spaced out before NF. In consequence, xiphoid sound was longer. The sounds heard before NF seemed to reflect intermittent passage. These "hiccups" may be due to dysfunction in the distal esophagus in which turbulence occurs and to variations in speed of peristalsis. Three-dimensional imaging of the LES has shown that the LES can be defective over the entire length of the sphincter, or only partially in the intra-abdominal portion.[9]

With a hiatus hernia, a bolus successively transverses two zones of differing resistance, as well visualized by the pressure topography[12] and pressure profile[22] of the EGJ. The duration of the xiphoid sound was correlated with displacement of the EGJ; in other words, the greater the LES–diaphragmatic displacement, the longer the duration. This would appear to explain the difficulties in the passage of a bolus to the EGJ. Optimum elasticity of the EGJ is achieved by superposition of the smooth muscle of the LES and the striated muscle of the diaphragm, a reduced zone which is distended by passage of the bolus.[33] This double musculature has an active part in the anti-reflux function.[34]

Xiphoid sound duration was shorter after NF (1,671 vs 758 ms) and there were fewer groups of vibrations. Kahrilas et al.[25] and Scheffer et al.[20] have shown that opening duration at the EGJ assessed with 10 ml barium suspension was unaffected by fundoplication, i.e., 13.4 vs 12.5 (supine) and 5.1 vs 5.0 s (upright), respectively. However, data on EGJ transit time before and after fundoplication are limited. A significant correlation between the increased EGJ transit time and the dysphagia score was reported.[35,20] EGJ transit time was 2.8 s before NF and 5.8 s after NF with dysphagia.[20] Our values were assessed before NF with hiatus hernia and after NF without dysphagia. Moreover, in all these techniques, the volume and consistency of the bolus were different. Our new acoustic technique using bolus of barium suspension and its results can be compared to other EGJ investigations to test differences, but more physiological boluses (water, semi-liquid, solid) might be used to standardize this noninvasive acoustic EGJ exploration. It can be hypothesized that the bolus traversed the EGJ under the effect of more regular pressure and that its passage was more rapid with a more compact bolus. Gastric wrap surrounds the esophagus over 3 cm and maintains high pressure throughout its length,[36] but the distensibility of this new muscle arrangement decreases.[37] Stretching of the body of the esophagus to make this wrap may contribute to the development of more effective peristalsis,[38] but only in certain patients.[39]

Conclusion

The digital acoustic recording technique for swallowing is noninvasive and permits evaluation of the passage of a swallowed bolus through the esophagogastric junction. We demonstrated for the first time that the xiphoid sound analysis can reveal the dissociation between the LES and the crural diaphragm in patients with GERD and the xiphoid sound modifications in the same patients after NF. Since it provides additional information, particularly concerning the displacement of a bolus, displacement through the EGJ appears to be regularized by the fundoplication. Studies combining acoustic and radiological techniques are in progress to visualize the bolus and the sound at the same time and to provide greater understanding of the origins of the acoustic changes.

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ORIGINAL ARTICLE

Immunohistochemical Expression of Osteopontin in Gastric Cancer

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Abstract
Background/Aims Osteopontin (OPN) is significantly overexpressed in a variety of malignancies. However, little is known concerning the significance of OPN expression in human cancers. Thus, the aim of this study was to determine the relationship between the degree of OPN expression, the proliferative activity of cancer cells, and the clinicopathological findings for surgically resected gastric cancer.
Methodology We evaluated the immunohistochemical expression of OPN in 85 specimens of cancer. Additionally, we investigated a cancer cell proliferative index using an anti-MIB-1 antibody and terminal deoxynucleotidyl transferase-mediated dUTP biotin nick end labeling staining. Levels of OPN expression in gastric cancers were classified into three groups. To compare the relationship between OPN expression and clinicopathological findings, the features of cancer lesions were classified using the TNM Classification of Malignant Tumors, 6th Edition.
Results Immunohistochemical examination of OPN expression in gastric cancer revealed diffuse granular staining in the cytoplasm. High OPN expression was observed in 37 of 85 carcinomas. Strong OPN expression was significantly associated with a low apoptotic index, a high proliferative index, depth of invasion, lymphatic invasion, and venous invasion. Pathologically, intestinal type carcinoma showed strong expression of OPN.
Conclusions These data suggested that OPN may play an important role in the invasiveness and the progressive nature of gastric cancer.

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Keywords Osteopontin · Gastric cancer · Apoptotic index · Proliferating index

Introduction

Advanced gastric cancer remains one of the most common neoplasms in Japan and has a poor prognosis. Even when curative surgery is performed, a considerable number of patients will die from cancer, with recurrence such as distant metastasis, lymph nodes metastasis, and carcinomatous peritonitis. Osteopontin (OPN) is a non-collagenous acidic bone matrix glycoprotein, which is sialated and phosphorylated, and has a cell-binding peptide sequence of glycine-arginine-glycine-aspartate-serine. OPN has been demonstrated in a limited number of organs such as bone, kidney, lung, breast, smooth muscle, and stomach.[1,2] OPN is also a cytokine that is

associated with a rapid T-cell-dependent response to bacterial infection.[3]

With respect to cancer metastasis, it has been suggested that OPN exhibits both cell attachment and cell signaling functions through integrin-mediated signal transduction,[4] although the function of OPN in tumor cells remains poorly understood. A correlation between OPN expression and clinicopathological findings has been previously shown in gastric cancer.[5,6] In vitro, Song et al. showed that the anti-apoptotic activity of OPN in gastric cancer cells was mediated, in part, through the PI3-K/Akt pathway via alpha v beta 3 integrins,[7] while Zhao et al. reported that OPN may facilitate tumorigenesis and metastasis through prevention of tumor cell apoptosis.[8] However, the exact role of OPN in regulating proliferative activity in gastric cancer is not fully understood.

Thus, the aim of the present study was to determine whether the expression of OPN in gastric cancer prevents apoptosis and correlates with clinicopathological characteristics.

Materials and Methods

Specimens were obtained from 85 patients (59 males and 26 females, mean age 60.9 years, 29 to 87 years old) with gastric cancer resected between 1998 and 2005 in our department at the time of operation. Freshly obtained cancerous and non-cancerous tissues were fixed with 4% paraformaldehyde in 0.1 M PBS at 4°C overnight, dehydrated in graded alcohols, and then embedded in paraffin. Next, 4-μm thick serial sections were processed for immunohistochemistry, in addition to routine hematoxylin and eosin staining. The depth of tumor invasion, lymphatic invasion, venous invasion, lymph node metastasis, and stage were determined according to the TNM Classification of Malignant Tumors, 6th Edition criteria. Gastric cancer was also classified as intestinal or diffuse type using the Laurens system.

Immunohistochemistry

Monoclonal antibodies against human OPN antibody and Ki-67 antigen (MIB-1; DAKO Corporation, Carpinteria, CA, USA) were evaluated. The OPN antibody was developed by M. Solursh and A. Franzen and was obtained from the Developmental Studies Hybridoma Bank developed under the auspices of the NICHD and maintained by the University of Iowa (Department of Biological Sciences, Iowa City, IA, USA). Sections were deparaffinized in xylene, dehydrated through graded ethanols, and treated with 3% H_2O_2 in methanol for 30 min at room temperature to eliminate endogenous peroxidase activity. After blocking nonspecific binding with 10% normal goat serum in PBS for 30 min at room temperature, reaction with the primary antibodies (OPN 1:100; MIB-1 1:50) was carried out at 4°C overnight. The sections were then incubated with EnVision™ (DAKO Corporation) for 60 min, in place of biotinylated goat anti-rabbit IgG secondary antibody and the streptavidin-peroxidase conjugate.[9] Color development was performed by incubation with 0.5% 3,3-diaminobenzidine solution containing 0.01% H_2O_2 in 0.05 M Tris-HCl buffer (pH 7.2) for two to 10 min as required for optimal staining. Sections were assessed and photographed under a light microscope. Control staining was performed with normal rabbit serum without the appropriate primary antibody.

Terminal Deoxynucleotidyl Transferase-Mediated dUTP Biotin Nick End Labeling Staining

To evaluate the incidence of apoptotic cells in gastric cancer, we used the terminal deoxynucleotidyl transferase-mediated dUTP biotin nick end labeling technique[10] using the TaKaRa In Situ Apoptosis Detection Kit (TaKaRa, Shiga, Japan). In brief, the deparaffinized and rehydrated 4-μm thick sections were digested with proteinase K (20 μg/ml; Sigma–Aldrich, St. Louis, MO, USA) for 20 min at room temperature. The slides were then washed in distilled water and immersed in 2% H_2O_2 in distilled water for 10 min to block endogenous peroxidase activity. The sections were washed in PBS (pH 7.4) and then incubated in equilibration buffer for 10 min at room temperature. The control sections were prepared in parallel with substitution of distilled water instead of TdT enzyme.

Immunohistochemical Evaluation

OPN immunoreactivity was evaluated in three areas of each slide for correlation and confirmation of the tissue diagnosis. The number of tumor cells with cytoplasmic staining of OPN was counted, and OPN expression was classified as follows: weak or focal expression (±), moderate expression with focal strong expression (1+), and strong expression (2+). OPN expression was evaluated by two of the authors without any prior knowledge of the patient's clinical information. If different grades were assigned, final agreement was obtained after careful review of the images on the same digital monitor screen.

Evaluation of Apoptotic and Proliferating Cells

For quantitation of apoptotic and proliferating cells, more than several hundred cancer cells from all patients were

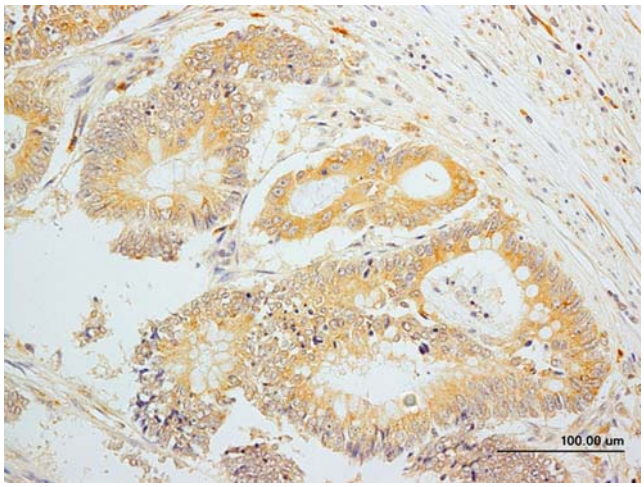

Figure 1 Immunoreactivity of Osteopontin in cancerous tissue. Fine and rough granular immunoreactivity was observed in the cytoplasm of cancer cells. ×40 magnification.

counted under a light microscope (×40 objective) within the arbitrary area. The ratio (%) of apoptotic- or proliferating-positive cells per 1,000 cancer cells were calculated and were termed the apoptotic index (AI) and the MIB-1 index (MI), respectively.[11]

Statistical Analyses

Statistical analyses were performed using Stat View® (SAS Institute Inc., Cary, NC, USA). The χ^2 test was used to analyze the association between OPN expression and clinicopathologic features of gastric cancers. The relationship between OPN expression and the MI or the AI was evaluated by the student *t* test. A difference of $P<0.05$ was considered significant.

Table 1 Association between Osteopontin Expression and Clinicopathological Characteristics of Gastric Cancer

Variables	OPN ±	OPN 1+	OPN 2+	*P* value
Depth of invasion				
Tis	13 (15)	10 (12)	6 (7)	<0.05
T1	3 (4)	6 (7)	4 (5)	
T2	5 (6)	1 (1)	15 (18)	
T3	2 (2)	6 (7)	7 (8)	
T4	1 (1)	1 (1)	5 (6)	
Lymph node metastasis				
N0	18 (21)	16 (19)	13 (15)	<0.05
N1	3 (4)	3 (4)	13 (15)	
N2	0 (0)	2 (2)	6 (7)	
N3	3 (4)	3 (4)	5 (6)	
Histological type				
Intestinal type	7 (8)	10 (12)	24 (28)	<0.05
Diffuse type	17 (20)	14 (16)	13 (15)	
Lymphatic invasion				
L0	20 (24)	15 (18)	8 (9)	<0.05
L1	4 (5)	9 (11)	29 (34)	
Venous invasion				
V1	21 (25)	23 (27)	23 (27)	<0.05
V2	3 (4)	1 (1)	3 (4)	
TNM stage				
0	13 (15)	10 (12)	6 (7)	<0.05
1A	2 (2)	4 (5)	2 (2)	
1B	3 (4)	3 (4)	6 (7)	
2	1 (1)	1 (1)	5 (6)	
3A	0 (0)	0 (0)	5 (6)	
3B	0 (0)	0 (0)	0 (0)	
4	5 (6)	6 (7)	13 (15)	

Figures in parentheses are percentage

OPN osteopontin

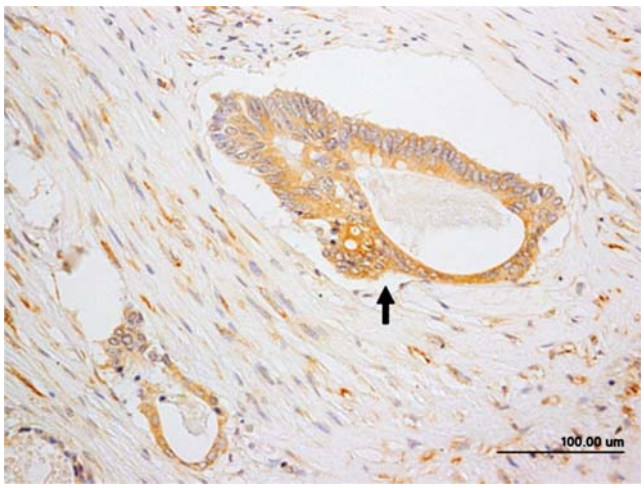

Figure 2 Intense immunoreactivity of OPN was seen in lymphatic invading cancer cells. ×40 magnification.

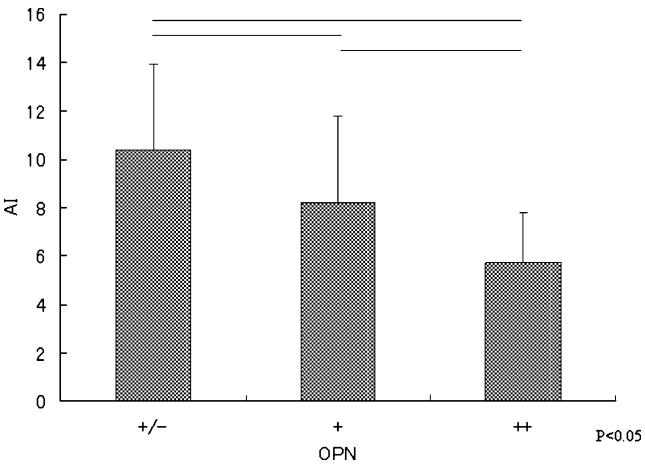

Figure 3 Osteopontin (*OPN*) expression in gastric cancer and apoptotic index (*AI*).

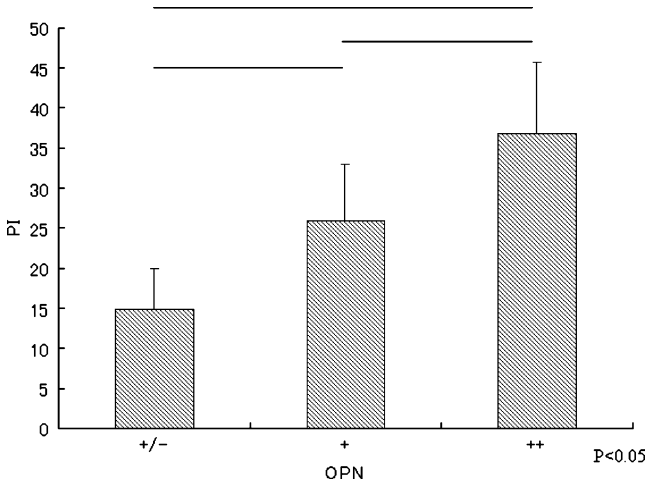

Figure 4 Osteopontin (*OPN*) expression in gastric cancer and proliferating index (*PI*).

Results

Specificity of Immunohistochemical Staining

The negative control sections incubated with the normal mouse immunoglobulin G showed no reaction products. Both smooth muscle cells and macrophages expressed intense OPN immunoreactivity.

Immunoreactivity of OPN in Normal Gastric Mucosa

In the area of the fundic gland, OPN immunoreactivity in normal gastric mucosa was mainly in the chief cells, with expression in some mucous neck cells. In the area of the pyloric gland, OPN immunoreactivity was observed in some mucous neck cells and pyloric gland cells.

Immunoreactivity of OPN in Gastric Cancer Tissue

OPN immunoreactivity in gastric cancer showed fine and rough granular immunoprecipitates in the cell cytoplasm (Fig. 1). Cancer cells invading in the lymphatic vessel revealed strong immunoreactivity (Fig. 2). A few inflammatory cells, mainly macrophages, also showed OPN immunoreactivity; in particular, macrophages in the tumor stroma expressed intense OPN immunoreactivity. At the area of the tumor invasion, both cancer cells and macrophages showed strong OPN immunoreactivity. However, the degree of macrophage infiltration in the cancerous tissue exhibited no relationship with the clinicopathological findings of the cancer.

There was an obvious correlation between the degree of OPN expression in cancer cells and the depth of invasion, lymph node metastasis, histological type, lymphatic invasion, venous invasion, and conclusive stage grouping (Table 1).

Apoptotic and MIB-1 Indices

The AI of cancer cells in the ± group, the 1+ group, and the 2+ group were 10.4±3.5, 8.2±3.6, and 5.7±2.1, respectively, with a significant difference between the ± group versus the 1+ group ($P<0.05$) and the 1+ group versus the 2+ group ($P<0.05$; Fig. 3). The MI of cancer cells in the ± group, the 1+ group, and the 2+ group were 14.9±5.1, 25.9±7.1, and 36.8±8.9, respectively, with a significant difference between the ± group versus the 1+ group ($P<0.05$) and the 1+ group versus the 2+ group ($P<0.05$; Fig. 4). Finally, in gastric carcinoma, there was a significant negative correlation of AI with MI (Fig. 5; $y=-2.9009x+50.089$; $R^2=0.7894$; $P<0.05$).

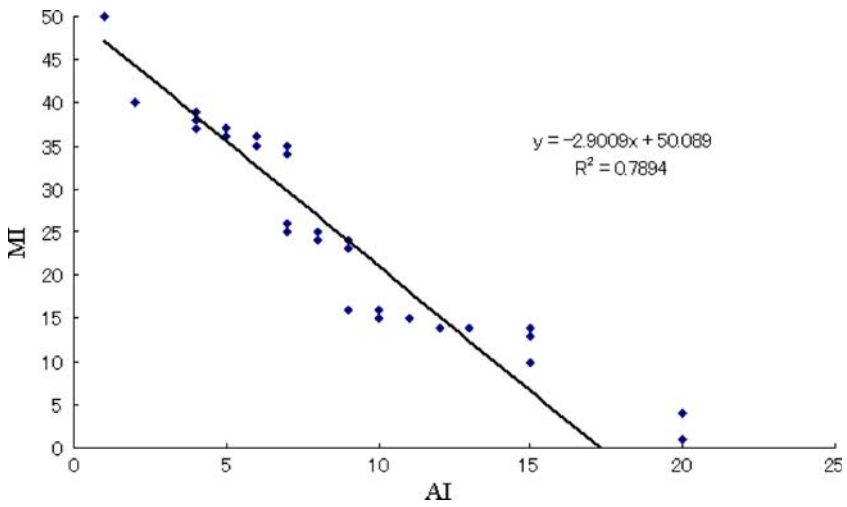

Figure 5 There was a significant negative correlation of *AI* with *MI* in gastric carcinoma ($y=-2.9009x+50.089$; $R^2=0.7894$; $P<0.05$).

Discussion

OPN is a calcium-binding phosphoprotein believed to play an important role in several different and apparently distinct cellular processes. Recently, expression of OPN has been linked to tumorigenesis[12] and metastasis[13] in several experimental animal models and human studies. In a previous study of OPN expression in human cancer tissue, including the colon, stomach, and duodenum, both cancer cells and macrophages were reported to show OPN immunoreactivity, while only macrophages exhibited OPN mRNA signals.[1] These findings suggest that OPN secreted by macrophages might bind cancer cells to each other via the alpha v beta 3 integrin. Moreover, the presence of OPN mRNA in macrophages was only observed at the front of tumor invasion, suggesting that OPN from macrophages affects cell adhesion, tumor cell invasion, and metastasis.[14] However, there are only a few reports describing the exact relationship between OPN expression and the clinicopathological features of gastric cancers. In one study, OPN protein expression was shown to be significantly associated with age, tumor depth, histological grade, and hematogenous metastasis, but there was no correlation with the development of lymph node metastasis.[5]. However, a correlation between OPN expression and depth of invasion, lymph node metastasis, and distant metastasis was reported for gastric cancer.[6]

In the present study, we examined the expression of OPN in 85 resected carcinomas of the stomach using immunohistochemical staining and compared the degree of OPN expression with the pathological features, AI, and MI of gastric cancers. Intense OPN immunoreactivity was detected in 37 of 85 cases (43.5%). The level of OPN immunoreactivity correlated with depth of invasion, lymphatic invasion, venous invasion, lymph node metastasis, and conclusive stage grouping. Gastric cancer cells that invaded lymphatic vessels showed intense OPN immunoreactivity and had a low apoptotic index and high proliferating index. There are contradictory data on the relationship between AI and MI. Kupnicka et al.[15] and Ikeguchi et al.[16] demonstrated a significant correlation between AI and MI in gastric carcinoma, while Lu et al.[17] and Shinohara et al.[18] found no significant correlations.

OPN can bind both extracellular matrix components such as collagen[19] and cell surface receptors. The prominent OPN–cell surface receptor interaction studied is that of arg-gyl-asp, as OPN receptors are alpha v beta 3, alpha v beta 1, and alpha v beta 5 integrins.[20,21] Certain variants of the hyaluronic receptor CD44 have also been shown to be receptors for OPN.[22] The signaling pathway for proliferation and apoptosis involves an early interaction of OPN with specific cell surface receptors.[21,23] Lin et al. demonstrated that in a synergistic reaction with GM-CSF, OPN stimulates growth of both the proB cell line Ba/F3 and IL-3-dependent mouse bone marrow cells via an interaction with CD44.[24] In endothelial cells, the interaction of surface-bound OPN with the alpha v beta 3 integrins has been shown to activate the NF-κB pathway and to inhibit apoptosis in these cells.[25] Potentially, in gastric carcinoma some surface receptors including CD44, alpha v beta 3 integrins, or other receptors are involved in cell proliferation or apoptotic reactions. Thus, these data suggest that OPN secreted from gastric cancer cells may play an important role in metastasis. In support of this, in the present study, expression of OPN was significantly associated with low AI and high MI in gastric carcinoma. Additionally, there was a significance negative correlation between AI and MI.

Recent studies have shown that OPN is a potential target for anticancer therapy.[26] The expression of OPN can be inhibited at both the transcription and the RNA message levels, while OPN protein can be blocked with antibodies or synthetic peptides. Furthermore, OPN receptors can be targeted; CD44 has been widely applied as a cytotoxic and immunological therapeutic target, while integrin alpha v beta 3 is being investigated as a therapeutic target using small molecular inhibitors as drug candidates.[27] The results of the present study provide further support for the targeting of OPN as a potential therapeutic strategy for prevention of cancer through induction of apoptosis and inhibition of cell proliferation. Moreover, it was also concluded that investigating the expression of OPN from preoperative tumor biopsy specimens obtained by endoscopy could lead to a way to tailor therapy.

Conclusion

We investigated OPN immunoreactivity in gastric cancer cells. The expression of OPN was correlated with depth of invasion, lymphatic invasion, lymph node metastasis, and conclusive stage. Because expression of OPN can reduce apoptosis and increase proliferation, OPN inhibitors may be a useful strategy for increasing apoptosis and inhibiting proliferation of gastric cancer cells.

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ORIGINAL ARTICLE

Impact of *KIT* and *PDGFRA* Gene Mutations on Prognosis of Patients with Gastrointestinal Stromal Tumors After Complete Primary Tumor Resection

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Abstract
Introduction To investigate the impact of *KIT* and *PDGFRA* gene mutations on the prognosis of gastrointestinal stromal tumors (GIST).
Material and Methods Tumor tissue from 184 patients with primary GIST was submitted to mutational analysis of exons 9, 11, 13, and 17 of the *KIT* gene and exons 12 and 18 of the *PDGFRA* gene. Clinical and pathological parameters were analyzed and correlated to the risk of recurrence and disease-free survival (DFS).
Results and Discussion The authors found that somatic mutations were detected in 162 tumors (88.0%). Age, clinical stage, mitotic count, and tumor size were of prognostic relevance on both univariate and multivariate analysis. Five-year DFS was 41.9%. While the presence of a *KIT* or *PDGFRA* mutation *per se* was not associated with tumor recurrence and/or disease-free survival, exon 11 deletion and hemizygous mutation status were both independent factors highly predictive for poor survival.
Conclusion The authors conclude that *KIT* exon 11 deletions and somatic loss of the wild-type *KIT* identified patients with poor prognosis. Age, clinical stage, tumor size, and mitotic count were standard clinicopathologic features that significantly influenced the prognosis. Mutation type of the mitogen receptor c-kit has a potential for predicting the course of the disease and might contribute to management individualization of GIST patients.

Keywords KIT · PDGFRA · Gene mutation · Gastrointestinal stromal tumors

Introduction

Gastrointestinal stromal tumor (GIST) is an unusual mesenchymal neoplasm, arising most frequently within the gastrointestinal tract. It has been shown that the gain-of-function mutations of the *KIT* gene leading to constitutive activation of the protein have a central role in the underlying pathogenesis in the majority of GISTs.[1] Moreover, in some GISTs, most of them originating from the stomach, mutations have been mutually found in the gene encoding the platelet-derived growth factor receptor alpha (PDGFRA).[2,3] Thus far, simultaneous mutations in *KIT* and

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PDGFRA have not been reported. *KIT* and *PDGFRA* both encode type III tyrosine kinases. While *KIT* and *PDGFRA* somatic mutations, detectable in 85% to 90% and 3% to 5% of GISTs, respectively, are clearly considered as the key players in the early tumorigenesis, additional oncogenic pathways are most likely responsible for the development of malignancy.[4–7] Analyzing the tumor for *KIT* or *PDGFRA* genetic alterations emerged as a most useful diagnostic tool for establishing the molecular diagnosis of a GIST, particularly for tumors that are negative for the standard immunohistochemical marker KIT (CD117), a protein that is expressed by differentiated interstitial cells of Cajal, generally presumed to be the pathophysiologic origin of GIST.[8]

In GISTs harboring *KIT* mutations, exon 11 is affected in up to 70% of the time. Less commonly, mutations in exons 9, 13, and 17 are detectable. The prognostic relevance of mutations found in the *KIT* oncogene, particularly *KIT* exon 11 mutations, has been investigated; however, the conclusions are not uniform.[9,10] In some studies, *KIT* exon 11 mutations have been assigned as indicators of poor prognosis.[11–14] Nevertheless, in other settings, this finding could not be confirmed.[15,16] Due to the observation of identical mutations in small incidentally disclosed GISTs and in larger or metastatic tumors, Corless et al.[17] postulated that *KIT* mutations *per se* are of low prognostic relevance.

The elucidation of the molecular background of GIST and the subsequent clinical introduction of tyrosine kinase inhibitors (TKIs) such as imatinib mesylate (STI571, Gleevec®, Novartis Pharmaceuticals, Basel, Switzerland)[18] and, more recently, sunitinib malate (SU11248, Sutent®, Pfizer, New York, USA),[19] which not only inhibits KIT and PDGFRA but also the vascular endothelial cell growth factor and fms-related tyrosine kinase 3 receptor, identified GIST patients as ideal candidates for molecular-targeted therapeutic strategies. The impact of TKIs in the management of patients with GIST has been clearly established for advanced and metastatic tumor stages in terms of increased resection rates and prolonged overall survival.[20–22] The necessity for multimodality treatment also appears obvious for patients with completely removed localized primary tumors since in two thirds of them recurrence can be expected. Surgical approaches alone have resulted in disappointing 5-year survival rates of only 42% to 54%.[23–25] Several clinical trials are currently testing the efficacy of TKIs in the neoadjuvant (RTOG 0132) and adjuvant (ACOSOG Z9001, EORTC 62024, SSG XVIII) setting.

It was our objective to determine whether the *KIT* and *PDGFRA* gene mutation status provides for a molecular marker that would in addition to commonly accepted clinicopathological features better assess prognosis of GIST patients after complete primary resection.

Material and Methods

Patients

From 1995 to March 2007, 213 patients with primary GIST underwent surgery at the University Hospital Essen, Germany (1999–March 2007) and at the Zhongshan Hospital, Fudan University, China (1995–December 2006), respectively. The hospital charts were evaluated with regard to standard demographic data, clinical features, operative records, histopathologic findings, and outcomes. All data were included in prospective databases. The institutional review boards approved tumor tissue collection and the following analyses.

Standard surgical approach including intraoperative ultrasound of the liver was accomplished depending upon tumor location. Only resections accomplished with microscopically negative surgical margins (≥1 mm) were considered as complete. Tumor tissue embedded in paraffin was available for each patient. Additional snap-frozen samples were obtained when possible. None of the patients received neoadjuvant or adjuvant treatment. Prospective follow-up with three to six monthly examinations including ultrasound and computerized tomography was carried out.

Pathologic Diagnosis and Classification

The diagnosis of GIST was assigned for all tumors by two independent expert pathologists (H. Y. Y. and G. F.). The pathologic diagnosis including specific staging and grading followed the current criteria.[26,27] All samples were subjected to a panel of antibodies including CD117 (A4502, *KIT* polyclonal rabbit, dilution 1:150, Dako, Glostrup, Denmark), CD34 (clone QBEnd 10, mouse, dilution 1:200, Dako), smooth muscle actin (SMA; 1A4, dilution 1:200, Dako), desmin (D33, dilution 1:200, Dako) and S-100 protein (polyclonal, dilution 1:300, Dako).

Analysis of *KIT* and *PDGFRA* Sequences

The sequence analysis of *KIT* (exon 9, 11, 13, and 17) and *PDGFRA* (exon 12 and 18) was performed according to the previously reported protocols.[4,28,29] Primer sequences are available upon request. In short, genomic DNA was isolated from paraffin-embedded tissue samples by using a standard phenol/chloroform organic extraction protocol. Sequencing reactions were conducted in forward and reverse direction, and the results were compared with the National Center for Biotechnology Information human *KIT* (NM_001093772) and *PDGFRA* (NM_006206) gene sequences.

Statistical Analysis

Each patient had a minimum follow-up of 6 months. Median follow-up was 78 months. Descriptive and explorative statistics consisting of the mean, median, range, and frequency were applied when appropriate. Risk of tumor recurrence and disease-free survival (DFS) were assessed as a function of various clinicopathologic variables and mutational status. Overall survival and DFS were measured from the time of surgery to the time of first recurrence or most recent follow-up or death and plotted by the Kaplan–Meier method. Long-rank test of survival analysis was used to compare DFS curves as functions of variables and to identify significant differences. The chi-squared test was used to compare proportions. Those variables of DFS that were deemed statistically significant by univariate analysis were entered into a multivariate analysis using the Cox's proportional hazard model. $p<0.05$ was considered statistically significant. Statistic analysis was carried out using SPSS 11.0 (SPCC, Inc., Chicago, IL, USA).

Results

Patient and Tumor Characteristics

Of the 213 cases recorded, 29 cases were excluded during the course of the study from further analysis, leaving 184 cases for the final study population. Reasons for exclusion were incomplete surgical resection (13 patients), death due to disease-unrelated reasons (two patients, of them one due to hepatocellular carcinoma 46 months after surgery and one due to traffic accident at 1 month after surgery), and lost to follow-up (14 patients).There were 104 men (56.5%) and 80 women, with a median age of 58 years (range, 17 to 81 years). Clinical history revealed four patients, two males and two females aged 37, 50, 57, and 61 years, respectively, with neurofibromatosis 1 (NF1). None of the four patients showed multifocal tumor occurrence, which is phenotypic for NF1. Additionally, three females aged 17, 25, and 27 years, respectively, displayed synchronous or metachronous pulmonary chondroma, a constellation typical for the Carney triad. The most common primary tumor sites were stomach (52.2%), small bowel (26.6%), anorectum (8.1%), and the duodenum (7.1%; Table 1). Complete tumor resection was achievable in all 184 patients. In nine of them, limited liver metastases were disclosed after laparotomy and synchronously resected with the primary tumor. The median primary tumor size was 6.5 cm (range, 0.7–25 cm).

Microscopically, 143 tumors (77.7%) displayed a spindle cell type. Of the remaining tumors, 20 showed epithelioid phenotype, whereas 21 were composed of both spindle and epithelioid tumor cells. Positive expression of CD117 and CD34 was evident in 94.0% and 78.3% of the tumors, respectively. Expression of SMA and S-100 protein was revealed in 28.8% and 12.0% of specimens, respectively. Only two tumors stained positive for desmin. When classified according to the National Institute of Health (NIH) risk level stratification system, 11 patients were assigned to a very low risk level, 45 to a low risk level, 30 to an intermediate risk level, and 98 to a high risk level (Table 1).

Table 1 Relationship Between Clinicopathological Variables and Risk of Recurrence

	Total	Recurrence, *n* (%)	Univariate	Multivariate
Sex				
Male	104	53 (51.0)	0.007	0.827
Female	80	25 (31.3)		
Age (year)				
<50	47	30 (63.8)	0.001	0.008
≥50	137	48 (35.0)		
Size (cm)				
<5	59	10 (17.0)	<0.0001	0.060
5 to 10	77	39 (50.7)		
≥10	48	29 (60.4)		
Site				
Stomach	96	27 (28.1)	<0.0001	0.065
Small bowel	49	29 (59.2)		
Duodenum	13	5 (38.5)		
Rectum + anus	15	11 (73.3)		
Others (esophagus, colon)	11	6 (54.5)		
Stage				
Stage I	175	69 (39.4)	<0.0001	0.731
Stage II	9	9 (100.0)		
Mitotic count (per 50 HPFs)				
<5	87	13 (14.9)	<0.0001	0.001
5 to 10	18	4 (22.2)		
≥10	79	61 (77.2)		
NIH risk level				
Very low	11	3 (27.3)	<0.0001	0.156
Low	45	3 (6.7)		
Intermediate	30	7 (23.3)		
High	98	65 (66.3)		

Of the 184 study patients, 162 (88.0%) were comprised of tumors with detectable mutations (Table 3). Mutations in exon 11 were observed in 151 tumors (93.2%). Lower mutation frequencies occurred for exon 9 (4.3%) and exon 13 (0.6%). All three *PDGFRA* mutations were localized in exon 18. Of the exon 11 mutations, there were 26.5% point mutations, 51.6% deletions, 14.6% point mutations and deletions, and 7.3% duplications. The majority of mutations were revealed in the known hot spot of *KIT* ranging from codons 549 to 569 (exon 11). The 3' region of exon 11

considered as another hot spot was the location of 25 mutations, whereas exon 9, a so-called third hot spot, was affected in seven patients, all of them exhibiting the insertion of the base pairs GCC TAT that resulted in the duplication of amino acid residues Ala502 and Tyr503. Of the patients in clinical stages I and II, 93 (53.1%) and seven (77.8%) had tumors harboring exon 11 deletion ($p=0.028$), respectively. The deletion affected codons 557–558 in four of the seven patients with stage II tumors (57.1%). All three *PDGFRA* mutations, namely a substitution of valine for aspartic acid at codon 842 (D842V) in two cases and a deletion IMHD843-846 in one case, occurred in gastric epithelioid tumors. Different exon mutations and mutation types were included in multivariate analysis for disease-free survival along with other clinicopathological variables such as age, tumor size, disease stage, and mitotic count.

Risk of Recurrence

The median follow-up time was 78 months, ranging from 6 to 144 months. During follow-up, 78 patients (42.4%) developed tumor recurrence. As shown in Table 1, recurrence was significantly associated with several clinicopathologic variables in the univariate analysis, including sex, age, tumor size, site of primary tumor, clinical stage, mitotic count, and NIH risk level criteria. In the multivariate analysis, only age ($p=0.008$) and mitotic count ($p<0.001$) continued to be of significance.

The most common sites of recurrence were peritoneal dissemination in 37 patients (47.4%) and liver metastases in 30 patients (38.5%). Neither the presence of a *KIT* or *PDGFRA* mutation ($p=0.88$) nor the exon affected ($p=0.461$) were associated with a risk of tumor recurrence (Table 3). When correlating recurrence with the subset of mutations, a trend toward statistical significance became evident ($p=0.054$). The results were similar when analyzing clinical stages I and II tumors as one group or when clinical stage I tumors alone were considered.

Overall Survival and Disease-Free Survival

The overall 5-year survival and the 5-year DFS for the whole group of 184 patients were 79.8% and 41.9%, respectively. When analyzed by clinical stage, the overall 5-year survival and the 5-year DFS were 81.6% and 44.5%, respectively, for stage I and 31.3% and 0% for stage II ($p<0.0001$).

Table 2 presents various clinicopathologic variables associated with DFS. On univariate analysis, sex, age, tumor size, site of tumor occurrence, clinical stage, mitotic count, and risk levels according to NIH criteria proved to be of significant value. The relationship between the risk level and DFS is illustrated in Fig. 1. The mean DFS for the very-low-risk group was 7.5 years but varied considerably from 3.8 to 11.0 years. Surprisingly, it was lower than in the low and intermediate-risk-level group both of which expressed similar values. All nine patients with liver metastases were in the high-risk-level group. Based on histopathological criteria such as microscopic invasion, coagulative necrosis, or severe nuclear atypia, 30 of 86 tumors (34.9%) assigned to the very low, low, and intermediate risk levels would have been considered as malignant. In fact, during the follow-up, 13 of these 30 patients developed tumor recurrence. In the multivariate model, age ($p=0.019$), tumor size ($p=0.009$), clinical stage ($p<0.001$), and mitotic count ($p<0.001$) remained significantly associated with DFS (Table 2).

When analyzing disease-free survival as a function of a presence of a mutation, no difference was evident between the patients who had tumors with a *KIT* or *PDGFRA* mutation compared with those who showed wild-type sequence for both the genes (Table 3). The 5-year DFS in patients with tumors having *KIT* exon 11 mutations was 41.8% and was comparable with the 5-year DFS of 40.3%

Table 2 Relationship of Clinicopathological Variables and 5-Year Disease-Free Survival

	5-year DFS (%)	Univariate	Multivariate
Sex			
Male	31.1	0.0159	0.582
Female	52.3		
Age (year)			
<50	23.7	0.0085	0.019
≥50	49.4		
Size (cm)			
<5	76.0	<0.0001	0.009
5 to10	27.1		
≥10	31.3		
Site			
Stomach	63.2	0.0134	0.391
Small bowel	30.9		
Duodenum	38.7		
Rectum + anus	11.3		
Others (esophagus, colon)	26.5		
Stage			
Stage I	44.5	<0.0001	0.001
Stage II	0		
Mitotic count (per 50 HPFs)			
<5	78.8	<0.0001	0.001
5 to 10	64.3		
≥10	13.3		
NIH risk level			
Very low	64.3	<0.0001	0.147
Low	80.3		
Intermediate	78.4		
High	22.2		

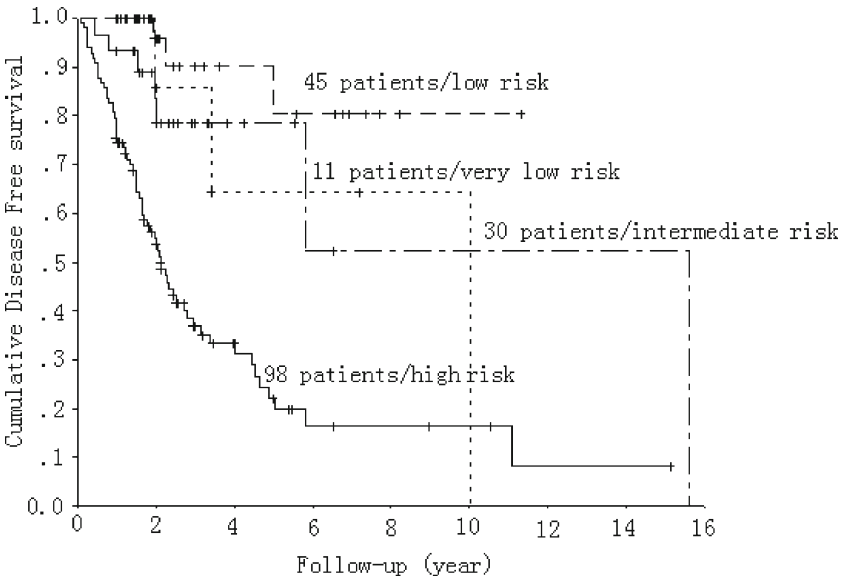


Figure 1 Kaplan–Meier representation of cumulative disease-free survival of the four risk levels ($p<0.001$) according to the NIH consensus criteria.

Risk (NIH)	Survival time (y)	Standard error	95% Confidence Interval
Very low	Mean: 7.45	1.82	3.88-11.02
Low	Mean: 9.81	0.82	8.20-11.42
Intermediate	Mean: 9.99	2.48	5.14-14.85
High	Mean: 3.97	0.60	2.80-5.15

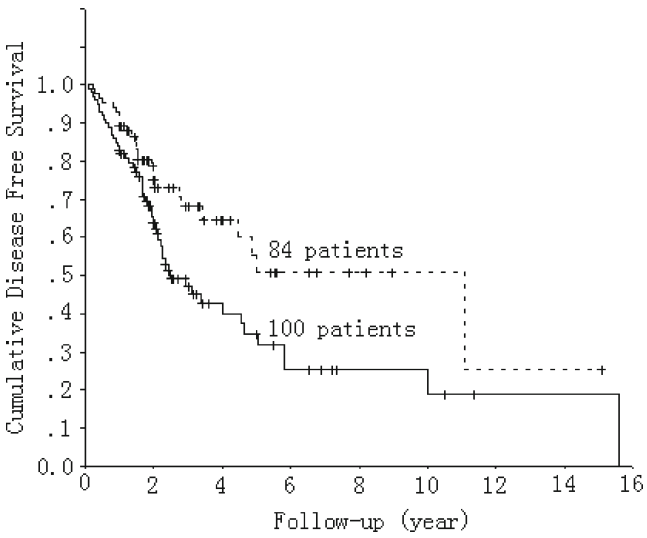
Table 3 Relationship Between *KIT* or *PDGFRA* Mutation and Risk Of Recurrence and 5-Year Disease-Free Survival

	Total	Recurrence, *n* (%)	*p* value	5-year DFS (%)	*p* value univariate	*p* value multivariate
KIT/*PDGFRA* mutation						
Yes	162	69 (42.6)	0.88	41.7	0.87	
No	22	9 (40.9)		40.3		
Exons of mutation						
Exon 11 (*KIT*)	151	65 (43.0)	0.461	41.8	0.0016	0.021
Exon 9 (*KIT*)	7	3 (42.9)		na[a]		
Exon 13 (*KIT*)	1	1 (100.0)		0.0		
Exon 18 (*PDGFRA*)	3	0 (0.0)		100.0		
No mutation	22	9 (41.0)		40.3		
Mutation type						
Exon 11 point mutation	40	10 (25.0)	0.054	52.9	0.0005	0.048
Exon 11 deletion	78	42 (53.8)		33.6		
Exon 11 point mutation and deletion	22	10 (45.5)		38.1		
Exon 11 duplication	11	3 (27.3)		71.6		
Exon 9 mutation	7	3 (42.9)		na[a]		
Exon 13 mutation	1	1 (100.0)		0		
Exon 18 mutation	3	0 (0.0)		100.0		
No mutation	22	9 (41.0)		40.3		

na not available

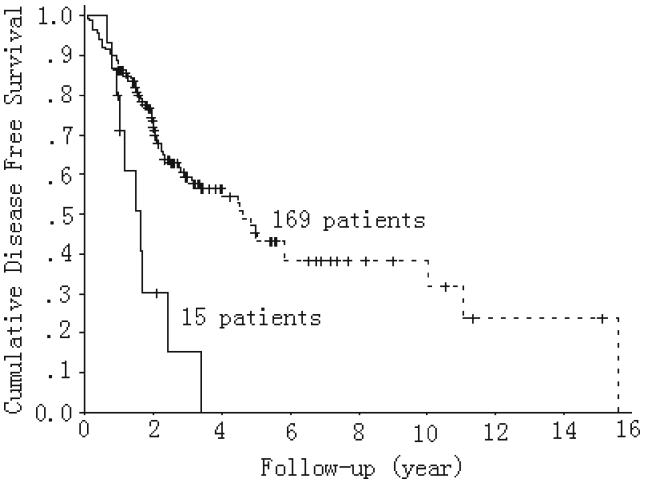
[a] Four patients with exon 9 mutations have been disease free at 2.0, 2.1, 2.5, and 2.6 years of follow-up (5-year DFS cannot be calculated)

in patients whose tumors contained no exon 11 mutation. In contrast, differences in survival became obvious when different exons affected by mutations and the subsets of mutations were considered. A mutation in exon 11 was associated with a 5-year DFS of 41.8%, while four of eight patients with exon 9 and exon 13 mutations developed recurrence within the same time. The value of this observation might be limited by the small sample size with exons 9 and 13 mutations, respectively. For patients with exon 11 point mutations or duplications, the 5-year DFS was 52.9% and 71.6%, compared to 33.6% and 38.1%, respectively, when a deletion or a point mutation in combination with a deletion was present (Fig. 2). Comparable results were found if patients with clinical stages I and II tumors or with clinical stage I tumors alone were considered. Furthermore, all 15 patients who had tumors containing a hemizygous *KIT* mutation were at significant risk for early tumor recurrence (p=0.0004; Fig. 3). According to the NIH risk level criteria, two of the 15 patients would be classified as being only at low risk. The most frequent alteration in this subgroup of mutations was exon 11 deletion. In all three *PDGFRA*-mutated tumors, all mutations occurred exclusively in exon 18, and all three affected patients were tumor free at 5 years postsurgery. Due to the small number of cases, no conclusion concerning the prognostic relevance of the type of the mutation (D842V versus IMHD843-846) can be considered



Exon 11 deletion	Survival time (y)	Standard error	95% Confidence Interval
Present	Mean: 5.43	0.81	3.85-7.01
Absent	Mean: 7.92	1.12	3.57-18.57

Figure 2 Kaplan–Meier representation of cumulative disease-free survival according to presence of exon 11 deletion (with or without point mutation). No exon 11 deletion = *dotted line*, exon 11 deletion (with or without point mutation) = *solid line* (p=0.014).



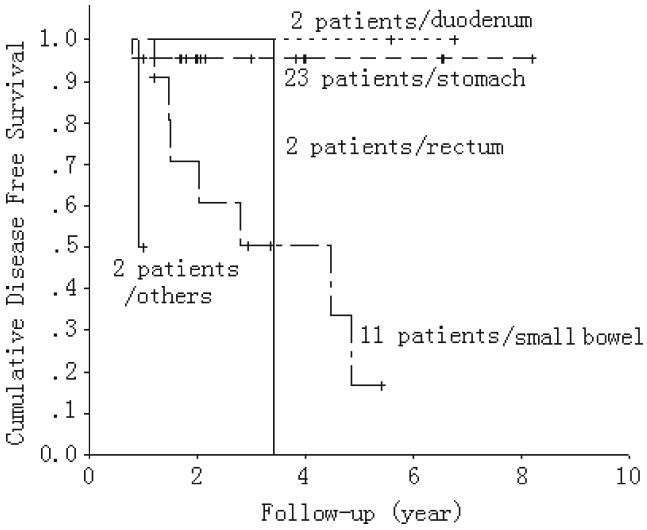
	Survival time (y)	Standard error	95% Confidence Interval
Hemizygous mutation	Mean: 1.75	0.28	1.20-2.30
Others	Mean: 6.88	0.74	5.43-8.34

Figure 3 Association of complete loss of the wild-type *KIT* allele indicating hemizygous mutation with DFS. Hemizygous mutation = *solid line*, other conditions = *dotted line* (p=0.0004).

reliable. Cumulative disease-free survival, according to tumor site for patients with tumors harboring exon 11 point mutation, is plotted in Fig. 4. Significantly better survival was seen in patients with tumors localized within the stomach or duodenum, when compared to other sites (p= 0.007). In contrast, when focusing on those patients with stomach GIST having exon 11 deletion, a decrease in the 5-year disease-free survival from 73.4% for tumors with no exon 11 deletion to 39.4% for tumors with exon 11 deletion became evident (Fig. 5, p=0.013).

Discussion

The introduction of *KIT* and *PDGFRA* genotyping in the management of patients with GIST not only contributes to the estimation of prognosis of primary disease but, more importantly, offers a tool to identify patients with tumors who would benefit from molecular-targeted therapy and patients in need for more intensive follow-up. In our study, *KIT* or *PDGFRA* mutations were detectable in 88.0% of GISTs according to the experience presented in most of the reports.[4,9,30–32] The prognostic relevance of the presence of a *KIT* mutation is under continuous debate. In the study of Kim et al., comprised of 86 patients with completely resected primary GISTs, the 5-year DFS was 21% for *KIT*-mutation-positive tumors compared with 60% in the group of patients having tumors without mutation.[33] Taking into consideration the mutational detection rate of 88%, no influence of the *KIT* or *PDGFRA* mutation status



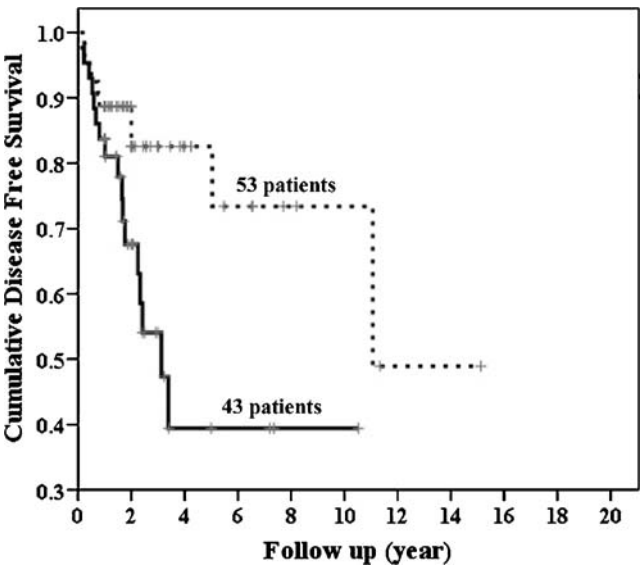
Tumor site	Survival time (y)	Standard error	95% Confidence Interval
Duodenum	na*		
Stomach	Mean: 7.89	0.32	7.27-8.51
Rectum and anus	Mean: 3.41	0.00	3.41-3.41
Small bowel	Mean: 3.38	0.51	2.37-4.39
Others	Mean: 0.96	0.03	0.90-1.02

Figure 4 Kaplan–Meier representation of cumulative disease-free survival of 40 patients with exon 11 point mutation according to the tumor site. *na* = not available, *asterisk* no recurrence after 4.5 and 7 years of follow-up.

on the 5-year disease-free survival was found in this series. According to DeMatteo,[34] the controversy concerning the impact of the presence of a *KIT* mutation on survival might mainly be due to the rather low rates of identification of mutations in the studies identifying the mutation status as indicative for poor prognosis.[14,33] The prognostic relevance of *KIT* mutation status *per se* can be questioned additionally by the observation that also GISTs with rather indolent clinical behavior display a relatively high frequency of *KIT* mutations.[4,30]

The reported frequency of exon 11 mutations varies between 20% and 92% and depends strongly upon tumor material available and method applied.[1,30,35] We were able to disclose these mutations in 98% of the 159 tumors harboring *KIT* mutation. A detailed analysis of subsets of exon 11 mutations suggested that exon 11 deletion adversely affected survival in our patients. Our finding is in accordance with observations made by Anderson et al.,[16] Wardelmann et al.,[36] Martin et al.,[37] and Singer et al..[9] Deletions affecting codons 557–558 as seen in 57.1% of our patients having tumors with exon 11 deletion were identified as independent prognostic factors for predicting metastatic behavior by some groups.[36,37] In a multicenter study from France with 276 patients with GIST, deletions of codons 562–561 were strongly associated with metastases.[38] Others have failed to confirm these observations.[16] Poor prognosis seems to be associated with the infrequently found mutations in exon 9 which affect predominantly GISTs arising from an intestinal site.[5,30] In this series, 71.4% of the tumors having exon 9 mutations were located in the small bowel and duodenum and four of the patients developed recurrence within 5 years after primary tumor resection. More aggressive clinical behavior was found in the subgroup of our patients with tumors showing a complete somatic loss of wild-type allele of the *KIT* gene indicating hemizygous mutation. Loss of heterozygosity could be another explanation for this observation.[39] Losses of genetic material on chromosome 22 are a known phenomenon in GISTs. Presumably, total losses on chromosome 22q are linked to malignancy.[40] Interestingly, due to the NIH criteria, three of our 15 tumors containing only the mutated *KIT* allele have been assigned to low risk level. Based on the mutational results, we would nowadays recommend adjuvant treatment in these three patients although being at low risk for recurrence according to standard tumor staging.

Mutations in the *PDGFRA* gene, as the second molecular marker of GIST, most frequently affect exon 18 and rarely exons 12 and 14. Similar to other reports, all three GISTs harboring a mutation of the *PDGFRA* gene in our study were gastric epithelioid lesions with exon 18 mutation. The



Exon 11 deletion	Survival time (y)	Standard error	95% Confidence Interval
Present	Mean: 5.26	0.81	3.46-7.08
Absent	Mean: 10.75	1.14	8.2-13.29

Figure 5 Kaplan–Meier representation of cumulative disease-free survival according to presence of exon 11 deletion (with or without point mutation) in patients with stomach GIST. No exon 11 deletion = *dotted line*, exon 11 deletion (with or without point mutation) = *solid line* (p=0.013).

excellent outcome of our three patients with *PDGFRA* mutant GISTs underscores the observed association of *PDGFRA* mutations with less aggressive gastric tumors.[41]

Independently from some still existing controversy concerning the prognostic value of *KIT* and *PDGFRA* mutations in primary GISTs, mutational status is of lifesaving relevance for patients with advanced tumors. Kinase-directed therapy emerged rapidly to a first-line treatment for metastatic GISTs, most often in combination with surgical resection.[20,22] Most of the lesions harboring the *KIT* exon 11 mutation respond, at least initially, to imatinib treatment. Secondary resistances, requiring switch to alternative TKIs such as sunitinib develop frequently and are induced by second-site *KIT* and *PDGFRA* mutations arising from imatinib-resistant tumor nodules. Secondary mutations are most frequently found in exon 17.[42] Tumors with exon 9 mutation are less suitable for kinase inhibitor therapy. A substantial number of *PDGFRA*-mutated GISTs are imatinib-resistant due to the presence of the D842V subset of mutations. Assessment of mutation status is of particular value in these patients in order to select them for second-line TKI therapy.

Apart from the observation that the presence of alterations of *KIT* or *PDGFRA* genes is associated with the outcome of patients with GIST, we need to acknowledge that this unique entity can develop as part of different hereditary tumor syndromes. In this study, four patients with *KIT* and *PDGFRA* wild-type genotype were associated with NF1. Additionally, three young patients with Carney triad harbored GIST but had wild-type *KIT/PDGFRA* genotypes. In total, 29.2% of our patients with *KIT* or *PDGFRA* wild-type genotype developed GIST as part of a hereditary disease. Other recent studies are in accordance with our findings.[43–45] Therefore, from a clinical standpoint, patients that are diagnosed with GIST and lack *KIT* or PDGFRA mutation need to be offered further genetic counseling to rule out hereditary disease.

When comparing reported disease-free survival status in patients with primary GIST who underwent complete tumor resection, considerable differences become evident. In our series, the 5-year DFS was 41.9% for the entire group of patients, and it increased to 44.5% when only stage I patients were considered. Kim et al. reported a 5-year DFS of 29% in their curatively resected patients and DeMatteo et al. of 54%.[23,33] In contrast, Singer et al. achieved a 5-year disease-free survival rate of 76% in patients with tumors resected completely.[9] The definition of completeness of resection varies between the studies. In some reports, as in the one from the Memorial Sloan-Kettering Cancer Center[23] and also in ours, also patients with completely resectable synchronous metastatic disease are considered as being curatively resected. These different experiences reflect the inconsistent biological behavior of GISTs and underline the necessity of better identifications of primary curatively resected patients who are at increased risk for disease relapse.

As clinicians, we feel that genotyping for *KIT* and *PDGFRA* mutations should become an integral part of the traditional prognostic assessment of GISTs based on clinicopathological parameters. Presently, the most widely accepted criteria for evaluating biological potential of GISTs are the NIH consensus criteria. One caveat, however, is that these criteria do not take clinically apparent tumor spread into consideration. In addition, in our study, we identified patients that developed tumor recurrence despite being considered having a low risk by NIH criteria alone. Although the NIH criteria provide an excellent estimation of tumor behavior, in our study, we were able to subclassify further using genetic information. *KIT* and *PDGFRA* gene mutation status *per se* has a limited prognostic value in patients with GIST and is in general subordinate to the traditional clinicopathologic risk factors. The specific type of *KIT* or *PDGFRA* mutation, nevertheless, is highly predictive for survival. Based on the results of this study, patients with exon 11 deletions or those with hemizygous mutations would be, despite complete tumor resection, candidates for adjuvant treatment. This is particularly germane for patients with tumors that would be classified low risk by standard criteria. It is a matter of speculation, if there is difference in susceptibility to imatinib or sunitinib in the presence of exon 11 deletion versus any other exon 11 mutation.

The concept to associating the tumor genotype with prognosis is a powerful tool for personalized medicine, for example, in medullary thyroid carcinoma. Somatic molecular information will continue to be a useful adjunct to the standard clinical information, in this case, to further subclass a group of identical appearing tumors that do not have uniform outcome. In this report, we show that some special subsets of mutations might allow for the molecular classification of high-risk patients. Gradually, GIST will become subclassified by *KIT* or *PDGFRA* genotype and patients selected for phenotype–genotype-adjusted clinical management.

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ORIGINAL ARTICLE

Prognostic Factors in Patients with Synchronous Peritoneal Carcinomatosis (PC) Caused by a Primary Cancer of the Colon

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Abstract
Background Peritoneal carcinomatosis (PC) is seen in about 10% of patients with colon cancer during the initial operation and has been considered a preterminal condition. The actual outcome can vary extensively depending on the presence/absence of metastases other than PC.
Methods A total of 975 consecutive patients with colon cancer who underwent resection were included. The extent of PC was determined at laparotomy. Metastases restricted to the adjacent peritoneum or a few metastases to the distant peritoneum were classified as "limited," whereas numerous metastases to the distant peritoneum were as "extensive" regardless of the sizes of the disseminated nodules.
Results PC group consisted of 75 patients (7.7%). The median survival time (MST) in the PC group was 6.8 months. Survival was significantly better in cases with limited PC (MST, 12.4 months), without lymph node involvement (20.8 months), with preoperative performance status of 0 or 1 (8.5 months), and who received chemotherapy more than 3 months (8.8 months). A multivariate analysis revealed that these four factors were significant predictors of better outcome.
Conclusions The extent of PC and lymph node involvement, even if the distribution is confined around the primary lesion, are more accurate prognostic factors than distant metastasis in patients with colon cancer and synchronous PC.

Keywords Colon cancer · Peritoneal carcinomatosis (PC) · Metastasis · Prognostic factor

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Introduction

In 2007, colorectal cancer was estimated to be the second most frequent cause of cancer-related death in both Europe and the USA.[1,2] The pattern of tumor recurrence after curative resection differs between colon cancer and rectal cancer. Peritoneal carcinomatosis (PC) is seen more frequently among cases of colon cancer than among cases of rectal cancer.[3–5] Brodsky et al.[6] reported that PC accounts for 25–35% of all recurrences after curative resection for colon cancer. Synchronous PC is seen in about 10% of patients with colon cancer during the initial operation.[7–9] One factor responsible for the high frequency of PC in colon cancer is the high likelihood of the cancer cells being shed into the peritoneal cavity following the serosal penetration.[10]

As described above, PC from colorectal cancer is not an uncommon mode of disease progression. To date, however, few reports have been published concerning the frequency

of PC or treatment methods for PC. In past reports, the data were often analyzed without distinguishing between synchronous PC and metachronous PC or between colon cancer and rectal cancer.[8,11–13]

In regard to the prognosis of colorectal cancer patients with metastasis to the peritoneum, the median survival time (MST) has been reported to be 5–7 months,[11,12] and colorectal cancer with peritoneal metastasis has been considered a terminal condition. The introduction of cytoreductive surgical techniques combined with intraperitoneal chemotherapy has improved the survival of selected patients with PC recently.[14,15] Under these circumstances, most patients have been treated with palliative surgery followed by systemic chemotherapy.

In recent years, new cytotoxic agents (e.g., oxaliplatin and irinotecan) and molecular-targeted drugs (e.g., bevacituzumab and cetuximab) have been developed. Multimodal regimens including these new drugs have markedly improved the MST of patients with metastatic colorectal cancer, with a reported MST of 20 months or longer in some studies.[16,17] The diagnostic accuracy of imaging using computed tomography (CT) is relatively low for PC, unless the metastatic nodule is 5 cm or larger in diameter.[18] Therefore, survival time is the only indicator that can be used to evaluate treatment response in many cases with PC. To date, very few reports have been published on the efficacy of chemotherapy in cases where PC is the only site of tumor metastasis.

All primary colon cancers with PC are classified as stage IV. However, these cases can vary from each other in terms of the presence/absence of metastases other than PC (e.g., metastasis to the liver, lung, lymph nodes, etc). This retrospective study explored the clinical and histological factors determining the postoperative prognosis of colon cancer patients found to have PC during their first operations.

Patients and Methods

Preoperative, operative, and follow-up data on all patients with colon cancer treated at Tokai University Hospital between January 1991 and December 2004 were retrieved from the databases of the Departments of Surgery and Pathology. The inclusion criteria were as follows: patients with colon cancer invading the proper muscle layer or deeper (T2-4) who underwent resection of the primary tumor. Patients were excluded from the study if the primary tumor was located in the rectum or if the tumor penetration was confined to the submucosal layer. Patients with cancer in the rectosigmoid were included in the present study.

PC was diagnosed at the time of laparotomy. Distant metastasis was diagnosed based on preoperative CT, abdominal ultrasonography, and chest X-ray findings. Liver metastases were found at the time of laparotomy in some cases. The site of the primary tumor was determined according to the Japanese guidelines[19]; tumors found in the cecum, ascending colon, and transverse colon were counted as right colon tumors, while those found in the descending colon, sigmoid colon, and rectosigmoid were counted as left colon tumors. The macroscopic findings at laparotomy, absence or presence, and extent of metastasis to the liver, peritoneum, and lymph node were recorded in the operation chart in accordance with the Japanese General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus.[19] The extent of PC had been determined based on the findings at laparotomy: metastases restricted to the adjacent peritoneum or a few metastases to the distant peritoneum were classified as "limited," whereas numerous metastases to the distant peritoneum were classified as "extensive" regardless of the sizes of the disseminated nodules.

Postoperative Follow-Up

As a rule, each patient underwent hematological testing, abdominal ultrasonography, and chest X-ray or thoracic/abdominal CT studies once every 3–4 months until 2 years postoperatively according to the guideline of our department. From the third year onwards, these checks were performed every 6 months. Examinations were also performed if the patients became symptomatic.

Chemotherapy

No standard postoperative chemotherapy regimens have been determined for patients with PC. Four patients received no chemotherapy. The remaining patients were treated with chemotherapy. Almost all of them were treated with oral fluorinated pyrimidine (primarily UFT). The concomitant use of leucovorin was started in September 2003 because of restrictions imposed by the Japanese National Health Insurance system. Recently, oxaliplatin- and irinotecan-based regimens have been used. Only four patients received regimen including leucovorin. We divided them into two groups according to the chemotherapeutic treatment duration: no treatment or less than 3 months and 3 months or longer.

Data Analysis

The clinical and histological parameters of the two groups were compared using the Mann–Whitney *U* test for continuous data and the chi-square test for categorical variables. Survival data were analyzed using the Kaplan–Meier method with log-rank significance testing. Variables found to be significant or nearly significant were subjected to Cox regression modeling to determine predictors of survival.

Approval was obtained from the hospital ethics committee for this study.

Results

A total of 993 patients with colon cancer were identified from the database. Eighteen patients had two or more colorectal cancer tumors simultaneously, and these cases were excluded from this study. The remaining 975 patients were included in the subsequent analyses.

The PC group consisted of 75 patients (7.7%) who were found to have PC intraoperatively. PC was confirmed histologically in 66 out of 75 patients. However, PC was not excised in any of the patients because PC had been regarded as an incurable condition in our institution. The non-PC group was composed of 900 patients (92.3%) who did not have PC. In the PC group, 37 patients (3.8%) had limited PC and 38 (3.9%) had extensive PC.

Clinical and Histological Features

The clinical and histological features of the two groups are shown in Table 1. The mean age was significantly lower in the PC group than in the non-PC group. Right colon cancer and synchronous distant metastasis were seen significantly more frequently in the PC group than in the non-PC group. Histologically, the incidence of lymph node metastasis and the percentage of cases with moderately differentiated or high-grade carcinomas were significantly higher in the PC group than in the non-PC group.

In the PC group, distant metastasis was observed in 33 patients. Thirty-two patients had liver metastases. Six patients presented with solitary liver metastasis, and two of these patients underwent partial hepatectomies. Twenty-six patients had multiple liver metastases. Of these patients, two had simultaneous lung metastases and one had a simultaneous bone metastasis. One patient had a pulmonary metastasis and PC only. Chemotherapy was administered for 3 months or longer to 57 of the 75 patients and for less than 3 months to the 14 patients. The remaining four patients received no chemotherapy.

Survival

Univariate Analysis The MST in the PC group was 6.8 months. Seventy-two patients died of the disease. Three patients were still alive on December 2006. Table 2 shows the relationship between each variable and survival. Survival differed significantly depending on the extent of PC, the presence/absence of lymph node metastasis, the duration of chemotherapy, and the grade of performance status (ECOG) before surgery. Figures 1, 2, and 3 show survival curves plotted according to the variables. Survival was significantly better in the cases with limited PC than in those with extensive PC, the MSTs being 12.4 and 4.4 months, respectively ($p=0.0006$). Survival was significantly better in the lymph node involvement-negative group than in the positive group, with the MSTs being 20.8 and 5.8 months, respectively ($p=0.002$). Survival was significantly better in the patients who received chemotherapy for more than 3 months than in those who received no

Table 1 Comparison of Clinical Characteristics of Patients with PC and Non-PC

	PC ($n=75$)	Non-PC ($n=900$)	p value
Sex ratio (M/F)	41:34	540:36	0.43
Median (range) age years	62 (15–85)	65 (23–96)	0.03
Site[a]			
Right colon	40 (53%)	358 (40%)	0.02
Left colon	35 (47%)	542 (60%)	
Lymph node metastasis			
Absent	14 (19%)	504 (56%)	<0.001
Present	61 (81%)	389 (43%)	
Unknown		7 (1%)	
Distant metastasis			
Absent	42 (56%)	759 (84%)	<0.0001
Present	33 (44%)	141 (16%)	
Histologic differentiation			
Well	23 (31%)	485 (54%)	<0.0001
Moderately	37 (49%)	363 (40%)	
Poorly	7 (9%)	23 (3%)	
Mucinous	7 (9%)	27 (3%)	
Signet ring cell	1 (2%)	2 (0%)	

[a] Right colon: cecum, ascending colon, transverse colon. Left colon: descending colon, sigmoid colon, rectosigmoid

Table 2 Patient and Treatment Characteristics with Median Survival of Different Subgroups in Patients with PC (Univariate Analysis)

Variable	No. of patients	Median survival (months)	*p* value
Gender			
Male	41	5.2	0.49
Female	34	8.2	
Age			
<65	43	7.7	0.97
≥65	32	6.8	
Site			
Right colon	40	8.2	0.43
Left colon	35	5.8	
PC			
Limited	37	12.4	0.0006
Extended	38	4.4	
T category			
T3	15	8.5	0.82
T4	60	6.2	
Lymph node metastasis			
Absent	14	20.8	0.002
Present	61	5.8	
Distant metastasis			
Absent	42	9.0	0.09
Present	33	5.0	
Histology			
Well/mod	60	6.7	0.8
Others	15	8.5	
Chemotherapy			
≥3 months	57	8.8	0.002
None or <3 months	18	2.9	
Performance status (ECOG)			
0/1	63	8.5	<0.0001
2	12	2.5	

chemotherapy or chemotherapy for less than 3 months, the MSTs being 8.8 and 2.9 months, respectively (p=0.002).

Survival was significantly better in the cases with preoperative performance status (PS) of 0 or 1 than in those with PS of 2, the MSTs being 8.5 and 2.5 months, respectively (p<0.0001). Survival did not differ significantly depending on the T category or the presence/absence of distant metastasis to the liver, lung, etc. (p=0.82, p=0.09; Fig. 3).

Multivariate Analysis Cox regression analyses were conducted using the five variables that were found in the univariate analyses to give significant or nearly significant influences on survival. Limited PC, the absence of lymph node metastasis, the administration of chemotherapy for more than 3 months, and the PS of 0 or 1 were identified as significant prognostic factors of a better outcome (Table 3).

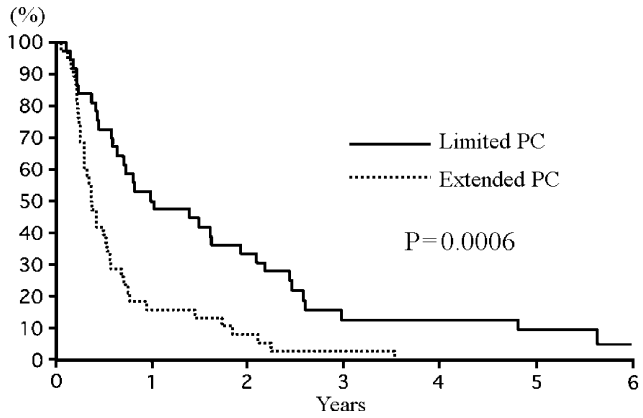

Figure 1 Survival curves of 75 patients with PC comparing the extent of PC.

Discussion

About 10% of all colon cancer patients already have PC at the time of their diagnosis.[7–9] However, little has been documented regarding the clinical and histological features of peritoneal carcinomatosis associated with primary cancer in the colon.

Chu et al.[8] and Sadeghi et al.[11] reported the outcomes of 100 and 118 cases with PC secondary to non-gynecologic malignancy, respectively. However, only 22 and 69 cases, respectively, had PC secondary to colon cancer at the time of the initial operation. Jayne et al.[12] collected data on 349 cases with PC arising from colorectal cancer, reporting that the PC was synchronous with the colon cancer in 101 cases. In the present study of 975 patients with colon cancer, synchronous PC was noted in 75 cases (8%). Thus, the

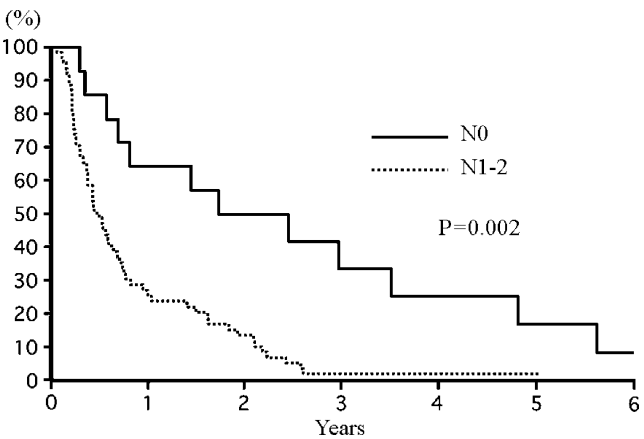

Figure 2 Survival curves of 75 patients with PC comparing N stages.

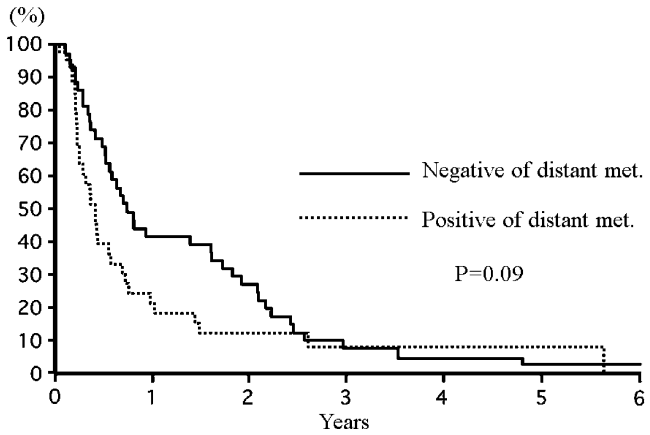

Figure 3 Survival curves of 75 patients with PC according to the presence or not of distant metastasis.

number of cases examined in the present study was equivalent to that in previously reported studies. The PC-positive rate among the subjects of the present study was also comparable to that in previous reports.

Following the recent introduction of chemotherapeutic regimens such as fluorouracil–leucovorin and irinotecan/oxaliplatin, the prognosis of patients with metastatic colorectal cancer has improved.[17] However, peritoneal carcinomatosis associated with colorectal cancer has been considered a preterminal condition for which palliative treatment is recommended because of the poor prognosis. The MST after the diagnosis of synchronous PC has been reported to be 4.1 or 7 months.[11,12] The MST in the present series was 6.8 months.

According to the current TNM staging system, colon cancers with PC are classified as stage IV. While PC is the only metastatic site in some cases, it may be associated with distant metastases or lymph node metastasis in other cases. Moreover, PC may be either localized or generalized within the peritoneal cavity. Patient outcome can vary extensively, depending on the features of the PC in individual cases. In our experience, colon cancer patients with PC but without lymph node metastasis around the primary lesion had a relatively good prognosis (MST=20.8 months), while colon cancer patients with PC and positive lymph node metastasis had a poor prognosis (MST=5.8 months), even when they had no distant metastases to other organs. It would, therefore, be desirable to develop a stage IV subclassification system that would allow the prognosis of patients with PC to be predicted more accurately.

Regarding the extent of PC, Verwaal et al.[20] divided the peritoneal cavity into seven segments and reported that the prognosis was poorer in patients with involvement in six or seven segments compared with that in patients with involvement in five or fewer segments. Gilly et al.[21] divided the peritoneal cavity into nine parts and classified PC into four stages, depending on the size and distribution of the metastases: stage 1 = malignant granulations less than 5 mm in diameter, localized to one part of the abdomen; stage 2 = malignant granulations less than 5 mm in diameter, diffusely distributed throughout the abdomen; stage 3 = malignant granulations ranging in diameter from 5 mm to 2 cm; and stage 4 = large malignant cakes (more than 2 cm in diameter). They classified stages 1 and 2 as limited PC and stages 3 and 4 as extensive PC. Jacquet and Sugarbaker[22] classified the condition of PC following cytoreductive surgery into four categories based on the size of the residual tumor. In the present study, PC was not excised in any of the patients. We classified PC into two categories (limited and extensive) depending on the area of distribution of the PC, regardless of the size of the disseminated nodules, in accordance with the current Japanese guidelines.[19]

Sadeghi et al.[11] and Jayne et al.[12] listed the extent of PC and the T stage of the primary lesion as prognostic factors in patients with colorectal cancer with PC. Chu et al.[8], however, reported that only ascites and lung metastasis affected the prognosis of these patients, casting doubt on the role of PC as a prognostic factor. Pelz et al.[13] reported that clinical symptoms, extent of PC, and histology of the primary tumor were significant predictors of overall survival. Lymph node metastasis around the primary lesion was not identified as a prognostic factor in any of these four reports. However, these four studies included not only cases of synchronous PC but also cases with recurrent (metachronous) PC. In the present study, only cases with synchronous PC were studied. Four significant prognostic factors were identified (extent of PC, presence/absence of lymph node metastasis around the primary lesion, duration of chemotherapy, and preoperative performance status). Distant metastasis to other organs was not identified as a significant prognostic factor.

Now, a new treatment method for patients with colorectal cancer and PC is being developed. Improved survival in

Table 3 Risks Influencing Survival by Multivariate Analysis (Cox Proportional Hazard Model)

Factors	Hazard ratio	95% CI	*p* value
Distant metastasis negative (vs. positive)	1.30	0.78–2.12	0.32
Lymph node metastasis negative (vs. positive)	2.78	1.40–5.55	0.004
PC limited (vs. extended)	2.91	1.71–4.93	0.000
Chemotherapy ≥3 months (vs. none or < 3 months)	5.32	2.79–10.14	0.000
Performance status 0/1 (vs. 2)	7.98	3.54–18.0	0.000

selected patients with peritoneal carcinomatosis has been reported with the introduction of cytoreductive surgical techniques combined with intraperitoneal chemotherapy.[14,15,23] In cases where complete cytoreduction was possible, the mean survival time was as long as 32 months, but the mortality was 4% and the incidence of major complications, including anastomotic leakage, was as high as 23%. When the selection criteria of cytoreductive surgery are established, longer survival may be obtained in patients with PC caused by a primary cancer of the colon.

In conclusion, the authors emphasize that it is essential to consider the extent of PC and lymph node involvement, even if the distribution of metastasis is confined to the area around the primary lesion, as prognostic factors rather than the presence/absence of distant metastasis in patients with colon cancer and synchronous PC.

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ORIGINAL ARTICLE

Diagnostic Accuracy of C-reactive Protein for Intraabdominal Infections After Colorectal Resections

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Abstract
Background Intraabdominal infections are caused mainly by anastomotic leaks and represent a serious complication. Diagnosis is usually made when patients become critically ill. Though inflammatory markers, including C-reactive protein (CRP) and white blood count (WBC), may contribute to an early diagnosis, their clinical roles remain unclear. The diagnostic accuracy of continuous tests depends on the choice of cut-off values. We analyzed the diagnostic accuracy of serial CRP and WBC measurements to detect infectious complications after colorectal resections.
Patients and Methods The CRP and WBC were routinely measured postoperatively in 231 consecutive patients undergoing colorectal resection. Clinical outcome was registered with regard to postoperative complications. The diagnostic accuracy of CRP and WBC was analyzed by receiver operating characteristics (ROC) curve analysis with intra- and extraabdominal infectious complications as the outcome.
Results Increased CRP levels on postoperative day (POD) 3 were associated with intraabdominal infections. The best cut-off value was 190 (sensitivity, 0.82; specificity, 0.73). The area under the ROC curve was 0.82. On POD 5 and 7, the diagnostic accuracy of CRP was similar.
Conclusion Serial CRP measurements are helpful for detecting intraabdominal infections after colorectal resection. Persistently elevated CRP values after POD 3 should be investigated for intraabdominal infection.

Keywords C-reactive protein · Diagnostic accuracy · Receiver operating characteristics curve analysis · Anastomotic leak · Diagnostic accuracy · Intraabdominal infection

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Introduction

Colorectal surgery is associated with overall complication rates of more than 30% and a perioperative mortality of 3–4%.[1–4] Despite the use of preoperative antibiotic prophylaxis, infections still represent the most frequent cause of perioperative morbidity.[5–8] Intraabdominal infections are related primarily to anastomotic leaks and are potentially life-threatening. Anastomotic leaks occur with a frequency of up to 23%.[9–11] In roughly half of patients, anastomotic leaks are clinically silent[11] and may first become evident after a median of 8 days, often when patients have developed critical illness.[12] Consequently, it is important to diagnose infectious complications early in order to initiate either surgical or conservative treatment, preventing serious postoperative morbidity or death. However, there is presently no reliable diagnostic test with sufficient accuracy available to detect anastomotic leaks at an early stage.[11,13]

Several biochemical tests are used to detect inflammatory activity in postoperative patients, including C-reactive protein (CRP), interleukins, and procalcitonin.[14–16] The measurement of CRP in the serum is the most available test and has been used widely in clinical practice to detect infections and monitor their treatment.[17–20] Recently, it was shown that CRP might be useful for diagnosing anastomotic leaks after pancreatic and rectal resections with sensitivities and specificities between 65% and 80%.[21,22] However, CRP levels change considerably during the postoperative course in both uncomplicated and complicated cases, and they are not specific to any one kind of complication.[22] Accordingly, it is important to take into account postoperative changes in CRP levels observed by serial measurements after surgery. In addition, other factors, like the nutritional state of the patient, may influence the response of biochemical tests and make the correct interpretation of test results difficult.[8,23]

C-reactive protein is measured as a continuous variable. The diagnostic accuracy of continuous variables strongly depends on the chosen cut-off value.[24] A correct statistical approach has been to analyze the complete spectrum of observed test results. Receiver operating characteristics curve (ROC) analysis is considered the appropriate statistical method for this purpose.[25]

In our department, CRP measurements are performed on scheduled postoperative days (POD) as a part of the follow-up for patients undergoing colorectal surgery. In this study, we wanted to analyze the diagnostic accuracy of serial CRP measurements after colorectal resections to detect intra-abdominal infections using ROC analysis in a large series of unselected consecutive patients.

Patients and Methods

Our institution offers surgical services as the only hospital for a population of 300,000. Between January and December 2004, 246 consecutive patients underwent colorectal resections at our department. Data regarding diagnoses and procedures, biochemical tests, and radiological procedures were retrieved from the electronic patient registry of our hospital. Patient charts were reviewed retrospectively with regard to the clinical details of postoperative complications or death. Complete data were available for the analysis of 231 (94%) patients.

Preoperative routines included high calorie carbohydrate drinks until 2 h before surgery, subcutaneous low molecular heparin, and antibiotic prophylaxis (400 mg doxycycline i.v. and 1.5 g metronidazole i.v. at least 30 min before surgery). Mechanical bowel preparation was not used routinely. Patients received peroral nutrition immediately after surgery according to their personal preferences and abilities and intravenous Ringer acetate if necessary.

On the day before the surgery, all patients had routine blood tests, including hemoglobin, creatinine, electrolytes, CRP, and white blood count (WBC). Postoperatively, all patients had a daily clinical assessment, and routine blood tests were repeated on POD 1, 3, 5, and 7. Additional investigations, including radiological or endoscopic procedures, were employed as indicated clinically.

Definitions

Postoperative complications were defined as all adverse events encountered during the first 30 days after surgery, which was until the discharge of the patient from the hospital or their readmission to our department or outpatient contact due to complications. Patients were examined for the presence of any infection according to general surgical practice: clinical symptoms, temperature ≥38°C, and/or increased inflammatory biochemical markers (i.e., CRP or WBC). *Intraabdominal infection* was defined as an infection, either diffuse or abscess, within the abdominal cavity or the presence of an anastomotic leak. An *anastomotic leak* was confirmed by radiology (i.e., contrast enhanced multi-detector CT scan or conventional radiology with water soluble contrast enema), endoscopy, or during surgical exploration. *Other infectious complications* were defined as extraabdominal infections, mostly urinary tract infections (i.e., bacteriuria >10,000/ml with or without clinical symptoms) or pneumonia (temperature ≥38°C, clinical findings, and/or pulmonary infiltration at chest X-ray), or *wound infections* (i.e., phlegmonous inflammation or abscess formation in the surgical wound). *Cardiovascular complications* included acute myocardial infarction, stroke, pulmonary thromboembolism, or deep venous thrombosis.

Biochemical Analysis

The WBC (reference range $4–10\times10^9$/L) was analyzed using a hematological blood analyzer (Advia 120, Bayer, or CellDyn, Abbott). The CRP concentration (normal range 0–10 mg/L) was measured by immunoturbidimetric assay (Roche, Switzerland).

Statistics

Data were analyzed using frequency tables for category variables. The median value was used as a measure of the central tendency for continuous variables with non-normal distributions. The chi-square test was used for comparing category variables and the Mann–Whitney *U* test for continuous variables. The diagnostic accuracy of inflam-

matory tests, CRP or WBC, was assessed by ROC curve analysis.[24–26] This method calculates the sensitivity and specificity of each observed test result with regard to a defined classification variable, identifying the best cut-off value as the test result with the highest sensitivity and specificity. A ROC curve is obtained by plotting the sensitivity (fraction of true positives, *y*-axis) against 1-specificity (fraction of false negatives, *x*-axis). The point on the ROC curve closest to the left upper corner represents the best cut-off value. The area under the ROC curve (AUC) is a direct measure of the diagnostic accuracy of the test. An AUC value greater than >50% indicates the ability of a test to significantly discriminate between positive and negative cases with regard to the classification variable (e.g., presence or absence of disease). A test with an AUC greater than 0.80 was considered as having a high diagnostic accuracy, which indicates that at least 80% of the patients with the disease were classified correctly.

A P value <0.05 (two-sided tests) was considered significant.

Results

Surgical Treatment

Two hundred and thirty-one patients (125 females, 54%) underwent colorectal resection (Table 1). The median age was 71 years (range, 18–93) in both sexes. Significantly more elderly patients (≥71 years of age) had comorbidities as expressed by ASA class III and IV (47% vs. 30%; $P<0.001$). The distribution of diagnoses and surgical procedures is

Table 1 Clinical Characteristics of 231 Patients Treated by Colorectal Resection, Including the Distribution of Diagnoses and Surgical Procedures

	Total number	P value[a]	Intraabdominal infection		Extraabdominal infection		P value[b]
			N	(%)	*N*	(%)	
Sex		0.24					0.45
Male	106		11	(5)	15	(6)	
Female	125		7	(3)	17	(7)	
Age group[c]		1					0.40
≤71	116		9	(4)	12	(5)	
>71	115		9	(4)	20	(9)	
ASA		<0.001					0.14
1	34		2	(1)	2	(1)	
2	107		4	(2)	14	(6)	
3	66		7	(3)	10	(4)	
4	24		3	(1)	6	(3)	
Emergency		<0.001					<0.05
No	176		10	(5)	20	(9)	
Yes	55		7	(3)	10	(5)	
Diagnosis		<0.001					0.14
CRC	146		9	(4)	21	(9)	
IBD	16		0	(0)	2	(1)	
Others	69		9	(4)	9	(4)	
Type of anastomosis		0.4					0.05
Entero-colic	97		4	(2)	16	(7)	
Colo-colic	60		10	(4)	4	(2)	
Pelvic	47		3	(1)	9	(4)	
Ostomy	27		1	(0)	3	(1)	

Other diagnoses included colorectal adenoma, complicated appendicitis, or diverticular disease. The number of infectious complications with regard to intra- and extraabdominal infections (i.e., pneumonia, urinary tract infection, or surgical site infection) are given

[a] P value between groups in category

[b] P value between groups of infection

[c] Age groups defined by median age

shown in Table 1. Most patients (77%) were operated electively. The majority of patients (n=146; 63%) were treated for colorectal cancer (CRC) and 16 (7%) for inflammatory bowel disease (IBD). The remaining patients (n=69; 30%) underwent surgery for various indications (i.e., diverticular disease, bowel obstruction, colorectal adenoma, and complicated appendicitis). Significantly more proximal resections, ileocecal resection and right colectomy, were done as emergency procedures (P=0.007). Resections were performed according to current surgical standards with both hand-sewn or stapled anastomoses. Rectal resections were performed with a triple stapling technique.[27] Most procedures were done by open surgery, and ten (4%) laparoscopy-assisted sigmoid resections were performed. Two hundred and one (87%) of the procedures included an anastomosis, mostly entero-colostomy (P=0.001).

Complications

Complications were encountered in 60 (26%) patients. The majority of complications were extraabdominal infections (n=33, 55%), followed by intraabdominal infections (n=18, 30%). Intraabdominal infections were diagnosed after a median time of 8 days (95% confidence interval, 4–9 days). There were eight cases of cardiovascular complications and two cases of other complications. Eight patients (13% of those with complications; 3% of all patients) died within 30 days after surgery. Seven of these eight postoperative deaths were related to complications, two to intraabdominal sepsis, three to other infections, and two to cardiovascular complications. The clinical characteristics with regard to extra- or intraabdominal infections are shown in Table 1. Complications were encountered significantly more often after emergency operations and were related to the type of anastomosis. Fifteen (83%) of the 18 patients with intraabdominal infections underwent either surgical treatment or percutaneous drainage, and three were treated conservatively.

Inflammatory Markers

The test results for inflammatory markers during the postoperative course and with regard to complications are shown in Table 2. On POD 1, increased CRP levels of approximately 100 Mg/L were observed in all patients. Eventually, CRP decreased in patients with an uncomplicated postoperative course (Fig. 1a). In contrast, CRP eventually increased over the following days when complications occurred. The increase was significantly higher in patients with intraabdominal complications as compared to other sites of infection (median, 257 Mg/L vs. 202 U/mL, P=0.024; Table 2). This difference was even greater on POD 5 and 7. The baseline course of CRP values was similar irrespective of IBD or CRC (Fig. 1b).

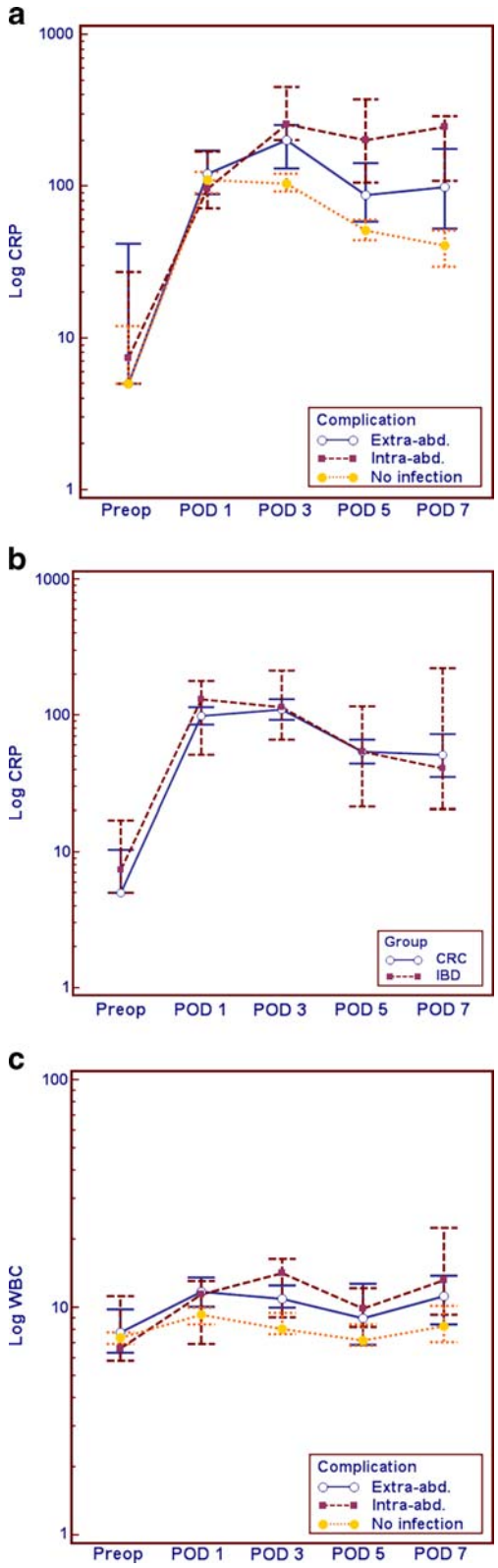
The postoperative WBC levels were less than 10.0 in patients without complications and were only slightly elevated in patients with extraabdominal infections (Fig. 1c). However, in patients with intraabdominal complications, a significantly increased WBC (median 14.2, P=0.02) was encountered on POD 3.

The results of the inflammatory marker ROC analysis with regard to intra- and extraabdominal complications are shown in Table 3. On POD 3, a cut-off value of >190 for CRP was associated with the occurrence of intraabdominal complications, providing a sensitivity of 82%, specificity of 73%, and a high diagnostic accuracy (AUC, 0.82; 95% CI,

Table 2 Test Results for C-reactive Protein (CRP) and White Blood Count (WBC) During the Postoperative Course of 231 Patients who Underwent Colorectal Surgery

	Median (lowest-highest) uncomplicated	Median (lowest-highest) intraabd. sepsis	Median (lowest-highest) other infection	P value
CRP preop.	5 (5–559)	8 (5–211)	5 (5–413)	0.95
CRP day 1	112 (12–462)	96 (35–331)	124 (15–463)	<0.001
CRP day 3	114 (5–548)	257 (74–586)	202 (26–424)	0.024
CRP day 5	54 (5–543)	202 (60–406)	87 (20–342)	0.0014
CRP day 7	48 (5–574)	246 (35–336)	99 (5–333)	0.003
WBC preop.	7.5 (0.6–33.4)	6.6 (2.5–16.5)	7.8 (0.6–14.6)	0.93
WBC day 1	9.5 (0.4–13.8)	11.4 (6.3–15.3)	11.4 (0.4–16.2)	0.31
WBC day 3	9 (0.4–22.7)	14.2 (7.2–18.4)	11.1 (0.5–13.7)	0.02
WBC day 5	7.6 (0.6–23.2)	9.9 (6.9–19.5)	9 (0.3–29.8)	0.36
WBC day 7	9 (0.7–19.4)	13.3 (7.5–24.8)	11.2 (5.4–31.3)	0.13

Tests were taken at postoperative days 1, 3, 5, and 7. The upper normal value of CRP was <10 u/mL and 10.0 for WBC. Median, lowest, and highest values are given for patients without complications, patients with intraabdominal infections, and patients with other infections. The median values for intraabdominal and other infections were compared by the Mann–Whitney U test



◀**Figure 1** Serial measurement of inflammatory markers in 231 patients undergoing colorectal resection. Median values with 95% confidence intervals are given. **a** C-reactive protein (*CRP*) increased in all patients on postoperative day (*POD*) 1. The CRP increase on POD 3 was highest in patients who developed intraabdominal infections, and it persisted on POD 5 and 7 (*red line*). In uncomplicated cases (*yellow line*), CRP decreased after POD 3. In patients with extraabdominal infections (*blue line*), the CRP increase was smaller and decreased after POD 3. **b** WBC changes were limited and showed small differences with regard to complications. **c** CRP values were similar during the postoperative course in patients undergoing surgery for inflammatory bowel disease or colorectal cancer.

0.76–0.87; P=0.0001; Fig. 2). On POD 5 and 7, similar results were found (Fig. 3). Cut-off values for WBC were only slightly increased above the upper normal limit and were associated with lower sensitivity and specificity. The diagnostic accuracy was lower for WBC, as expressed by AUC values <0.80.

The ROC analysis of CRP with regard to other infections resulted in AUC values with significant information on POD 3 and 5 compared to POD 1 for WBC (Table 3). However, the AUC values were less than 0.70. In general, the cut-off values of WBC with the highest diagnostic accuracy were mostly within the normal range or showed a mild increase and had low sensitivity and specificity.

Discussion

In our study, an infectious complication was encountered after colorectal resection in one out of every four patients, and one third of the infectious complications were localized in the abdomen. Intraabdominal infections are mostly caused by anastomotic leaks, which are still a potentially life-threatening condition. Unfortunately, the diagnosis is often made on POD 8 or later, when many patients present with signs of serious illness or even sepsis, which was also true in the present study.[12] Thus, a method for the early identification of patients at risk for intraabdominal infection would be of clinical importance. Inflammatory markers like CRP and WBC are part of the standard repertoire of available biochemical blood tests and have been used in clinical practice for years. However, the surgical literature is sparse with regard to the systematic use of CRP and WBC in this aspect. Recently, the possible role of CRP to detect anastomotic leaks after rectal resection was addressed in two studies.[22,28] Both studies reported persistently increased CRP values after POD 2–4 in patients later diagnosed with an anastomotic leak. Matthiessen et al.[28] prospectively studied several risk factors for anastomotic leaks in 33 patients, and Welsch et al.[22] compared 48 patients with anastomotic leaks to 48 matched patients with an uncomplicated postoperative course from a large database. However, in both studies, the median CRP values were used as cut-offs with their corresponding diagnostic accuracy.

Our study reports on serial postoperative CRP measurements on a routine basis in 231 consecutive patients

Table 3 Receiver Operating Characteristics Curve Analysis of C-reactive Protein (CRP) and White Blood Count (WBC) During the Postoperative Course of 231 Patients After Colorectal Surgery

	Cut-off value	Sensitivity (95% CI)	Specificity (95% CI)	AUC (95% CI)	*P* value	Cut-off 90% sens.	Cut-off 90% spec.
Intraabdominal infection							
CRP day 1	89	50 (25–75)	61 (53–69)	0.53 (0.46–0.6)	0.66	226	45
CRP day 3	190	82 (56–96)	73 (66–79)	0.82 (0.76–0.87)	<0.001	81	269
CRP day 5	154	75 (48–93)	86 (80–91)	0.87 (0.88–0.92)	<0.001	65	171
CRP day 7	215	75 (48–93)	94 (88–97)	0.86 (0.79–0.91)	0.001	35	–
WBC day 1	10.6	62 (32–86)	63 (54–71)	0.58 (0.49–0.66)	0.38	6.5	–
WBC day 3	13.1	69 (39–91)	82 (74–88)	0.76 (0.68–0.83)	0.002	7.2	14.8
WBC day 5	9.4	80 (44–97)	72 /62–81)	0.72 (0.63–0.81)	0.02	6.9	18.4
WBC day 7	12.5	67 (35–90)	80 (68–89)	0.77 (0.66–0.86)	0.001	7.5	15.1
Extraabdominal infection							
CRP day 1	77	89 (70–97)	31 (24–39)	0.59 (0.51–0.66)	0.17	59	323
CRP day 3	114	78 (60–91)	52 (44–60)	0.66 (0.59–0.72)	0.005	57	270
CRP day 5	65	72 (53–87)	57 (49–65)	0.62 (0.55–0.69)	0.045	29	211
CRP day 7	57	73 (52–88)	56 (46–66)	0.62 (0.53–0.70)	0.07	13	228
WBC day 1	10.2	72 (53–92)	64 (54–72)	0.69 (0.61–0.77)	0.005	8.8	15.3
WBC day 3	9.7	82 (60–95)	60 (50–69)	0.62 (0.53–0.70)	0.09	6.6	–
WBC day 5	8.6	61 (36–73)	62 (51–73)	0.62 (0.52–0.73)	0.12	6.2	13.5
WBC day 7	7.6	94 (71–99)	36 (27–49)	0.62 (0.50–0.73)	0.13	7.5	15.1

Analysis was performed with regard to intraabdominal infections and other infectious complications. The best cut-off value, sensitivity, specificity, area under the ROC curve (AUC), and 95% confidence intervals (95% CI) are given, as well as values for 90% sensitivity and specificity. The *P* value of the AUC indicates the statistical ability to discriminate between positive and negative cases (AUC>0.50)

undergoing colorectal resection. We elaborated the cut-off values with the highest diagnostic accuracy by ROC analysis on each POD with the scheduled blood tests. The advantage of our statistical approach is the possibility to consider the complete spectrum of the observed test results, not only a single value like the median. In our study, the cut-off value with the highest diagnostic accuracy was found to be lower than the median values. Our results clearly support the findings from earlier studies[22,28] showing that increased CRP values on POD 3 strongly indicate a high risk for developing an anastomotic leak

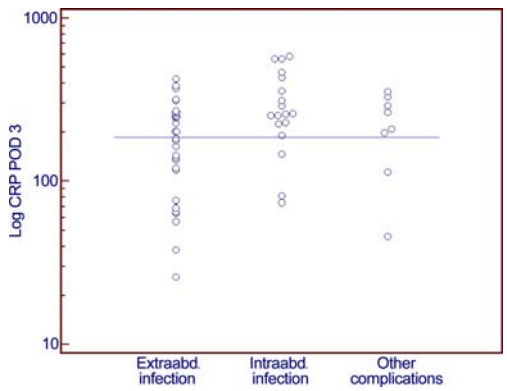


Figure 2 Dot diagram of CRP values on POD 3 of all patients according to type of complication. The *dotted line* indicates the cut-off value with highest sensitivity and specificity as revealed by ROC analysis. CRP values greater than 190 Mg/L were observed in 15 of 18 patients (83%) with intraabdominal infection.

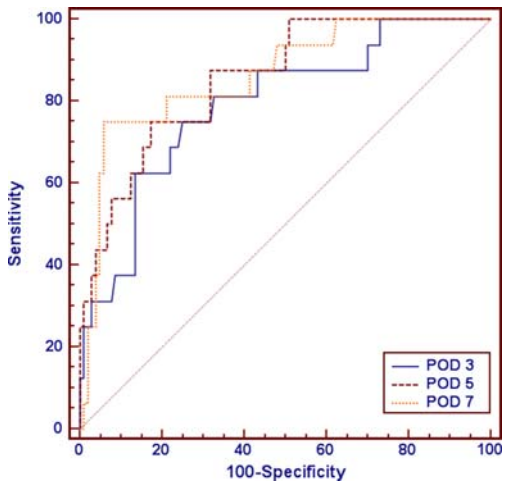


Figure 3 Diagnostic accuracy (DA) of CRP with regard to intra-abdominal infections after colorectal resection as expressed by the ROC curve. Comparison of ROC curves shows that the diagnostic accuracy was similar on POD 3, 5, and 7, as expressed by the AUC values of 0.82, 0.87, and 0.86, respectively.

during the later course. The diagnostic accuracy of CRP on POD 3 was as high as it was on POD 5 and 7. Accordingly, in patients with high CRP levels on POD 3, an undetected anastomotic leak should be suspected if the increased CRP levels are not easily explained by some other obvious diagnosis or condition. This view is challenged by others[29] who analyzed the perioperative use of CRP measurements in 201 patients undergoing elective general surgery. The study did not recommend the routine use of measuring CRP but only when clinically indicated. However, the study focused on perioperative CRP measurements, which were not taken according to a routine schedule. Furthermore, their study did not report on the details of the surgical procedures or complications. However, our results indicate that serial postoperative CRP measurements in patients undergoing colorectal resection after POD 3 may contribute to an earlier diagnosis of an anastomotic leak.

The aforementioned studies[22,28] related their findings to surgically homogenous patient groups undergoing rectal resection. However, CRP is not specific for any organ site or particular procedure. Our study on unselected patients undergoing colorectal resection for the most common indications (CRC, IBD, or common colorectal emergencies) shows that similar findings apply as for rectal resection. Other reports demonstrated similar unfavorable results in patients with a persistent increase in CRP undergoing pancreatic resection[21] or combined pancreas–kidney transplantation.[30]

Our findings are based on a retrospective evaluation of 231 consecutive patients. In line with others, the number of clinical events (18 patients with intraabdominal infections) was rather low, which limits the statistical power of our analyses. Consequently, our findings must be interpreted with caution. Prospective studies are warranted to evaluate the clinical validity and relevance of our findings. However, despite this limitation, our study provides support for the view that serial measurements of CRP after colorectal resection are useful for identifying patients at risk for developing intraabdominal infections. We suggest that, in patients with persisting high, or even increasing, CRP values after POD 3, diagnostic efforts should be considered to exclude any anastomotic leak, particularly when other causes of increased CRP levels are unlikely.

Conclusion

Increased CRP values of 190 Mg/L or more on POD 3 after colorectal resections were associated with anastomotic leak in four of every five patients, particularly when CRP did not decrease the following days. Serial CRP measurements are helpful for detecting intraabdominal infections after colorectal resection. Persistently elevated CRP values after POD 3 should be investigated for intraabdominal infection.

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ORIGINAL ARTICLE

Idiopathic Hypertensive Anal Canal: A Place of Internal Sphincterotomy

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Abstract
Background Hypertensive anal canal is frequently known to be associated with the presence of anal fissure. Based on clinical experience, we hypothesized that idiopathic anal sphincter hypertonia was a condition equivalent to anal fissure, and therefore, it could be treated the same way.
Patient and methods Sixty-three patients complaining of anal pain without any anal pathology and ten healthy volunteers were examined. All patients underwent clinical evaluation, neurological examination, anorectal manometry, and measurement of pudendal nerve terminal motor latency. All patients with hypertensive anal canal were randomized into three groups. Group I (surgical group) underwent closed lateral sphincterotomy (LS), group II using nitroglycerine ointment (GTN), and group III received injection of botulinum toxin in internal sphincter. Post-procedures data were recorded at follow-up period.
Results The mean resting anal pressure (MRAP) was significantly higher in the patient group (114.6±7.4 mmHg) than control group (72.5±6.6 mmHg, $P<0.001$). Anal pain is the main presenting symptoms aggravated by defecation and not relived by analgesics or local anesthetics. After LS, pain visual analogue scale decreased significantly at follow-up period than after chemical sphincterotomy using GTN or BTX ($P=0.001$). There was a significant decrease in MRAP postoperatively from 114.6±7.4 to70.8±5.5 mmHg than after using GTN or BTX ($P=0.03$).
Conclusion Idiopathic hypertensive anal canal is a fact and already exists presented by anal pain aggravated by defecation. It can be managed safely by closed lateral sphincterotomy, but chemical sphincterotomy had a minor role in its management.

Keywords Anal hypertonia · Sphincterotomy · Incontinence · Manometry

Introduction

The human internal anal sphincter (IAS) is in a state of partial contraction and relaxes in response to rectal distension through the rectoanal inhibitory reflex.[1,2]

Many reports have documented that anal hypertonia means elevated maximal resting anal pressures (RAP) higher than 90 mmHg[3–6] and is related to the internal anal sphincter because resting pressures returned to normal values after internal sphincterotomy.[7,8] Anal hypertonia of IAS produces ischemia of the posterior commissure of the anus.[6,9,10] It has long been postulated that increased anal pressure precedes the development of anal fissure, and there is evidence that psychological stress produces a sustained tonic rise in anal canal pressure, translating into an increased tone in the IAS.[9–12]

Lateral internal sphincterotomy (LIS) has been proven highly effective in curing anal fissure. LIS is currently considered the "gold standard" of treatment.[13,14] The incidence of post-LIS incontinence can be as high as 10%.[15] Hence, the interest, in the last two decades, in seeking medical treatments is directed at lowering the tone of the IAS. Glycerin trinitrate (GTN), botulinum toxin, and

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topical calcium channel blockers are all able to lower the IAS tone (chemical sphincterotomy).[15]

We have observed many patients with anal sphincter hypertonia without fissure, and we view it as equivalent to anal fissure in terms of presentation and physiology. So we aimed at treating those patients as anal fissure.

Patients and Methods

This study enrolled 63 patients, in the period from September 2002 to April 2008, who suffered persistent anal pain (in all patients, anal pain was described as continuous pain aggravated by defecation for at least 6 months that had failed to resolve on analgesic or local anesthetics) and some difficulty in defecation without any anorectal finding, and none of the patients complained of tenderness of the coccyx. They were admitted to the Colorectal Surgery Unit, Mansoura University Hospital, Egypt.

Exclusion criteria were patients who had any pathological anorectal lesions such as anal fissure, piles, rectal prolapse, intussusception, ansimus, cancer, and patients with normal anal pressure. Moreover, patients who previously had anorectal surgery, chemical or surgical sphincterotomy, anal dilatation, inflammatory bowel disease, venereal disease, neurological disorder, or systemic gastrointestinal disease were also excluded.

Informed consent was obtained from all patients to be included in the study after explanations of the nature of the disease and possible treatment. This study was approved by the local ethical committee.

All patients underwent clinical evaluation, proctoscopic examination, and sigmoidoscopy. In addition to endoanal ultrasound to assess anatomy and lesions of anal sphincter, anorectal physiology evaluation and defecography were also done.

All patients were subjected to neurological examination to exclude any neurological disorder, especially intradural and extradural compression of the cauda equine, demylinating disorders, and neurofibrimata or peripheral nerve lesions. Women were subjected to gynecologic examination.

Anorectal physiology studies consisted of anal manometry and measurement of pudendal nerve terminal motor latency (PNTML) to exclude pudendal nerve entrapment syndrome.

A group of ten healthy age-matched subjects (eight men and two women) with a mean age 42±5.2 years (20–60 years) served as a control group for the manometry study and measure PNTML. The control subjects had normal bowel habits and no defection disorders. They also underwent computerized anorectal manometry and measure PNTML.

Defecography With the patient in the left lateral position, the rectum was filled with 120 ml of barium paste, then the patient was seated upright on a specially designed commode and asked to empty the rectum as rapidly and completely as possible. Plain x-rays were taken under fluoroscopic control with the patient at rest, with voluntary anal contraction and during defecation.[16,17]

A disposable St. Mark's electrode (Dantec, Scovlunde, Denmark) was used to evaluate PNTML according to the technique described by Kiff and Swash.[18] Patients received a disposable enema on the morning of the study. Patients were then placed in the left lateral decubitus position. The St. Mark's electrode was properly mounted onto the index finger of the gloved right hand, which was then inserted into the rectum. After locating the sacral bone, the finger was maneuvered around to the ischial spine. Once in the vicinity of the main branch of the pudendal nerve, the pudendal nerve was stimulated using the cathode-stimulating electrode at the very tip of the finger. Stimulus current was repeatedly delivered at 30 mA at 60% current for 100 ms as the fingertip with the electrode was adjusted to obtain an optimum position. At least three reproducible compound muscle action potentials were recorded on each side. Pudendal neuropathy was considered any latency >2.3 ms.[19] Absent or unelicited latency was also considered pathologic.[20]

Conventional manometry was performed using a standard low compliance water perfusion system and eight-channel catheters with pressure transducer connected to 5.5 mm manometric probe with spirally located ports at 0.5-cm interval, which measures the pressure along the length of the anal canal. The protocol performance is stationed pull-through technique with recording the functional length of the anal canal (FL), mean maximum resting pressure (MRP), and the mean maximum squeeze pressure (MSP). Pressures were recorded using a computerized recording device (Sandhill Bioview program, USA) which included menu-driven software to aid with data acquisition. Data were analyzed with the use of a complied software package that automatically produced numeric reports and graphs.

All patients proved to have idiopathic hypertensive anal canal (maximal RAP) higher than 90 mmHg without anorectal pathology.

The patients were then randomized into three groups. The randomization was achieved through computer-generated schedule and its results were sealed into 63 envelopes. The responsible surgeon opened randomly an envelop and, in accordance with the protocol, the patients were asked to sign informed consent.

Group I patients (lateral internal sphincterotomy, 21patients) underwent closed lateral internal sphincterotomy under local anesthesia at 3 o'clock in lithotomy position reaching up to the dentate line.

Table 1 Descriptive Analysis of Manometric Finding and Bowel Frequency/Week Between Control and Patients

Variables	Control (10, mean±SD)	Patients (63, mean±SD)	*P* value
Age (years)	42±5.2 (20–60)	41±6.5 (18–61)	0.45
FACL (cm)	3.1±0.36	3.5±0.55	0.034
MRAP (mmHg)	72.5±6.6	114.6±7.4	0.000
MSAP (mmHg)	163.3±10.06	184.4±15.68	0.038
Bowel frequency/week	8.7±1.8	5.1±1.5	0.001
Duration of pain (month)	–	4.5+1.2	
PNTML (ms)	1.8+2.1	1.9+1.2	0.84

FL functional length of the anal canal, *MRP* mean maximum resting pressure, *MSP* mean maximum squeeze pressure

Group II patients (GTN group, 21patients) were instructed to apply the GTN ointment 0.2% twice a day to the edge and just inside the anal canal for an 8-week course.

Group III patients (botulinum toxin "BTX-A" injection, 21 patients) were injected with BTX-A in the left lateral position; anesthesia was not required. The anal canal was cleaned with povidone iodine. A vial of Dysport, 500 U (Dysport, Ipsen, UK), is dissolved in 2.5 ml isotonic saline. A volume of 0.5 ml of dissolved toxin, i.e., 100 U Dysport, is injected in each patient. The injection is given with an insulin syringe fitted with a needle size of 21-gauze and 3.75 lengths. Injection into the IAS was done with the patient awake, in the left lateral position in the outpatient clinic in the 3 and 9 o'clock positions. The need for further injection was assessed on each follow-up. Each patient who failed the first injection was given a second trial. Failing two injections was a marker for exclusion from the study. All injections were performed by the same person.

Postoperative pain was evaluated in first day, 1 week, 1 month, and 1 year after the procedure using a visual analog scale (VAS) with which each patients noted the severity of pain at each evaluated time using a linear between 0 (no pain) and 10 (severe pain); also, we recorded the change of bowel habit and postoperative complication. Also, anorectal manometry was performed 1 month after the procedure.

The statistical analysis of the data in this study was preferred using the SPSS version 10. Analysis of data was by intension-to-treat. For continuous variables, descriptive statistics were calculated and were reported as mean±SD. Categorical variables were described using frequency distributions. One way analysis of variance test was used to detect differences in more than two groups. A value of $P<0.05$ was considered to be significant.

Results

This study was carried out from September 2002 to April 2008. Sixty-three patients (47 men and 16 women) with a mean age 41±6.5 years (18–61 years) and had persistent anal pain without any pathological anal diseases were included in this study and admitted at the Colorectal Unit, Mansoura University Hospital, Egypt.

Table 2 Comparative Study Between Surgical, GTN, and Botulinum Toxin Groups

Variables	Surgical sphincterotomy	GTN	Botulinum toxin	*P* value
Presence of pain				
Preoperative	21 (100%)	21(100%)	21 (100%)	0.54
1 week postoperative	2 (9.2%)	10 (47.6%)	8 (38.1%)	0.05
1 month postoperative	1 (4.8%)	12 (57.1%)	15 (71.1%)	0.005
1 year postoperative	1 (4.8%)	12 (57.1%)	15 (71.1%)	0.001
VAS				
Preoperative	4.16±2.32	4.18±2.52	4.2±2.42	0.23
1 week postoperative	2.25±2.49	3.55±2.39	3.35±3.19	0.05
1 month postoperative	1.62±1.57	3.72±2.57	3.62±2.47	0.02
1 year postoperative	0.58±1.52	3.58±2.62	3.58±2.52	0.001
Bowel frequency/week				
Preoperative	5.1±1.5	5.2±2.1	5.3±1.9	0.35
1 week postoperative	6.1±±2.2	6±2.2	6.1±0.9	0.03
1 month postoperative	7.8±1.5	5.9±1.6	5.9±1.5	0.02
1 year postoperative	8.6±1.2	5.8±1.3	5.6±1.8	0.001

Table 3 Manometric Changes

Variables	Surgical sphincterotomy	GTN	Botulinum toxin	*P* value
FACL (cm)				
Preoperative	3.5±0.55	3.4±0.75	3.4±0.95	0.65
1 month postoperative	3.3±0.45	3.4±0.35	3.4±0.25	0.04
MRAP (mmHg)				
Preoperative	114.6±7.4	115.6±6.4	113.6±8.3	0.33
1 month postoperative	70.8±5.5	90.8±4.2	95.8±6.2	0.03
MSAP (mmHg)				
Preoperative	184.4±15.68	182.2±12.72	183.7±13.61	0.75
1 month postoperative	174.4±14.68	177.4±13.23	175.4±16.45	0.03

All patients had normal PNTML which was below 2.3 ms, and all patients had normal anorectal reflexes. Defecography revealed normal finding (no intussusception, prolapse, ansimus, or rectocele).

The functional anal canal length was shorter in the control group than patient group (3.1±0.36 vs. 3.5± 0.55 cm); this difference was statistically significant ($P<0.05$). Also, the MMR anal pressure was higher in the patient group than control group (72.5±6.6 vs. 114.6± 7.4 mmHg), and this difference was highly significant ($P<0.001$). There was higher mean maximum squeeze anal pressure in the patient group (143.3±10.06 vs. 184.4± 15.68 mmHg, $P<0.05$; Table 1).

All patients were suffering from anal pain which increased with defecation, with a mean VAS 4.16±2.52. Stool frequency/week were less in the patient group than control group (5.1±1.5 vs. 8.7±1.8, $P<0.001$; Table 1).

After doing lateral conventional sphincterotomy to the patients, anal pain disappeared in 20 cases (95.2%), but residual pain persisted only in one case and the mean preoperative VAS was 4.16±2.32, which decreased significantly after the first week, 1 month, and 1 year postoperative (2.25±2.49, 1.62±1.57, and 0.58±1.52, respectively). Stool frequency/week postoperatively were significantly decreased in all patients from 5.1±1.5 to 8.6±1.2 times/ week after closed lateral sphincterotomy (Table 2).

In GTN group and BTX group, post-procedure pain disappeared in nine cases (42.9%) and in six cases (29.9%), respectively. No significant changes as regards VAS of pain and bowel frequency per week in both groups were observed. Lateral conventional sphincterotomy produced significant changes in presence of pain, severity of pain, and in bowel frequency/week when compared with GTN group and BTX group (Table 2).

As regard the postoperative manometry, we found a significant decrease in functional anal canal length, significant decrease in mean MRP and decrease in the mean squeeze pressure in surgical group than in GTN and BTX groups (Table 3).

In group I, four complications occurred; incontinence to flatus was found in two cases (9.2%). According to Pescatori et al.,[21] scoring of incontinence in one patient (4.8%) who had grade A1 incontinence improved with time, and one patient had grade A2. Anal irritation was reported in one case (4.8%). In group II, 33 complications occurred in the form of headache which was found in six cases (28.6%), flashing was observed in six cases (28.6%), anal irritation occurred in 12 cases (57.1%), and allergy was observed in two cases (9.2%). In group III, 18 complications were noticed: incontinence to flatus was found in one case (4.8%), anal irritation in two cases (9.2%), and infective in 12 cases (71.1%; Table 4).

Discussion

Except for those due to organic lesions, anal pains are generally classified into three groups: proctalgia fugax, coccygodynia, and chronic idiopathic anal pain.[22] Proctalgia fugax is characterized by nocturnal, short, cramp-like

Table 4 Complications

Variables	Surgical sphincterotomy	GTN	Botulinum toxin
Headache	0	6 (28.6%)	0
flashing	0	6 (28.6%)	0
Incontinence	2 (9.2%)	0	1 (4.8%)
Anal irritation	1 (4.8%)	7 (33.3%)	2 (9.2%)
Ineffective after 1 month	1 (4.8%)	12 (57.1%)	15 (71.1%)
Allergy	0	2 (9.2%)	0

rectal pain.[23] Coccygodynia is characterized by vague ache often localized in the sacral and coccygeal areas and reproducible by internal and external mobilization of the coccyx.[22] Chronic idiopathic anal pain is characterized by either rectal or anal pain, incapacitating because of its recurrence and, occasionally, chronicity. The various treatments proposed for all anal pains, particularly in the case of idiopathic pain, remained ineffective.[23]

The cause of anal fissure is still unknown, but hypertonia of IAS associated with the passage of hard stools is likely one of the main factors implied. As a matter of fact, an elevated mean resting pressure of the IAS is the most consistent finding in patients with fissures.[15]

Many investigators found that a high anal resting pressure was related to the internal anal sphincter because resting pressure returned to normal value after internal sphinecterotomy.[7,8] Anal pressure was found to be higher in patients with anal fissure, and those patients should benefit from lateral subcutaneous sphincterotomy.[24]

Gibbons and Read[9] reported that increased anal resting pressure is a prerequisite for anal fissure not to self-heal because such anal hypertonia results in low perfusion and ischemia of the overlying anoderm. They speculate that pain in anal fissure is of ischemic origin, while lack of epidermal regrowth and of basal granulation in this condition may also be the result of ischemia, contradictory to the speculation that anal hypertonia is secondary to spasm induced by defecation.[25]

In our study, all patients were complaining of anal pain and had difficult defecation, decreased stool frequency, and anal sphincteric hypertonia without having anal fissure. This observation raises the question about the presence of idiopathic anal hypertonia (fissure equivalent).

The internal anal sphincter is the smooth muscle component of the anal sphincter complex, and it has an ambiguous role in maintaining the anal continence. Despite its significant contribution to resting anal canal pressure, even total division of the internal anal sphincter in surgery for anal fistula may fail to compromise continence in otherwise healthy subjects. However, recently reported abnormalities of the innervations and reflex response of internal anal sphincter in patients with fecal incontinence indicate its significance in maintaining continence.[26,27]

LIS has been proven highly effective in curing anal fissures in a number of randomized clinical trials, with success rates higher than 90%.[13,14,28–31] It encompasses an overall risk of incontinence, which can be as high as 10%.[15] Hence, the interest in seeking new medical treatments is directed at lowering the tone of the IAS. GTN and botulinum toxin are all known to be able to lower the IAS tone.[15]

So, we decide to do either lateral conventional sphincterotomy or chemical sphincterotomy (using either GTN or BTX) for patients with high resting pressure (mean resting pressure, >90 mmHg), had anal pain, and decreased bowel frequency. In our study, the results were highly significant regarding the improvement of pain and bowel frequency after lateral conventional sphincterotomy, but no significant changes after both GTN and BTX injection.

The efficacy of GTN for treating anal fissure has been evaluated in several randomized studies, and although the overall healing rate for GTN estimated in a meta-analysis of the published randomized trials is about 50%, it is established as a first-line therapy in many centers because of convenience, safety, and costs.[32] The mechanism of action of GTN should be to reduce anal canal pressure by an increase in local anodermal blood flow through the release of nitric oxide.[33] The amount of pressure reduction seems to vary from 25% to 40% of basal pressure.[32–35] The main drawbacks of GTN treatment are recurrence, tachyphylaxis, anal burning, hypotension, and the risk of headache that can be so severe so as to cause many patients to abandon therapy.[15]

The botulinum toxin is believed to act at the postganglionic level reducing noradrenaline output from sympathetic neural terminals in the internal sphincter and possibly also by reducing myogenic tone in this tissue. A single botulinum injection is well tolerated, with minor side effects, thus eliminating non-compliance issues. It reduces maximum resting pressure by a similar proportion to that of GTN (25–30%) over a 2- to 3-month period of time.[36]The most common side effect is transient incontinence to flatus (up to 10%) or feces (up to 5%).[37] Recurrence are common but may be easily treated with a good rate of healing even if up to 20% of patients will need LIS.[38–40]

Sultan et al.[41] reported that fecal incontinence after internal sphinecterotomy is attributed to pre-exciting occult sphincteric injury, and Zebra et al.[42] also reported that the cause of incontinence after internal sphinecterotomy are probably multifactorial and do not only seem to rely entirely on the presence of occult pre-exciting sphincteric defector and inadevent intraoperative injury to the external anal sphincter but also on the extent of division of internal sphincter, the presence of constitutionally short anal canal functional variation in the intrinsic behavior of the IAS, and poor distal anatomic IAS/external anal sphincter overlap might also be an important functional outcome. We agree with Brown et al.[43] who reported that LIS is superior to medical sphincterotomy and does not compromise long-term fecal incontinence.

Conclusion

Idiopathic hypertensive anal canal is a fact and already exists and is presented by persistent anal pain with changes in the frequency of defecation. It can be managed safely by

closed lateral conventional sphincterotomy. Chemical sphincterotomy had a minor role in its management. Further studies with large numbers of patients are needed.

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ORIGINAL ARTICLE

Short-Term Outcomes of Laparoscopic Rectal Surgery for Primary Rectal Cancer in Elderly Patients: Is it Safe and Beneficial?

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Abstract
Purpose The role of laparoscopic resection in management of rectal cancer is still controversial. The purpose of this study was to evaluate whether laparoscopic rectal resection for rectal cancer could be safely performed in elderly patients.
Methods Forty-four elderly patients (≥75 years) undergoing laparoscopic rectal resection (group A) were compared with 228 younger patients (<75 years) undergoing laparoscopic rectal resection (group B) and 43 elderly patients (≥75 years) undergoing open rectal resection (group C).
Results The American Society of Anesthesiologists' status was significantly higher in group A than in group B. Operative procedure, operating time, and estimated blood loss were comparable, and overall postoperative complications did not differ significantly between groups A and B (13.6% vs. 11.8%). Operating time was longer (256 vs. 196 min), but estimated blood loss was significantly less (25 vs. 241 ml) in group A than in group C. The rate of postoperative complications was lower (13.6% vs. 25.6%) in group A than in group C, but the difference was not statistically significant. Time to flatus (1.3 vs. 3.7 days), time to liquid diet (2.2 vs. 7.0 days), and hospital stay (19 vs. 22 days) were significantly shorter in group A than in group C.
Conclusions Laparoscopic rectal resection for elderly patients can be safely performed with similar postoperative outcomes as in younger patients and may have advantages in terms of faster gastrointestinal recovery and shorter length of hospital stay compared with open surgery.

Keywords Laparoscopic rectal resection · Rectal cancer · Elderly patients

Introduction

Treatment of rectal cancer has improved in recent years because of the introduction of total mesorectal excision (TME), which has been shown to decrease local recurrence.[1] Recent randomized trials comparing laparoscopic with open colon resection have demonstrated that the two approaches have similar short-term outcomes.[2–4] The short-term benefits of laparoscopic colon resection, such as reduced blood loss, less intense postoperative pain, faster gastrointestinal recovery, and reduced postoperative ileus rate have been demonstrated.[2–4] However, laparoscopic rectal surgery is technically difficult and requires advanced laparoscopic surgical skills.[3] Although recent nonrandomized studies have suggested that laparoscopic rectal surgery is safe and feasible, high conversion rates and long operating times have been reported.[5–8]

The aging of the population requires colorectal surgeons to evaluate and operate on increasingly older patients. Previous studies have reported that open colorectal surgery in the elderly is associated with increased morbidity and mortality and prolonged hospital stay.[9,10] The use of a laparoscopic approach in the elderly who are at high risk of developing postoperative complications seems particularly interesting as the reduced surgical trauma can potentially

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lead to a reduction in postoperative complications. Previous studies have reported that laparoscopic colorectal resection is a safe option for elderly patients and is associated with more favorable short-term outcomes.[11–19] However, to the best of our knowledge, there have been few studies evaluating the outcomes of laparoscopic resection in the elderly, with a focus on the rectum. The purpose of this study was to evaluate whether laparoscopic rectal resection was safe and beneficial in elderly patients.

Materials and Methods

Patient Selection

From January 2001 to August 2008, we evaluated consecutive patients with rectal adenocarcinoma within 15 cm from the anal verge, who were undergoing rectal resection. All patients treated by a laparoscopic approach (introduced in July 2005) were subdivided into group A (≥75 years) and group B (<75). Group C comprised patients aged ≥75 years who were undergoing open rectal resection. Group A was compared with groups B or C. The basic indications for laparoscopic surgery in our institution include maximal tumor size <6 cm, no evidence of invasion to adjacent organs, no evidence of ileus, and no evidence of lateral lymph node metastasis. There is no difference in the eligibility criteria of a laparoscopic approach between the elderly and the younger. After the introduction of a laparoscopic approach, 11 patients aged ≥75 years were treated by an open approach. The reasons for an open approach in these patients were tumor size >6 cm in two patients, suspected invasion to the prostate in one patient, subileus in one patient, synchronous resection of other organs in three patients, no consent of a laparoscopy in two patients, severe sigmoid diverticulosis in one patient, and multiple previous operations in one patient. The basic indications for neoadjuvant chemoradiation therapy in our institution were full-thickness rectal cancers (T3 or T4) located below the peritoneal reflection staged by magnetic resonance imaging and/or node-positive disease, no evidence of distant metastases, no history of prior radiation therapy to the pelvis, and patients aged <75 years. Data were prospectively collected for age, gender, body mass index, the American Society of Anesthesiologists' (ASA) score, International Union Against Cancer tumor staging, duration of operation, amount of blood loss, conversion to open surgery, and postoperative data including pathology, time to flatus, time to liquid diet, hospital stay, 30-day morbidity and mortality.

Surgical Procedure

The surgical technique was standardized for both open and laparoscopic approaches. For open procedures, a midline laparotomy was performed from the pubis to at least 5 cm above the umbilicus. For the laparoscopic approach, a five-port technique was employed, as we described previously.[20,21] TME with preservation of pelvic plexuses was performed for mid- and low-rectal cancers, whereas partial mesorectal excision was performed for upper cancers. 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 electronic cautery 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. 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. 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. 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

Patient characteristics are summarized in Table 1. There were 44 patients in group A, 228 in group B, and 43 in group C. Based on the study design, there was a significant difference in mean age between groups A and B (79 vs. 59 years), but there was no significant age difference

Table 1 Patient Characteristics

	Group A (n=44)	Group B (n=228)	Group C (n=43)	P value (A vs. B)	P value (A vs. C)
Mean age (year; range)	79 (75–90)	59 (33–74)	79 (75–86)	<0.0001	0.9625
Male/female ratio	21/23	138/90	23/20	0.1335	0.67
Mean body mass index (kg/m^2)	22.1 (15.4–29.7)	22.7 (14.8–35.2)	21.8 (14.0–28.8)	0.2787	0.9054
ASA score				<0.0001	0.8204
1	2 (4.5%)	120 (52.6%)	3 (7.0%)		
2	36 (81.8%)	105 (46.1%)	33 (76.7%)		
3	6 (13.6%)	3 (1.3%)	7 (16.3%)		
Mean tumor distance from the anal verge (mm; range)	83 (25–150)	79 (0–150)	86 (0–150)	0.5774	0.6918
Final TNM stage				0.0462	0.0062
CR	0	3 (1.3%)	2 (4.7%)		
0	3 (6.8%)	3 (1.3%)	0		
I	16 (36.4%)	111 (48.7%)	13 (30.2%)		
II	6 (13.6%)	44 (19.3%)	13 (30.2%)		
III	18 (40.9%)	57 (25.0%)	8 (18.6%)		
IV	1 (2.3%)	10 (4.4%)	7 (16.3%)		

ASA American Society of Anesthesiologists, *CR* complete response

between groups A and C (both 79 years). ASA score was significantly higher in group A than in group B, but comparable between groups A and C. There were no significant differences between groups for gender, body mass index, and mean tumor distance from the anal verge. Tumor stage was more advanced in group A than in group B. In group C, stage IV was more frequent than in group A.

The surgical background is summarized in Table 2. Operative procedure, rate of temporary diversion, rate of neoadjuvant radiotherapy, mean operating time, mean estimated blood loss, and mean number of lymph nodes harvested were all comparable between groups A and B. Operative procedure was different between groups A and C, with abdominoperineal resection and Hartmann's procedure being more frequently performed in group C. Mean operating time was significantly longer (256 vs. 196 min), but mean estimated blood loss was significantly lower (25 vs. 241 ml) in group A than in group C.

The surgical outcome is summarized in Table 3. The rate of postoperative complications did not differ significantly between groups A and B (13.6% vs. 11.8%). The rate of postoperative complications in group C was higher than in group A (13.6% vs. 25.6%), but the difference was not statistically significant. The rate of anastomotic leakage was comparable between groups A and B (2.3% vs. 3.1%), but tended to have a higher incidence (2.3% vs. 4.7%) in group C than in group A. There was no mortality in groups A and B. There was one patient (83 years old) who died from anastomotic leakage in group C. Time to flatus was comparable (1.3 vs. 1.3 days), but time to liquid diet was unexpectedly shorter in group A than in group B (2.2 vs. 3 days). Mean length of hospital stay did not significantly differ between groups A and B (19 vs. 15 days). Time to flatus (1.3 vs. 3.7 days), time to liquid diet (2.2 vs. 7.0 days), and mean length of hospital stay (19 vs. 22 days) were all significantly shorter in group A than in group C.

Discussion

The present study showed that laparoscopic rectal surgery in the elderly could be safely performed without increasing postoperative mortality or morbidity rates, compared with younger patients. Moreover, comparing laparoscopic with open rectal resection in elderly patients suggested that laparoscopic rectal resection had the benefits of less blood loss, faster gastrointestinal recovery, and shorter hospital stay.

The population in western and eastern countries is aging, and life expectancy is increasing. Therefore, it is not surprising that more elderly patients need surgical treatment. There is no consistent definition of the elderly patient population in published series. Age 75 years was used as a cutoff in the present study because age ≥75 years has been reported to be a significant risk factors for increased postoperative complications in laparoscopic or open colorectal surgery.[22,23]

Some recent studies have shown that laparoscopic colorectal surgery in the elderly can be safely performed with acceptable morbidity.[11–19] However, those studies included various types of laparoscopic resection with heterogeneous pathology and had little specific information about patients with rectal cancer who had undergone laparoscopic rectal

Table 2 Surgical Backgrounds

	Group A (n=44)	Group B (n=228)	Group C (n=43)	P value (A vs. B)	P value (A vs. C)
Operative procedure				0.8939	0.0063
Anterior resection	8 (18.2%)	30 (13.2%)	14 (32.6%)		
Low anterior resection	16 (36.4%)	94 (41.2%)	10 (23.3%)		
Superlow anterior resection	13 (29.5%)	64 (28.1%)	8 (18.6%)		
Intersphincteric resection	5 (11.4%)	22 (9.6%)	0		
Abdominoperineal resection	2 (4.5%)	17 (7.5%)	6 (14.0%)		
Hartmann's procedure	0	1 (0.4%)	5 (11.6%)		
Temporary diversion	10/42 (23.8%)	48/210 (22.9%)	4/32 (12.5%)	0.8439	0.2484
Neoadjuvant radiotherapy	1 (2.3%)	23 (10.1%)	3 (7.0%)	0.143	0.3604
Mean operating time (min; range)	256 (121–450)	248 (143–548)	202 (101–375)	0.6066	0.0003
Mean estimated blood loss (ml; range)	25 (0–220)	33 (0–740)	250 (15–1200)	0.627	<0.0001
Positive distal margin	0	1 (0.4%)	0		
Positive circumferential margin	0	1 (0.4%)	0		
Mean no. of lymph nodes harvested (range)	15 (8–25)	16 (1–52)	16 (3–46)	0.0707	0.9898
Conversion to open surgery	0	1 (0.4%)			

resection. Cheung and colleagues[15] reported the early and late outcomes of laparoscopic colorectal resection in the patients older than 80 years, including 44 sphincter-preserving rectal excision, eight abdominoperineal resection, and one Hartmann's procedure. The authors concluded that laparoscopic colorectal resection is safe and feasible, but no specific comparison with younger patients or an open approach was performed. The study by Chautard and colleagues[11] compared the outcome of laparoscopic rectal resection for cancer and other benign diseases in patients older than 70 years (n=27) with a younger case-matched cohort (n=34). There was no significant difference in terms of mean operating time, mortality and morbidity rates, and mean length of hospital stay. The present study reports the early outcome of laparoscopic rectal resection for only rectal cancer in the elderly.

In the present study, in order to assess the role of laparoscopic rectal resection in the elderly, we compared 44 patients older than 75 years with 228 patients younger than 75 years undergoing laparoscopic rectal resection and 43 patients older than 75 years undergoing open rectal resection. Although elderly patients had significantly higher ASA status compared with younger patients, we did not observe significant differences in postoperative mortality and morbidity rates. This result is consistent with the previous study by Chautard and colleagues.[11] Furthermore, we observed significantly less blood loss, faster gastrointestinal recovery, and shorter hospital stays for laparoscopic

Table 3 Surgical Complications

	Group A (n=44)	Group B (n=228)	Group C (n=43)	P value (A vs. B)	P value (A *vs.* C)
Postoperative complication	6 (13.6%)	27 (11.8%)	11 (25.6%)	0.8006	0.1855
Anastomotic leakage	1 (2.3%)	7 (3.1%)	2 (4.7%)		
Wound infection	3 (6.8%)	7 (3.1%)	2 (4.7%)		
Persistent ileus		1 (0.4%)	2 (4.7%)		
Enteritis		3 (1.3%)	2 (4.7%)		
Anastomotic bleeding		3 (1.3%)			
Stoma-related complication	1 (2.3%)	3 (1.3%)	1 (2.3%)		
Other	1 (2.3%)	3 (1.3%)	2 (4.7%)		
Mortality	0	0	1 (2.3%)		
Time to flatus (postoperative days; range)	1.3 (0–5)	1.3 (0–4)	3.7 (2–7)	0.9366	<0.0001
Time to liquid diet (postoperative days; range)	2.2 (2–7)	3 (2–21)	7 (4–17)	0.0032	<0.0001
Mean hospital stay (days; range)	19 (7–123)	15 (5–55)	22 (12–55)	0.0829	0.002

rectal resection compared with the open approach in patients older than 75 years. The shorter length of hospital stay observed in the laparoscopic group may be ascribed to the earlier recovery of bowel function and to the better recovery to full independence. As regards length of hospital stay, similar findings were reported by others.[13,14,16,19] These results suggest that laparoscopic rectal resection in the elderly can be performed safely and have some advantages compared with open approaches.

The relatively low incidence of postoperative complications in laparoscopic rectal resection compared with the open approach in the elderly is noteworthy. Although simple comparison is difficult because of the difference of surgical procedures performed between both groups, the laparoscopic approach may be more advantageous in the elderly patients with poor reserve than in the general population.

There is a limitation of this study to be noted. The percentage of patients with ASA III status in the elderly in the present study is lower than that reported previously from western countries.[13,16,17] The reason is unclear, but this may be due to the difference of race or our hospital's role as a specialized facility exclusively treating cancer patients. However, a recent study showed that age ≥75 years is one of the independent predictive factors besides ASA status for postoperative complications by analyzing 1,316 patients undergoing laparoscopic colorectal surgery.[22] We believe that our study suggests that laparoscopic rectal resection can be safely performed to elderly patients despite a higher incidence of comorbid conditions, and the short-term surgical outcomes are similar to those in younger patients. Furthermore, laparoscopic rectal resection in the selected elderly patients may be advantageous in terms of faster gastrointestinal recovery, shorter hospital stay, and reduced postoperative complications compared with open surgery. However, prospective randomized trials would be necessary whether laparoscopic rectal resection is truly beneficial compared with open surgery in the elderly.

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ORIGINAL ARTICLE

Impact of Hospital Case Volume on the Quality of Laparoscopic Colectomy in Japan

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Abstract
Introduction The increased use of laparoscopic colectomy for colon cancer requires the evaluation of hospital case volume, quality care, and training systems, considering the difficulty of this surgery for various tumor locations.
Materials and methods We assessed the quality of this procedure in Japan, based on hospital case volume and tumor location. A total of 3,765 patients were enrolled across 567 hospitals between July and December 2007. We analyzed patient characteristics, postoperative surgical complications, the administration of stapling devices or chemotherapy, hospital volume and teaching status, postoperative length of stay, total charges, and operating room time. Hospitals were classified into four case-volume categories: high (≥5 cases per month), intermediate to high (3–4), low to intermediate (1–2), and low (<1). Multivariate analysis was used to test the impact of hospital category and tumor location.
Results Ten high-volume hospitals performed 401 cases, while 355 low-volume hospitals did 903. Hospital case volume, operating time, and complications affected postoperative stay and total costs. Longer procedural time was an independent predictor of complications. Tumor location, case volume, and teaching status explained the variations in procedural time individually but not complications. Training systems highlighting the applicability of techniques are important to promote the quality of laparoscopic colectomy.

Keywords Laparoscopic colectomy · Hospital volume · Tumor location · Quality

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Introduction

Short- or long-term outcomes derived from observational or randomized control studies in single or community-based hospitals have confirmed the benefit of laparoscopic colectomy (LC). This has gained a reputation of greater safety and efficacy than conventional open colectomy.[1–9] In Japan, the number of LCs performed has increased from about 5,000 in 2003 to 8,400 in 2007.[10,11]

The diffusion of innovative surgical practices such as LC has required much training in operating room (OR) or skill-based laboratories, and effective training programs in endoscopic surgery need to be developed by clinical experts or societies. However, working time restrictions might limit the smooth progress of surgical training. In addition, the demand for efficiency in healthcare economics has forced institutions to reprocess or redeploy single-use devices for performing LC.[12,13] These are complex circumstances concerning newly emerging surgery, and questions about the relationship between hospital case volume and the quality of patient care following LC procedures must be answered.

Previous randomized control studies on LC have often excluded cases involving surgery on the transverse colon. Moreover, there are different levels of difficulty in performing LC for the cecum through the sigmoid colon. Typically, difficulty has been measured by operative time, which might bias the results of any study on the association between case volume and healthcare quality for patients undergoing LC.[14,15] Furthermore, high case-volume hospitals often accommodate healthier patients, even though such hospitals tend to attract integrated multidisciplinary teams who can offer quality care during the peri- or postoperative periods.[16,17] There should be attention paid to the analysis of patient mix and disease mix, as these might cause variations in resource use or OR time associated with postoperative complications such as surgical site infection.[18] Otherwise, centralization of complex surgery or technical credentialing toward high-volume hospitals or surgeons might diminish patient accessibility or adversely affect the appropriate care or timing in hospitals expected by healthcare decision makers.

In this context, it would be helpful to explore the association of hospital volume and the quality of LC by examining the effects of tumor location and procedural time on postoperative resource use or on complication rates. This would allow healthcare administrators to evaluate the contribution of hospital case volume to outcomes and to updating LC training systems. In addition, it will help in determining policies for the valid regionalization of surgical procedures. The aims of this study were to analyze the descriptive characteristics of patients with colonic cancer who were treated by LC, according to hospital case-volume category. We also examined the effect of OR time on the rate of complications as well as the relationship between hospital volume, OR time, and complications.

Materials and Methods

Database

We used the Japanese administrative healthcare database to analyze cases including patients treated by LC for colonic cancer at hospitals participating in our research project during 2007. The Ministry of Health, Labor, and Welfare originally constructed this database to develop the Japanese case-mix classification system in 2002. This was used to profile hospital performance and to assess hospital payments across 1,428 hospitals (83 academic hospitals and 1,345 community hospitals) in 2007.

These hospitals deliver acute care, further the aims of medical research, and educate students and postgraduate trainees. The database includes discharge summaries and claims data for every hospital. This information is collected between July 1 and December 31 annually. Our research project, covering 965 voluntary attending hospitals (84 academic hospitals and 891 community hospitals), was for the purpose of refining Japanese case-mix classification as well as the contribution to the health policy. This project was approved by the ethics committee of the University of Occupational and Environmental Health in Kitakyushu, Fukuoka, Japan.

Definitions of Variables

The study variables included age, gender, mortality, presence of comorbidities, tumor location, administration of chemoagents, the quantity of blood transfused, the number of days postoperative pain control needed, use of stapling devices (circular or linear staplers), and the hospital case volume or function. We also examined complications attributable to the diagnostic and therapeutic procedures, operating room time (in minutes), postoperative length of stay (LOS, in days), and total costs (TC; US$1=¥100). Postoperative care processes or resource usage were counted from the first postoperative day.

Patients were categorized by age into two groups: <65 and ≥65 years of age. Therapeutic chemoagent use was used as a proxy indicating an advanced gastric cancer stage. Diagnoses in this database were coded according to the International Statistical Classification of Diseases, 10th version (ICD10). Up to four comorbidities were recorded per patient. We used the Charlson Comorbidity Index (CCI) to measure the severity of chronic comorbid conditions.[19] A maximum of four complications were also recorded, defined as unexpected events after admission. Postoperative surgical complications were defined as any of the following ICD10 codes: bleeding or hematoma (T810); bowel

obstruction (K650, K658-9, K660, K913); peritonitis or intra-abdominal abscesses (K560, K562, K565-7); acute pancreatitis (K85); perforations (T812) or wound infections (T813, T816).[20] LC cases that were converted to open colectomy (OC) were recorded as OC cases. This database also contains the date of medical practices administered. We calculated the postoperative LOS or TC billed during admission, which are deemed as proxies for in-hospital costs. Japanese charges for hospital care are determined by a standardized fee-for-service payment system and are considered good measures of overall healthcare costs.[21] TC in this study included physician fees, instrument costs, costs of laboratory or imaging tests, and administration fees, all of which are listed in the national uniform tariff table. OR time was defined as the total time required for anesthetists' procedures, for preparation and positioning of video-images, and active operative time by the surgeons.

Based on the number of LCs performed in a 6-month study period, hospitals were classified into four case-volume groups. Any hospital providing fewer than one LC per month was considered a low case-volume hospital (LVH). Hospitals providing one through two LCs per month were deemed low to intermediate (LIVH), and those providing three to four LCs per month were recorded as intermediate to high (IHVH). Those delivering five or more LC per month were deemed high volume hospitals (HVH).[17] They were also divided into community and academic (teaching) hospitals.

Statistical Analysis

Categorical data were reported in number and proportion by hospital case-volume category and compared using Fisher's exact test. Continuous variables were compared across hospital volume categories using analysis of variance. A multiple linear regression model was used to determine the effect of hospital volume on postoperative LOS, TC, and OR time. Multiple logistic regression models were used to identify the impact of hospital volume or OR time on the occurrence of complications. Statistical analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). All reported p values were two-tailed, and the level of significance was set to 0.05.

Results

Of 2,716,219 patients from the 965 hospitals in this administrative database, 3,765 undergoing LC were identified for primary colonic cancer treatment across 567 hospitals (698 cases from 66 academic hospitals and 3,067 cases from 501 community hospitals). Ten HVHs treated 401 patients, 43 IHVHs treated 939 patients, 159 LIVHs treated 1,522 patients, and 355 LVHs treated 903 patients (median LC caseload per 6 months: HVH=36.5, IHVH=21, LIVH=9, and LVH=2). For the patient characteristics, the mean patient age, proportion of patients aged ≥65 years, proportion of male patients, mortality rate, and tumor locations were not statistically different across hospital volume categories. The overall proportion of postoperative surgical complications was also not statistically different (3.7% in HVH, 4.8% in IHVH, 5.3% in LIVH, and 5.6% in LVH, p=0.502). HVHs accommodated more patients with no chronic comorbid conditions (84.3%), while IHVHs treated the fewest (71.6%). The proportion of patients treated in academic hospitals was higher in HVHs than in LVHs (Table 1).

Regarding postoperative care, the proportions of patients receiving a blood transfusion and the amounts of blood transfused did not vary significantly between hospital categories (p=0.210 and 0.115, respectively). The use of stapling devices was more frequent in HVHs, whereas there was less administration of chemoagents, less indication of epidural anesthesia, and fewer postoperative fasting days in HVHs. Once indicated, days of epidural anesthesia were longer in HVHs. Postoperative LOS and TC were all significantly greater in LVHs (15.5 days and US$ 3,907, respectively) than in IHVH (12.2 days and US$ 3,305, respectively). OR time was significantly longer in LVHs (283 min) than in HVHs (270 min; Table 2).

Tumor location, use of stapling devices, and hospital case-volume category were not significantly related with the occurrence of complications. Longer OR time was a significant determinant of more frequent complications (adjusted odds ratio [aOR] 1.003, 95% confidence intervals [CI] 1.002–1.005). No significant difference in complication rate was observed between academic and community hospitals (aOR 0.780; 95% CI 0.515–1.183; Table 3).

After adjusting for covariates, having a CCI score recorded, complication rate, use of chemoagents, and longer OR times were significantly associated with more postoperative LOS and TC. Among tumor location categories, the transverse colon was a significant determinant only for postoperative LOS. In terms of hospital volume, IHVHs consumed fewer postoperative resources. Transverse and descending colon locations were significant predictors of longer OR time. HVHs recorded significantly shorter OR times than ILVHs or LVHs, and the academic hospitals used longer OR times than did community hospitals (Table 4).

Discussion

Using this large Japanese administrative healthcare database, we investigated the relationship of case volume in community-based hospitals to the quality of care among patients receiving LC. This study disclosed

Table 1 Patient Characteristics by Hospital Case-Volume Category

Hospital case volume	High	Intermediate to high	Low to intermediate	Low	*P*
N	401	939	1,522	903	
Number of hospitals, median number of LC cases	10, 36.5	43, 21	159, 9	355, 2	
Age					
Mean [SD]	67.2 [11.4]	67.6 [11.4]	67.7 [11.1]	67.3 [10.7]	0.819[a]
65 years or more	243 (60.6)	585 (62.3)	972 (63.9)	576 (63.8)	0.593
Gender					
Male	220 (54.9)	516 (55)	827 (54.3)	521 (57.7)	0.433
Outcome					
Mortality	3 (0.7)	3 (0.3)	3 (0.2)	2 (0.2)	0.319
Tumor location: *n* (%)					0.425
Cecum to ascending colon	150 (37.4)	361 (38.4)	627 (41.2)	341 (37.8)	
Transverse colon	63 (15.7)	121 (12.9)	179 (11.8)	118 (13.1)	
Descending colon	29 (7.2)	69 (7.3)	121 (8.0)	62 (6.9)	
Sigmoid colon	159 (39.7)	388 (41.3)	595 (39.1)	382 (42.3)	
Charlson comorbidity index: *n* (%)					<0.001
1	25 (6.2)	125 (13.3)	189 (12.4)	126 (14.0)	
2	16 (4.0)	67 (7.1)	105 (6.9)	64 (7.1)	
3 or more	22 (5.5)	75 (8.0)	96 (6.3)	36 (4.0)	
Postoperative surgical complications: *n* (%)					
Overall	15 (3.7)	45 (4.8)	80 (5.3)	51 (5.6)	0.502
Peritonitis or intra-abdominal abcess	9 (2.2)	28 (3.0)	34 (2.2)	33 (3.7)	0.185
Bowel obstruction	5 (1.2)	16 (1.7)	34 (2.2)	15 (1.7)	0.510
Bleeding or hematoma	1 (0.2)	10 (1.1)	10 (0.7)	7 (0.8)	0.422
Others	2 (0.5)	7 (0.7)	21 (1.4)	10 (1.1)	0.310
Hospital category					
Academic	142 (35.4)	246 (26.2)	236 (15.5)	74 (8.2)	<0.001

LC laparoscopic colectomy

[a] Compared by analysis of variance; others by Fisher's exact test

instructive findings different from some previous articles, which had demonstrated that hospital case volume influenced postoperative resource use, but not the occurrence of procedure-related complications. Surgery to the transverse or descending colon and procedures carried out in ILVHs and LVHs consumed more OR time, which led to greater postoperative resource usage and more complications.

The OR time in this study was 60 to 120 min longer than in previous reports based on a single center or a highly selected institution.[2,4,14,17,22,23] This was because additional time was counted as being spent on procedures by the attending anesthesiologists, the preparation of video images, or positioning of patients in addition to the actual procedural "skin-to-skin" time. To access the efficiency advantages of laparoscopic surgery over conventional open surgery or to clarify the time-consuming problems in operating room, we believe that additional "real" costs such as the OR time included in our study should be included in any future analysis. Such an economic or quality evaluation in healthcare should clarify the comparative benefits of laparoscopic surgery or the contributions of sophisticated skill training or team expertise. However, the procedural time in our study was still slightly longer than those noted in the studies by Austin et al.[22] or the COLOR Study Group.[14] The latter study reported that median OR theater time ranged from 190 min in high-volume hospitals to 240 min in low-volume ones.[14,23] That might be because our study was community based or because some of the participating hospitals might prioritize lymph node dissection or the completion of a totally laparoscopic procedure.

Hospital case volume did not correlate directly with complications but with OR time and postoperative resource use, which was also associated with the complication rate. Supposing that hospital case volume might exert an indirect

Table 2 Care Processes and Resource Use by Hospital Case-Volume Category

Hospital case volume	High	Intermediate to high	Low to intermediate	Low	*P*
Blood transfusion					
n (%)	15 (3.7)	59 (6.3)	74 (4.9)	44 (4.9)	0.210
Total mL, mean [SD]	1,013 [639]	1,354 [2,040]	892 [542]	855 [513]	0.115[a]
Use of stapling devices					
n (%)	352 (87.8)	790 (84.1)	1,191 (78.3)	666 (73.8)	<0.001
Mean [SD}	2.5 [1.5]	2.3 [1.4]	2.2 [1.5]	2.0 [1.6]	<0.001[a]
Administration of chemoagents					
n (%)	13 (3.2)	58 (6.2)	89 (5.8)	78 (8.6)	0.002
Postoperative fasting period (days)					
Mean [SD]	3.3 [2.3]	3.6 [1.8]	4 [2.1]	4.5 [2.5]	<0.001[a]
Use of epidural anesthesia					
n (%)	279 (69.6)	742 (79.0)	1,256 (82.5)	708 (78.4)	<0.001
Days, mean [SD]	5.1 [2.8]	4.5 [2.7]	4.2 [2.4]	4.4 [2.9]	<0.001[a]
Operating room time (min)					
Mean [SD]	270.0 [69.1]	272.2 [75.2]	279.6 [80.7]	283.0 [81.0]	0.004[a]
Postoperative LOS (day) [SD]	13.2 [10.5]	12.2 [8.0]	14.0 [8.6]	15.5 [9.6]	<0.001[a]
Postoperative TC ($) [SD]	3,504 [3,920]	3,305 [4,129]	3,473 [2,399]	3,907 [2,879]	0.001[a]

[SD] standard deviation. *LOS* length of stay, *TC* total charges

[a] Compared by analysis of variance, others by Fisher's exact test

impact on complications, we should pay careful attention to this factor. This is because it would include surgeons' or hospital experience such as proficient procedures or skill training delivered, as well as expert teams providing multidisciplinary medical care throughout hospitalization.[16,17] Contrary to the finding by Chen et al. that operative time is a poor surrogate measure for evaluating the quality of LC, the OR time in this series was significantly associated with the occurrence of complications and resource use.[18,23] Tumor location also helped explain the variations in OR time and postoperative LOS. Regardless of the surgeon's skill training level or operating staff education, either in the operating theater directly or in a skill-training laboratory, there might still be many important aspects relevant to the credentialing of surgical organizations. These would include the mastery of many steps of LC, skillful use or appropriate delivery of auxiliary devices for reducing blood loss or operating theater time, along with attempts to complete surgery totally by laparoscope.[14,24–26] Through measuring the OR time, the present study also included a quantitative comparison of the difficulty of performing LC for four types of tumor locations, providing evidence relevant to that of the qualitative study by Jamali et al.[27] Development of some targeted skill training for resource-intense type of colectomy would help diminish the difference of OR time between the groups according to teaching status or case volume.

Given the demands of a case-volume-based referral policy, the need to assure patient safety and pressure on the medical staff or hospitals to reduce costs, imprudent "quality improvement initiatives" could inhibit appropriate access to general surgery beyond LC. This would not help the goals of good medical practice or outcomes, especially in the evolving field of laparoscopic surgery.[28,29] Healthcare policy makers should make more efforts to resolve the "miasma" of the volume–quality relationship in laparoscopic surgery and to supply sufficient financing for medical staff education.

There were some limitations to the methodology of this study. First, it was purely observational, and information was gathered from discharged patients during only 6 months in 2007, which may limit our ability to generalize from these results. However, this database also covered around one half of all LCs performed in Japan in 2007, and almost all of the hospitals delivering LC were covered in this study.[11] Moreover, every hospital case-volume category in this study included sufficient caseload to allow valid comparisons with other studies. Second, there was a shortage of some important clinical data, including cancer stage or body mass index. In fact, tumor stages were gathered voluntarily in this administrative database, but there were many missing values. This database did not adhere to the "intention-to-treat" principles, and conversion rate was not considered. Registries managed by some relevant clinical societies should be included to improve

Table 3 Factors Associated with Postoperative Surgical Complications

	Odds ratio	[95% CI]	*p*
Age			
Under 65 years	1.000		
65 years or more	1.064	[0.777–1.456]	0.699
Gender			
Female	1.000		
Male	1.920	[1.39–2.652]	<0.001
Charlson comorbidity index			
Absent	1.000		
1	1.537	[1.034–2.285]	0.033
2	1.497	[0.89–2.517]	0.128
3 or more	1.233	[0.675–2.255]	0.496
Location of primary tumor			
Cecum to ascending colon	1.000		
Transverse colon	1.012	[0.645–1.59]	0.957
Descending colon	0.919	[0.521–1.623]	0.772
Sigmoid colon	0.788	[0.56–1.11]	0.173
Chemoagent use			
Absent	1.000		
Present	1.042	[0.576–1.885]	0.891
Postoperative pain control			
Absent	1.000		
Present	0.925	[0.642–1.333]	0.677
Number of stapling devices			
Hand sewing	1.000		
1	0.744	[0.42–1.316]	0.309
2	1.399	[0.893–2.194]	0.143
3	1.037	[0.605–1.778]	0.893
4 or more	1.077	[0.699–1.66]	0.737
Operating room time			
1 min	1.003	[1.002–1.005]	<0.001
Case volume			
	1.000		
Intermediate to high	1.154	[0.629–2.117]	0.643
Low to intermediate	1.233	[0.692–2.195]	0.477
Low	1.273	[0.694–2.336]	0.435
Hospital type			
Community	1.000		
Academic	0.780	[0.515–1.183]	0.243
Goodness of fit for the model			0.916

CI confidence intervals

data on the quality of surgical procedures, in cooperation with the Japanese administrative database. In terms of body mass, obesity does not have a significant effect on operative time, according to the findings by Austin et al.[22,30]. Asian people tend to be leaner than those in western countries, so we believe that this factor would not change the general applicability of the ordinal results derived from this study. Third, postoperative LOS for all hospital admissions in Japan is double that of hospitals in Western countries because Japanese hospitals generally supply nursing services in addition to acute medical care.[2,4,5,31] The fiscal impact of a longer LOS thus reflects the real costs in LCs.

Conclusions

We used an administrative database to analyze LC procedures in Japan among four categories of hospital case

Table 4 Factors Associated with Postoperative Length of Hospital Stay (Days), Total Charge (in US$) and Operating Room Time

	Postoperative LOS			Postoperative TC			OR time		
	Estimation	95% CI	*p*	Estimation	95% CI	*p*	Estimation	95% CI	*p*
Intercept	7.5	[6–9]	<0.001	1,503	[957–2,049]	<0.001	235.0	[223.1–246.9]	<0.001
Age	1.3	[0.7–1.8]	<0.001	331	[131–530]	0.001	0.0	[−5.1 to 5.2]	0.989
Male	0.0	[−0.5 to 0.6]	0.900	38	[−155 to 231]	0.700	15.5	[10.5–20.4]	<0.001
Charlson comorbidity index (for zero)									
1	1.1	[0.3–1.9]	0.009	340	[45–634]	0.024	15.7	[8.1–23.3]	<0.001
2	0.3	[−0.8 to 1.4]	0.579	192	[−193 to 577]	0.328	10.7	[0.7–20.6]	0.035
3 or more	1.9	[0.8–3.1]	0.001	831	[425–1,237]	<0.001	10.5	[0.0–20.9]	0.050
Postoperative surgical complications									
Present	11.0	[9.8–12.2]	<0.001	3,553	[3,118–3,988]	<0.001		–[a]	
Location of primary tumor (for cecum to ascending colon)									
Transverse colon	1.0	[0.2–1.9]	0.015	184	[−123 to 491]	0.241	10.0	[2–17.9]	0.014
Descending colon	0.4	[−0.7 to 1.4]	0.464	−4	[−389 to 381]	0.983	34.8	[24.9–44.7]	<0.001
Sigmoid colon	−0.3	[−0.9 to 0.3]	0.311	−30	[−247 to 187]	0.787	2.6	[−3.0 to 8.2]	0.367
OR time									
More than one minute	0.011	[0.008–0.015]	<0.001	4	[3–5]	<0.001		–[a]	
Chemoagent use									
Present	9.3	[8.2–10.4]	<0.001	2,849	[2,454–3,244]	<0.001	4.1	[−6.1 to 14.3]	0.435
Postoperative pain controll									
Present	0.5	[−0.1 to 1.2]	0.111	90	[−148 to 328]	0.458	6.4	[0.3–12.6]	0.040
Number of stapling devices (for hand sewing)									
1	1.3	[0.4–2.2]	0.006	416	[85–748]	0.014	20.4	[11.8–28.9]	<0.001
2	0.5	[−0.4 to 1.3]	0.261	110	[−190 to 411]	0.471	7.5	[−0.2 to 15.3]	0.057
3	1.7	[0.7–2.6]	<0.001	779	[440–1,118]	<0.001	6.0	[−2.8 to 14.7]	0.180
4 or more	0.2	[−0.6 to 0.9]	0.639	125	[−148 to 399]	0.370	5.4	[−1.7 to 12.4]	0.136
Case volume (for high)									
Intermediate to high	−1.6	[−2.6 to −0.6]	0.001	−378	[−729 to −27]	0.035	2.6	[−6.4 to 11.7]	0.571
Low to intermediate	0.2	[−0.7 to 1.1]	0.723	−185	[−519 to 150]	0.279	12.6	[4.0–21.2]	0.004
	1.4	[0.5–2.4]	0.004	193	[−168 to 554]	0.294	17.4	[8.1–26.7]	<0.001
Hospital (for community)									
Academic	−0.3	[−1 to 0.4]	0.448	136	[−120 to 392]	0.299	18.7	[12.1–25.2]	<0.001

F test for the model; $p<0.001$. Coefficient of determination: postoperative LOS, 0.189; TC, 0.146; OR, 0.050

CI confidence interval

[a] Not included in the model

volume. We estimated the effects of tumor location, case volume, and procedural time on complication rates and on postoperative resource use, using multivariate analysis. Our analysis demonstrated that hospital case volume was not significantly associated with complication rates but with postoperative resource use and operating room time. Procedural time was an independent determinant of complication rates. Tumor location, hospital case volume, and hospital teaching status were also associated with operating room time. To further the use of innovative technologies such as LC, training systems to develop skills by attending medical staff including surgeons are required. Health policy makers and clinical experts should acknowledge the risk of extended procedural times and tumor location rather than the impact of hospital case volume. Clinical experts should develop focused skill training programs in performing LC efficiently for difficult and resource-intense tumor locations. Sufficient financing for innovative skill education should be assured by healthcare policy makers before hastening to a case-volume-based set of qualifications for surgeons or hospitals.

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ORIGINAL ARTICLE

Long-term Outcomes and Prognostic Factors of Elderly Patients with Hepatocellular Carcinoma Undergoing Hepatectomy

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Abstract
Objective The present study aimed to evaluate the long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma (HCC) undergoing hepatectomy.
Material and Methods From January 1983 to December 2006, 2,283 patients with HCC received hepatectomy in Sun Yat-sen University Cancer Center. The clinicopathological data and treatment outcomes of 67 elderly HCC patients (elderly group, ≥70 years of age) and 268 patients (control group, <70 years of age) who were selected randomly from the 2216 younger patients were compared retrospectively.
Results The elderly HCC patients had lower hepatitis B surface antigen-positive rate ($P<0.001$), lower rate of marked α-fetoprotein elevation ($P=0.004$), higher infection rate of hepatitis C virus ($P=0.010$), more preoperative comorbidities ($P<0.001$), higher rate of tumor encapsulation ($P=0.040$), and better overall survival rate ($P=0.017$); whereas there were no significant differences between these two groups in other factors, including gender ratio, liver function, accompanying cirrhosis, pathological tumor–node–metastasis (pTNM) staging, satellite nodules, vascular invasion, tumor rupture, resection margin, intraoperative blood loss, incidence of postoperative complications, hospital mortality, and disease-free survival rate. Multivariate analysis showed that pTNM staging was an independent prognostic factor of long-term survival in elderly patients with HCC.
Conclusion HCC in the elderly was less HBV-associated, less advanced, and less aggressive. Hepatectomy for selected elderly patients with HCC possibly have a better curative effect compared with younger patients. For the elderly patients without preoperative comorbidities or with controlled comorbidities, hepatectomy is a safe and effective treatment. pTNM staging is the only independent predictor of postoperative overall survival in elderly HCC patients.

Keywords Elderly · Hepatocellular carcinoma · Hepatectomy · Prognosis

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Introduction

HCC is an extensively malignant tumor with poor prognosis.[1,2] The incidence of the disease is the fourth highest among all the tumors, while it has been continuously increasing in recent years.[1,3] In elderly population, this increase was more obvious because of the life span expansion per capita.[4,5] With the advancement of surgical techniques and perioperative management, hepatectomy, which may offer a potential cure of HCC, has been regarded the most effective and commonly used treatment for the malignancy. However, old age has been regarded as an adverse factor for surgical treatment; elderly patients are still considered a high-risk group for high incidence of postoperative morbidity.[6,7] Furthermore, the current studies

on curative effect of hepatectomy for HCC in the elderly have revealed different results.[7–11] Although the number of elderly patients with HCC who underwent hepatectomy is persistently increasing, little has been addressed in the literature on the exact role and especially the long-term outcomes of elderly patients with HCC undergoing hepatectomy. In this study, we analyzed the clinicopathological features, intraoperative data, and long-term results of elderly patients with HCC by comparing them with those of younger patients. In addition, prognostic factors affecting overall survival were determined by univariate and multivariate analysis.

Material and Methods

Patients

In a period of 23 years from January 1983 to December 2006, 7,939 patients with newly diagnosed HCC were treated at the Sun Yat-sen University Cancer Center. Of these patients, 424 (5.3%) cases were aged ≥70 years, and the remaining 7,515 (94.7%) cases were aged <70 years. The patients aged ≥70 years were defined as elderly in this study.[11,12] Sixty-seven (67/424, 15.8%) elderly patients and 2,216 (2,216/7,515, 29.5%) younger patients underwent hepatectomy. In this series, all 67 elderly patients were selected as the elderly group, and according to the same time distribution, using the random numbers generated from the software, we selected 268 cases (four times of the elderly group) from the 2,216 patients who were <70 years as the control group. The total 335 patients of the two groups did not receive any treatments before operation. Diagnoses of HCC were all confirmed by histology.

Preoperative evaluation was taken into consideration before the decision on hepatectomy was made. The resectabililty of each tumor mass was assessed cautiously by imaging examinations, including ultrasonography, computed tomography (CT) scan and magnetic resonance imaging (MRI). Liver function was also assessed carefully, including biochemistry tests and Child–Pugh grading. Patients over 60 years old and those with significant comorbidity were routinely sent for formal cardiopulmonary evaluation. Patient selection criteria for both groups were as follows: (1) performance status, 0–2; (2) Child–Pugh class A or B; and (3) solitary or multiple tumors (no more than three) were limited with at least two segments free of lesion. Absolute contraindication for hepatectomy included the following: (1) tumor thrombus in the trunk of portal vein, major hepatic veins, or inferior vena cava; (2) extrahepatic metastasis; (3) Childe–Pugh class C; and (4) patients with significant comorbid risk factors, such as ischemic heart disease, heart failure, or severe chronic obstructive airway disease. Relative contraindication included the following: (1) tumor thrombus in one of the major branches of portal vein and (2) less severe medical conditions, such as hypertension, mild ischemic heart disease, and diabetes mellitus.

Major hepatectomy was defined by resection of three or more hepatic segments according to Couinaud's classification, and minor hepatectomy was defined by resection of less than three hepatic segments.[13,14] Hepatectomy on patients with tumor rupture, vascular invasion, regional lymph node metastasis, or residual tumor were suggested to be palliative. Hospital mortality was defined as death within the same hospital admission. The preoperative data included gender, age, hepatitis B and C virus infection, liver function, value of α-fetoprotein (AFP), Child–Pugh grading, and comorbidities before hepatectomy. Meanwhile, the postoperative clinicopathological data and treatment results included radical or palliative resection, operative procedure, blood loss, resection margin, liver cirrhosis, tumor size, tumor rupture, tumor encapsulation, satellite nodules, vascular invasion, postoperative complications, 1-, 3-, and 5-year disease-free survival, and overall survival.

Follow-up

The follow-up duration was calculated from the day of operation to either the day of death or the day of last follow-up visit. The study was censored on April 30th, 2008. The median follow-up was 30.4 months (range, 3.1–250.9 months) for the elderly group and 21.3 months (range, 2.6–254.0 months) for the younger group. All patients were followed up every 2–3 months in the first year and every 3–6 months thereafter. The visit consisted of physical examination, blood routines, liver function tests, serum AFP level, abdominal ultrasonography or CT, and chest X-ray. Angiography, MRI, or bone scan was performed when there were strong suspect of intrahepatic recurrence or distant metastasis.

Statistics

The statistical differences of categorical and continuous numerical variables between the elderly and control group were calculated, respectively, by using the Pearson chi-square test with Fisher's exact test and the unpaired Student's *t* test. Overall and disease-free survival rates and curves were analyzed by the Kaplan–Meier method, and the differences between the two groups were compared by the log-rank test. Patients who underwent palliative resections were excluded from the analysis of disease-free survival. Multivariate analysis of prognostic factors was done by using Cox proportional hazard model. A P value<0.05 was defined to be statistically significant. All statistical analyses

in this study were done using software package SPSS15.0 (SPSS Inc., Chicago, IL).

Results

Clinicopathological Features

Clinicopathological features of the elderly and control groups are shown in Table 1. The mean age of the two groups was 72.3±2.5 years (ranged from 70 to 79 years) and 48.1±11.4 years (ranged from 13 to 69 years), respectively. The elderly group, including 58 men and nine women patients, had a similar gender proportion with that of the control group, which included 222 men and 46 women (P=0.581). Compared to controls, patients in elderly group were characterized by significantly lower positivity rate of hepatitis B surface antigen (HBsAg), higher rates of hepatitis C virus (HCV) infection, lower rates of marked AFP elevation, less abnormity of alanine aminotransferase (ALT), higher rate of tumor encapsulation, and better tumor differentiation (Edmondson–Steiner grading). However, no significant differences were found in Child–Pugh's grading, liver cirrhosis rates, tumor sizes, satellite nodules, tumor rupture rates, vascular invasion rates, adjacent organs invasion rates, and pTNM staging[15] between the two groups. Compared with the younger HCC patients, the elderly patients had significantly higher incidence of preoperative comorbidities (P<0.001) without significant differences in the incidence of postoperative complications (P=0.220).

Intraoperative Data and Operative Procedures

There were no significant differences of intraoperative data, including resection margin, portal vein clamping time, and blood loss, between the elderly and control group (Table 2). Although the elderly patients had a higher radical resection rate than the younger group, the difference was not significant (70.1% versus 59.3%, P=0.123). The majority of the patients in both groups underwent minor hepatectomy (83.6% in the elderly versus 79.5% in the control group, P=0.497). The operative procedures of the two groups were shown in Table 2.

Recurrence and Postoperative Therapy

The recurrence rate of the elderly group was 55.3% (26/47), which tended to be lower than that of the control group (63.5%, 101/159), while the difference was not significant (P=0.393). Multimodality therapies, including repeated hepatic resection, transcatheter arterial chemoembolization (TACE), percutaneous ethanol injection therapy, percutane-

Table 1 Clinicopathological Features of the Elderly Group and Control Group

	Elderly group (n=67)	Control group (n=268)	P value
Gender			0.581
Male	58 (86.6%)	222 (82.8%)	
Female	9 (13.4%)	46 (17.2%)	
Child–Pugh grading			0.511
Grade A	63 (94.0%)	257 (95.9%)	
Grade B	4 (6.0%)	11 (4.1%)	
HbsAg			<0.001
Positive	44 (65.7%)	238 (88.8%)	
Negative	23 (34.3%)	30 (11.2%)	
Hepatitis C			0.010
Positive	5 (7.5%)	3 (1.1%)	
Negative	62 (92.5%)	265 (98.9%)	
AFP (ng/ml)			0.004
≥400	19 (28.4%)	131 (48.9%)	
<400	48 (71.6%)	137 (51.1%)	
Liver function			
ALT (U/l)	33.9±20.6	47.9±31.7	0.004
AST (U/l)	47.5±30.7	52.4±34.5	0.331
Albumin (g/l)	40.0±4.4	41.0±4.4	0.100
TBIL (μmol/l)	17.9±16.0	19.5±14.7	0.489
Liver cirrhosis			0.219
Present	52 (77.6%)	217 (81.0%)	
Absent	15 (22.4%)	51 (19.0%)	
Tumor size (cm)	7.3 ± 3.7	7.4 ± 3.9	0.774
Tumor rupture			0.159
Present	5 (7.5%)	40 (14.9%)	
Absent	62 (92.5%)	228 (85.1%)	
Tumor encapsulation			0.040
Complete	41 (61.2%)	125 (46.6%)	
Incomplete/absent	26 (38.8%)	143 (53.4%)	
Adjacent organs invasion			0.359
Present	8 (11.9%)	45 (16.8%)	
Absent	59 (88.1%)	223 (83.2%)	
Vascular invasion			0.178
Present	6 (9.0%)	44 (16.4%)	
Absent	61 (91.0%)	224 (83.6%)	
Satellite nodule			0.289
Present	15 (22.4%)	80 (29.9%)	
Absent	52 (77.6%)	188 (70.1%)	
Hospital mortality	1 (1.5%)	3 (1.1%)	>0.999
Edmondson–Steiner grading			0.002
I	17 (25.4%)	24 (9.0%)	
II	37 (55.2%)	152 (56.7%)	
III	12 (17.9%)	85 (31.7%)	
IV	1 (1.5%)	7 (2.6%)	
pTNM staging			0.397

Table 1 (continued)

	Elderly group (n=67)	Control group (n=268)	P value
I	39 (58.2%)	125 (46.6%)	
II	7 (10.5%)	27 (10.1%)	
IIIa	9 (13.4%)	50 (18.7%)	
IIIb	10 (14.9%)	60 (22.4%)	
IIIc	2 (3.0%)	6 (2.2%)	
IV	0	0	
Preoperative comorbidities			< 0.001
Present	32 (47.8%)	52 (19.4%)	
Absent	35 (52.2%)	216 (80.6%)	
Postoperative complications			0.220
Present	6 (9.0%)	12 (4.5%)	
Absent	61 (91.0%)	256 (95.5%)	

Continuous data are expressed as mean±standard deviation.
AST aspartate aminotransferase, *TBIL* total bilirubin

ous microwave coagulation therapy, radio-frequency ablation, systemic chemotherapy, radiotherapy, biotherapy, and bronchial arterial infusion for lung metastasis were used in the recurrent patients and those with palliative hepatectomies. The type of treatments for the patients with recurrent HCC had no difference between the two groups (Table 3).

Survival

The hospital mortality rate was 1.5% (1/67) in the elderly group and 1.1% (3/268) in the control group, without significant difference (P>0.999). One patient in the elderly group died of postoperative upper gastrointestinal hemorrhage and liver failure, and three patients in the control group died due to liver failure. The longest disease-free survival time was 250.9 months in the elderly group and 254.0 months in the control group. Six patients in the elderly group and eight in the control group survived more than 10 years. The overall survival rates after hepatectomy at 1-, 3-, and 5-year were 83.3%, 54.6%, and 43.2% in the elderly group, respectively, and 71.6%, 39.9%, and 31.4% in the control group, respectively (Table 4). The postoperative long-term survival of the elderly group was significantly better than that of the control group (P=0.017; Fig. 1). The disease-free survival rates after hepatectomy at 1, 3, and 5 years were 66.8%, 57.7%, and 47.0% in the elderly group, respectively, and 65.2%, 40.8%, and 36.2% in the control group, respectively. The disease-free survival of the elderly group seemed to be better than that of the control group, but the difference was not significant (P= 0.157; Fig. 2).

Prognostic Factors of the Elderly Patients After Hepatectomy

For the elderly patients after hepatectomy, pTNM staging, adjacent organs invasion, and AFP level were found to be significantly risk factors for overall survival by univariate analysis (P<0.05; Table 4). While some factors such as Child–Pugh grading, anti-HCV positive rate, serum albumin level, tumor rupture, vascular invasion, and postoperative complications were not fit for univariate analysis

Table 2 Intraoperative Data and Operative Procedures of the Elderly Group and Control Group

	Elderly group (n=67)	Control group (n=268)	P value
Resection margin (cm)	1.7±0.7	1.6±0.9	0.516
Portal vein clamping time (minutes)	10.2±9.5	11.6±9.4	0.271
Blood loss (ml)	334.8±334.3	428.9±468.9	0.123
Radical resection	47 (70.1%)	159 (59.3%)	0.123
Major hepatectomy	11 (16.4%)	55 (20.5%)	0.497
Right trisegmentectomy	1	19	
Right hepatectomy	1	5	
Extended right hepatectomy	0	2	
Left trisegmentectomy	0	5	
Left hepatectomy	1	11	
Extended left hepatectomy	4	5	
Trisegmentectomy IV, V and VI	2	7	
Trisegmentectomy IV, V and VIII	2	1	
Minor hepatectomy	56 (83.6%)	213 (79.5%)	
Combined bisegmentectomy	5	57	
Segmentectomy	27	86	
Left lateral segmentectomy	11	34	
Irregular hepatectomy	13	36	

Continuous data are expressed as mean±standard deviation

Table 3 Treatments for Recurrent HCC of the Elderly Group and Control Group

	Elderly group (n=26)		Control group (n=101)		P Value
	N	%	n	%	
Transcatheter arterial chemoembolization	18	69.2	68	67.3	>0.999
Repeat hepatic resection	5	19.2	16	15.8	0.768
Percutaneous ethanol injection treatment	1	3.8	7	6.9	>0.999
Percutaneous microwave coagulation therapy	1	3.8	4	4.0	>0.999
Radiofrequency therapy	2	7.7	11	10.9	>0.999
Systemic chemotherapy	1	3.8	11	10.9	0.457
Radiation	2	7.7	4	4.0	0.602
Biological therapy	0	0	1	1	>0.999
Bronchial arterial infusion	0	0	2	2	>0.999
Observation	1	3.8	16	15.8	0.193

because the cases were too less or the censor rate was over 50%. Multivariate analysis (Cox regression) showed that pTNM staging was the only independent prognostic factor for overall survival of the elderly patients after hepatectomy (Table 5).

Discussion

Hepatectomy has been generally considered to be an effective way, which may offer potential cure for patients with HCC.[12] However, preoperative comorbid conditions in elderly patients, which may increase substantial risk of operation, including cardiovascular disease, respiratory disease, and diabetes mellitus, are more frequent than those in younger patients.[12,16] Previous studies had reported various outcomes of elderly patients who underwent hepatectomy.[8,11,17–19] However, few large series of long-term outcomes in elderly patients with HCC who underwent hepatectomy have been reported. The exact role of hepatectomy in elderly patients with HCC remains unclear.

The patients with HCC in Japan and Taiwan area were mainly infected by hepatitis C.[11,20] While in China mainland, the majority of HCC patients were infected by hepatitis B.[4,12,21] In this study, while compared with the younger patients, we found that the elderly patients with HCC significantly presented a lower HBsAg-positive rate and a higher HCV-positive rate. Similar results were found by other studies, suggesting a possible difference in the carcinogenesis of HCC in the elderly.[12,22,23]

The significance of AFP has still not been well-defined. Many studies demonstrated that AFP was associated with differentiation and prognosis of HCC,[24–27] and some studies even confirmed AFP to be a unique variable expressing the grade of malignancy and has suppressive effects on the immunologic reaction against tumor cells.[28,29] In our series, the elderly HCC patients had a significantly lower frequency of raised AFP level, compared with the younger patients. In univariate analysis, we also found that the prognosis of elderly HCC patients with AFP<400 ng/ml had significantly better overall survival than those with AFP≥400 ng/ml. Therefore, a lower frequency of increased AFP level could be an indicator of less malignant degree of HCC in the elderly patients.

In our series, a significantly higher frequency of tumor encapsulation in elderly HCC patients was found by comparing the histological characters of the resected tumors. In a previous study, tumor encapsulation have been reported as a favorable prognostic factor for HCC.[30] In addition, Yeh et al.[20] have reported that the higher the incidence of tumor encapsulation is, the higher differentiation of HCC and less incidence of vascular invasion will be. We also found that the elderly HCC patients had significantly better tumor differentiation in the two groups, by comparing Edmondson–Steiner grading of HCC (P= 0.002). Thus, the results suggest that a higher frequency of tumor encapsulation might be an indicator for less malignant degree of the elderly patients with HCC. Although the elderly HCC patients tended to have earlier pTNM staging (68.6% vs. 56.7%, patients in stages I and II), smaller tumor sizes, fewer incidences of satellite nodules, vascular invasion, and tumor rupture in our study, no significant differences were found in the above pathological features.

The differences of pre- and intraoperative features might have implications on the survival of surgically treated patients. In our series, most of the patients' liver function belonged to Child–Pugh A grading. There was no significant difference in the patients liver function between the

Table 4 Prognostic Factors for Overall Survival of Elderly Patients with HCC

	Overall survival		
	n	5-year survival rate (%)	*P* value
Gender			0.253
Male	58	53.3	
Female	9	42.1	
Child–Pugh grading			_[a]
Grade A	63	42.8	
Grade B	4	50.0	
HBsAg			0.655
Positive	44	39.0	
Negative	23	49.2	
Hepatitis C			_[a]
Positive	5	0.0	
Negative	62	44.0	
AFP (ng/ml)			0.011
≥400	19	22.3	
<400	48	47.9	
ALT (U/l)			0.879
≥40	19	40.9	
<40	48	43.3	
AST (U/l)			0.576
≥45	30	38.5	
<45	37	46.9	
Albumin (g/l)			_[a]
≥35	63	43.4	
<35	4	33.3	
TBIL (μmol/l)			0.103
≥20	14	25.7	
<20	53	48.3	
pTNM staging			<0.001
I	39	55.8	
II	7	21.4	
IIIA	9	32.4	
IIIB and IIIC	12	0.0	
Adjacent organs invasion			<0.001
Present	8	0.0	
Absent	59	47.3	
Liver cirrhosis			0.090
Present	52	37.6	
Absent	15	61.3	
Tumor size (cm)			0.323
>5	41	40.2	
≤5	26	50	
Tumor rupture			_[a]
Present	5	0.0	
Absent	62	45.2	
Tumor encapsulation			0.667
Complete	41	47.1	
Incomplete/absent	26	35.8	

Table 4 (continued)

	Overall survival		
	n	5-year survival rate (%)	*P* value
Vascular invasion			_[a]
Present	6	0.0	
Absent	61	46.3	
Satellite nodule			0.406
Present	15	33.9	
Absent	52	45.7	
Blood loss (ml)			0.274
≥500	15	30.5	
<500	52	46.8	
Portal vein clamping time (min)			0.434
≥10	37	50.9	
<10	30	35.4	
Resection margin (cm)			0.898
≥1.5	43	44.6	
<1.5	24	37.9	
Edmondson–Steiner grading			0.059
I	17	58.4	
II	37	42.5	
III and IV	13	26.4	
Preoperative comorbidities			0.551
Present	32	35.6	
Absent	35	43.7	
Postoperative complications			_[a]
Present	6	0.0	
Absent	61	41.2	

[a] The absence of *P* value means the sample is not enough ($n \leq 6$) for univariate analysis or the censor rate is over 50%.

two groups. Previous studies reported different liver cirrhosis rates between the elderly sand younger patients with HCC.[18,22] In our series, liver cirrhosis rates in the two groups were similar. Although the elderly patients with HCC in our series presented a significantly higher frequency of preoperative comorbidities, including cardiovascular diseases, respiratory disorders, and diabetes mellitus, most of the comorbidities had been well-controlled before operation. Moreover, the types of surgical procedures and operative data such as resection margin, portal vein clamping time, and intraoperative blood loss were similar in the two groups. Because of higher ratio of preoperative comorbidities, tolerance of elderly HCC patients for surgical resection was one of the critical problems worried by surgeons. What gratified us is that similar morbidity and hospital mortality rate were found in the two groups. These results were also confirmed by other studies.[12,21,31] Therefore, the risk of hepatic resection for the elderly might not be as high as imaging. For patients with resectable HCC, the tolerance of the elderly without

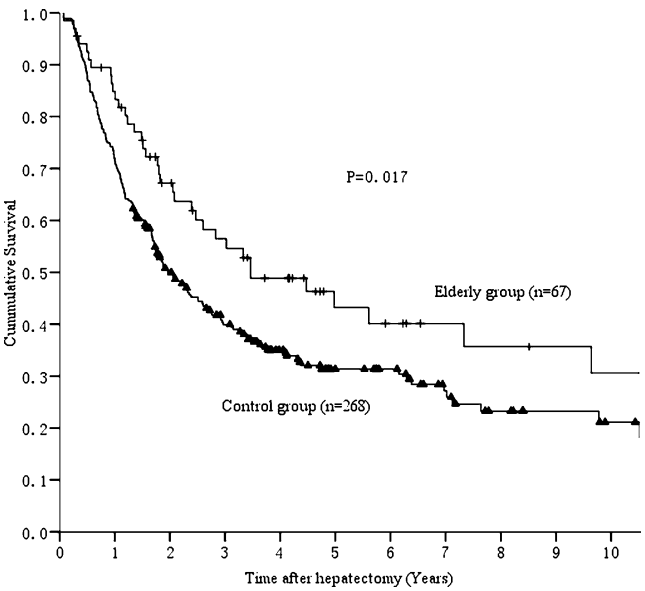

Figure 1 Cumulative overall survival for elderly and control group patients with hepatocellular carcinoma after hepatectomy.

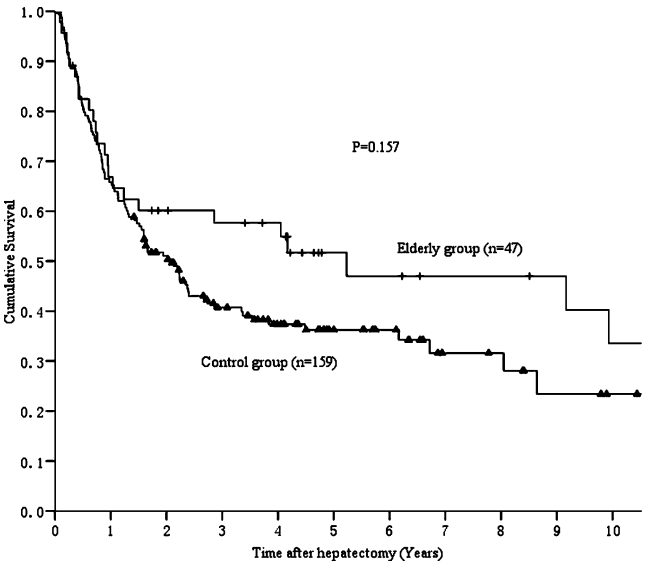

Figure 2 Cumulative disease-free survival for elderly and control group patients with hepatocellular carcinoma after hepatectomy.

preoperative comorbidities or with well-controlled preoperative comorbidities to surgery was good enough and similar to that of non-elderly ones.

Postoperative recurrence of HCC is the most important factor affecting the survival of patients who underwent radical resection. In our series, there were no significant differences in the treatment strategies of recurrent HCC between the two groups. We found that most of the patients with recurrent HCC underwent palliative treatments, mainly TACE, because of advanced tumors or low functional reserve of remnant liver, as Lee et al. reported.[32] In our series, five patients who underwent repeat hepatectomy have survived more than 5 years, and three of them are still alive without recurrence after repeated hepatectomy. Repeated hepatectomy has been suggested to be the most effective treatment for recurrent HCC.[33] Even for the elderly patients with recurrent HCC, repeated hepatectomy was also recommended to achieve better survival if the tumors were resectable.[11]

So far, most previous studies showed a similar long-term survival in the elderly and the younger patients with HCC.[11,20,21,31] However, few papers had consisted large series within a retrospective analysis of over 20 years. Beyond our expectation, we found that the long-term survival of the elderly HCC patients in our series was significantly better than that of the control group (P=0.017). The overall 5-year survival rates after hepatectomy were 43.2% in the elderly group, compared to 31.4% in the control group. Meanwhile, the 5-year disease-free survival of the elderly group tended to be better than that of the control group (47.0% vs. 36.2%), although there was no significant difference. These results suggested that the elderly patients with HCC possibly had a longer tumor-bearing survival than that of the younger patients.

Various predictors have been reported to be risk factors for poor prognosis of postoperative HCC patients, such as liver cirrhosis, Child–Pugh grading, tumor size, satellite nodules, and vascular invasion.[11,21,34,35] For the elderly patients with HCC, predictors of postoperative survival have not been well known. So far, only a few papers revealed different findings by multivariate analysis. Hanazaki et al.[11] reported that liver cirrhosis and vascular invasion were independent prognostic factors for the survival of postresectional elderly HCC patients. Zhou et al.[21] found that Child–Pugh grading, portal vein tumor thrombus, and Edmondson–Steiner grading were prognostic factors. However, literatures failed to yield similar results. In our series, univariate analysis revealed that pTNM staging, incidence of adjacent organs invasion, and AFP level were potential prognostic factors. By multivariate analyzing, we found that pTNM staging was the only independent prognostic factor for the postoperative survival of the elderly patients with HCC.

Table 5 Independent Prognostic Factors for Overall Survival of Elderly Patients with HCC

	P value	RR	95.0% CI
pTNM staging I	0.008		
II	0.305	1.710	0.614–4.768
IIIIA	0.400	1.571	0.548–4.502
IIIB and IIIC	0.001	7.541	2.347–24.232
Adjacent organs invasion	0.728	1.295	0.302–5.558
AFP (≥400 ng/ml)	0.296	1.565	0.675–3.628

Conclusion

In conclusion, HCC in the elderly was less HBV-associated, less advanced, and less aggressive. Hepatectomy is safe enough for the elderly HCC patients without preoperative comorbidities or with well-controlled preoperative comorbidities. In precondition of careful selection, elderly patients with HCC can obtain even more benefits from hepatectomy than younger patients. Age by itself should not be regarded as a contraindication for hepatectomy. Postresection long-term prognosis in the elderly was determined by pTNM staging.

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ORIGINAL ARTICLE

Negative Impact of Blood Transfusion on Recurrence and Prognosis of Hepatocellular Carcinoma After Hepatic Resection

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Abstract
Background In perioperative management of hepatic resection for hepatocellular carcinoma, excessive blood loss and blood transfusion greatly influence postoperative complications and prognosis of the patients. We evaluated the influence of blood products use on postoperative recurrence and prognosis of patients with hepatocellular carcinoma.
Methods The subjects were 66 patients who underwent elective hepatic resection for hepatocellular carcinoma without concomitant microwave or radiofrequency ablation therapy nor other malignancies between January 2001 and June 2006. We retrospectively investigated the influence of the use of blood products including red cell concentration and fresh frozen plasma on recurrence of hepatocellular carcinoma and overall survival.
Results In multivariate analysis, the dose of blood products transfusion was a significant predictor of disease-free and overall survival. Both disease-free and overall survival rates of those who were given blood products were significantly worse than those who did not receive. On the other hand, in univariate analysis of disease-free and overall survival after hepatic resection and clinical variables, the amount of blood loss was not a significant predictor of recurrence or death.
Conclusion Transfusion of blood products is associated with increased recurrence rate and worse survival after elective hepatic resection for patients with hepatocellular carcinoma.

Keywords Transfusion · Hepatectomy · Hepatocellular carcinoma

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequent malignancies in the world. Although operative mortality of elective hepatic resection in patients with HCC has been minimized by improvements in surgical techniques, instruments, and perioperative managements, recurrences of HCC remains high after hepatic resection.[1–5] Factors associated with such recurrence, include tumor size, vascular invasion, intrahepatic metastasis, and excessive blood loss.[6–10] In addition, hepatic resection, especially for cirrhotic patients, remains to be associated with rather high incidence of blood transfusions that consists of red cell concentration (RC), fresh frozen plasma (FFP), platelet concentration, and albumin products. Recent studies have reported that allogenic blood transfusion exerts immunomodulatory effects,[11–15] and blood transfusion may affect postoperative complications and prognoses of HCC[16–21] as other malignancies.[22–35] We and others have reported that blood transfusions in patients after elective hepatic resection for HCC is associated with postoperative infectious complications, such as pneumonia and surgical site infections.[36,37] However, the association between blood transfusion and recurrence-free survival of HCC remains controversial.[38–41] In this study, we retrospectively investigated the relation between perioperative blood transfusion and disease-free survival as well as overall survival after hepatic resection for HCC.

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Patients and Methods

Between January 2001 and June 2006, 75 patients underwent hepatic resection for HCC in the Department of Surgery, Jikei University Hospital, Tokyo, Japan. Of these, nine patients were excluded, including five patients for concomitant microwave coagulation or radiofrequency ablation therapy, two patients for additional procedures for other malignancies, and two patients who were lost to follow-up, leaving the remaining 66 patients for the study. Generally, the extent of hepatic resection was determined based on ICG_{R15} before surgery and in reference to hepatic reserve described by Miyagawa et al.[42] The use of blood products and the dose were determined by the preference of attending surgeons based on intra-operative blood loss as well as postoperative data of hemoglobin, platelets, serum albumin, and the prothrombin time. Since 2003, we started to follow the guidelines for administration of blood products by the Japanese Ministry of Health and Welfare settled in 1999.[43] The tumor factor (T factor) staging was based on the General Rules for the Clinical and Pathological Study of Primary Liver Cancer by the Liver Cancer Study Group of Japan.[44] The type of resection was classified into two types: anatomical resection (extended lobectomy, lobectomy, segmentectomy, or subsegmentectomy) and non-anatomical limited partial resection.

Table 1 Univariate Analysis of Disease-Free and Overall Survival After Hepatic Resection

Factor	Parameter (*N*)	Disease-free survival		Overall survival	
		Median (year)	*p* Value	Median (year)	*p* Value
Age (years)					
<60	27	2.51	0.061	3.27	0.388
≥60	39	2.15		2.93	
Gender					
Male	56	2.37	0.001	3.26	<0.001
Female	10	1.40		2.65	
ICG_{R15} (%)					
<15	44	2.38	0.003	3.50	0.020
≥15	22	1.52		2.61	
Child classification					
A	60	2.37	0.119	3.26	0.062
B or C	6	1.78		2.02	
MELD score					
<10	61	2.36	0.034	3.07	0.118
≥10	5	1.42		3.02	
T factor					
T1 or T2	46	2.60	0.013	3.26	0.032
T3 or T4	20	1.48		2.86	
Type of resection					
Anatomical	22	2.28	0.679	3.82	0.747
Partial	44	2.36		2.98	
Duration of operation (min)					
<300	38	2.60	0.528	3.55	0.825
≥300	28	2.23		2.37	
Blood loss (g)					
<1,000	44	2.36	0.670	2.98	0.215
≥1,000	22	2.23		3.36	
Hepatitis virus					
HBV	26	2.44	0.182	3.29	0.767
HCV	28	2.10		3.00	
No	12	2.31		3.10	
Blood products transfused					
With	22	1.51	0.038	2.59	0.001
Without	44	2.40		3.16	

MELD model for end-stage liver disease, *T factor* tumor factor, *HBV* hepatitis B virus, *HCV* hepatitis C virus

Table 2 Multivariate Analysis of Disease-Free Survival After Hepatic Resection

Factor	Odds ratio (95%CI)	*p* Value (multivariate)
Gender (female)	2.773 (1.044–7.367)	0.041
ICG_{R15} (%)	1.013 (0.978–1.050)	0.464
MELD score	1.027 (0.855–1.233)	0.777
T factor (T1 or T2)	2.975 (1.332–6.644)	0.008
Total blood products transfused (units)	1.017 (1.006–1.028)	0.002

MELD model for end-stage liver disease score, *T factor* tumor factor

At first, in order to evaluate the clinical variables in relation to early recurrence of HCC, the association of disease-free and overall survival after hepatic resection were evaluated by univariate and multivariate analyses using the following 11 factors: age, gender, preoperative ICG_{R15}, child classification, model for end-stage liver disease (MELD) score, T factor based on tumor pathology, type of resection, duration of operation, blood loss, hepatitis virus status, and the dose of perioperative blood products transfused, including RC and FFP.

Next, we analyzed the effect of the administration of blood products on the recurrence of HCC, using the following 10 factors: age, gender, preoperative ICG_{R15}, child classification, MELD score, T factor based on tumor pathology, type of resection, duration of operation, blood loss, and hepatitis virus status. Then, we compared the disease-free and overall survival in relation to blood products administration.

The recurrence of HCC was defined as newly detected hypervascular hepatic or extrahepatic tumors by ultrasonography, computed tomography, magnetic resonance image, or angiography with or without increase in serum α-fetoprotein or protein induced by vitamin K absence or antagonist-II. For recurrent HCC in the liver, repeated hepatic resection, local ablation therapy, or transarterial chemo-embolization was given based on hepatic functional reserve judged mainly by ICG_{R15}. Extrahepatic recurrence was mainly treated conservatively.

Statistical Analysis

The data were expressed as a mean ± SD. Univariate analysis was performed using nonpaired Student's *t* test and Chi-square test. Analysis of disease-free and overall survival was performed using the Log rank test. Factors that were found to significantly influence disease-free or overall survival were then used in the Cox proportional regression model for a multivariate analysis. All *p* values were considered statistically significant when the associated probability was less than 0.05.

Results

Univariate and Multivariate Analysis of Disease-Free and Overall Survival After Hepatic Resection and Clinical Variables

Table 1 lists the relationship between the clinical variables and disease-free as well as overall survival after hepatic resection. In univariate analysis, disease-free survival was worse in female ($p=0.001$), high preoperative ICG_{R15} ($p=0.003$), and high MELD score ($p=0.034$) and positively correlated with T factor of tumor pathology ($p=0.013$) and perioperative blood products transfused ($p=0.038$). Overall survival was worse in female ($p<0.001$) and high preoperative ICG_{R15} ($p=0.020$) and positively correlated with T factor of tumor pathology ($p=0.032$) and perioperative blood products transfused ($p=0.001$). However, the amount of blood loss did not correlate with both disease-free and overall survival. In multivariate analysis, female gender ($p=0.041$, $p<0.001$), T factor of tumor pathology ($p=0.008$, $p=0.008$), and the dose of blood products transfusion ($p=0.002$, $p<0.001$) were significant predictors of both disease-free (Table 2) and overall survival (Table 3).

Association Between Clinical Variables and Blood Products Given

Table 4 lists the relationship between clinical variables and perioperative blood products transfusion. In univariate analysis, blood products transfusion was more common in

Table 3 Multivariate Analysis of Overall Survival After Hepatic Resection

Factor	Odds ratio (95%CI)	*p* Value (multivariate)
Gender (female)	11.595 (2.771–48.515)	<0.001
ICG_{R15} (%)	1.022 (0.973–1.073)	0.387
T factor (T1 or T2)	7.653 (1.701–34.433)	0.008
Total blood products transfused (units)	1.027 (1.014–1.040)	<0.001

T factor tumor factor

Table 4 Univariate Analysis of Patient Characteristics in Relation to Blood Products Transfused During Elective Hepatic Resection

Factor	Blood Products		*p* Value (univariate)
	Transfused (*n*=22)	Not transfused (*n*=44)	
Age (years)	64.8±10.5	60.4±10.4[a]	0.116
Gender (male/female)	16:6	40:4	0.052
ICG_{R15} (%)	16.3±11.4	13.5±8.8	0.291
Child classification (A/B/C)	20:2:0	40:4:0	0.999
MELD score	7.2±2.2	7.2±2.4	0.970
T factor (T1/T2/T3/T4)	0:13:7:2	9:24:10:1	0.089
Type of resection (anatomical/partial)	13:9	9:35	0.002
Duration of operation (min)	344.8±128.2	259.8±93.9	0.003
Blood loss (g)	1,898.5±1,525.0	580.6±449.7	<0.001
Hepatitis virus (HBV/HCV/no)	9:7:6	17:21:6	0.302

MELD model for end-stage liver disease score, *T factor* tumor factor, *HBV* hepatitis B virus, *HCV* hepatitis C virus

[a] Mean±SD

anatomic resection (p=0.002) and was positively correlated with the length of operation (p=0.003) and the amount of intra-operative blood loss (p<0.001). In survival analysis, the administration of blood products was associated with worse disease-free and overall survival than those who were not transfused (Fig. 1A: p=0.038, B: p=0.001).

Discussion

In cancer surgery for malignancy in various organs, including the colon and rectum, lung, breast, and stomach, harmful effects of perioperative blood transfusions on recurrences of malignancies have been reported.[22–35] However, contrary results, i.e., no association between perioperative blood transfusion and recurrence have been described.[45–49] In colorectal cancer, it has been reported that perioperative blood transfusion was associated with decreased overall survival but not with recurrence.[50] On the other hand, another investigator has reported that perioperative blood transfusion is associated with decreased time to recurrence as well as overall survival after resection of colorectal cancer liver metastasis.[27] Similar to other malignancies, the association with the postoperative recurrence of HCC and perioperative blood transfusion remains unclear.[16–21,38–41] Several investigators reported that perioperative blood transfusion significantly decreased both disease-free and overall survival rates after hepatic resection.[16,19,51] As to HCC, it has been reported that blood transfusions are significantly associated with increased the incidence of tumor recurrence especially in patients who were stages I or II[21] and HCC without angio-invasion.[16] These studies suggest that the impact of blood transfusions on tumor recurrence is pronounced in patients with

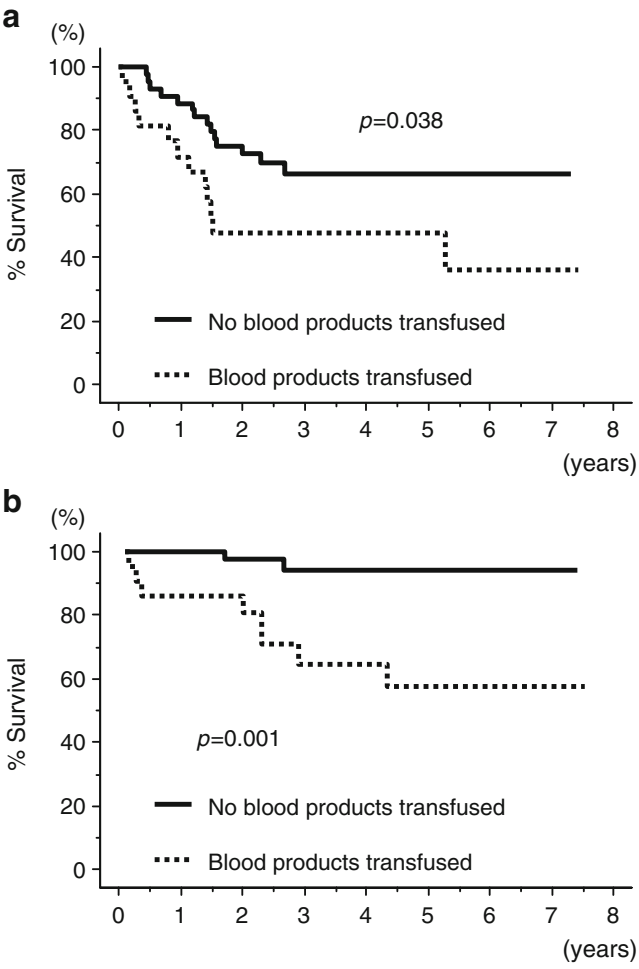

Figure 1 The administration of blood products was associated with significantly worse disease-free survival (**A**; p=0.038) and overall survival (**B**; p=0.001) than those who were not given blood products.

relatively early stages of HCC.[52] On the other hand, other reports on hepatic resection for HCC described that intra-operative blood transfusion adversely affected overall survival rates but not disease-free survival.[21,40] Another study on HCC reported that a large number of perioperative blood transfusions adversely affected overall survival.[53] In the present study, a large number of perioperative blood transfusions significantly associated with both decreased disease-free and overall survival in multivariate analysis. The result of our study seems to strengthen the negative impact of RC or FFP transfusion on recurrence and prognosis of HCC after elective hepatic resection.

Although the mechanism of the adverse effect of blood transfusion remains to be clarified, several reports describe an association between the immune system and the growth of HCC,[54,55] including the influence of immune status on the spontaneous regression of HCC.[56–59] In a report, the absolutely count of peripheral blood lymphocyte in the early postoperative period was significantly decreased in patients who underwent intra-operative blood transfusion compared to that in those who did not.[21] Concerning the mechanism of immunosuppressive effect of blood transfusion, it has been reported that soluble HLA class I molecules and soluble Fas-ligand released by leukocytes present in blood products inhibit the activity of NK cells and cytotoxic T cells, which are known to reduce immune capacity and, therefore, may predispose to postoperative infections.[15,37,60–64]

Conclusion

In spite of recent improvements in the outcome of elective hepatic resection,[65–67] some complex surgical procedures still require blood transfusion as compared to other types of surgery. In order to improve prognosis after resections of malignancies, it is important not only to minimize blood transfusion but also to investigate the mechanism of immunosuppression by blood transfusion.

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ORIGINAL ARTICLE

Long-Term Results of Hepatectomy After Hepatic Arterial Infusion Chemotherapy for Initially Unresectable Hepatic Colorectal Metastases

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Abstract
Background The prognosis of unresectable hepatic colorectal metastases is poor even if chemotherapy is administered. The purpose of this study was to evaluate the long-term efficacy of hepatic arterial infusion (HAI) chemotherapy and hepatectomy following HAI for such condition.
Methods Seventy-two patients with unresectable hepatic colorectal metastases received continuous HAI of 5-fluorouracil.
Results The overall response rate was 38%. The median survival of all patients was 18 months. The overall 3-year survival rate was 18%. Seven patients (10%) survived more than 58 months. Of the eight patients with a complete response, seven developed liver and/or lung metastases, and of these, one patient undergoing additional hepatectomy has been disease-free and the other six receiving chemotherapy died of disease. Another complete-response case died of liver abscess. Of the 19 patients with a partial response, six could undergo hepatectomy after HAI. The overall 5-year survival rate of seven patients undergoing hepatectomy was 71%, whereas for patients without hepatectomy, the rate was 0%.
Conclusions Most patients showing response after HAI for unresectable hepatic colorectal metastases had relapses. The long-term prognosis of patients undergoing hepatectomy after HAI was favorable. Therefore, when HAI makes liver metastases resectable, they should be resected.

Keywords Colorectal cancer · Liver metastasis · Hepatic arterial infusion · Neoadjuvant therapy · Liver resection

Introduction

Colorectal cancer is the leading cause of cancer death in developed countries.[1] The prognosis of patients with colorectal cancer is affected not only by surgical treatment for primary tumors but also by management of liver metastases because up to 50% of patients with primary colorectal cancer develop liver metastases synchronously or metachronously.[2,3]

The treatment strategy for hepatic colorectal metastases is still controversial. Although surgical resection is the best treatment option for resectable metastases[4] and the 5-year survival rates after hepatectomy are 37–58%,[5–10] unresectable metastases remain a serious problem. In general, systemic chemotherapy is recommended for such condition.[11] When using current systemic regimens for disease limited to the liver, chemotherapy enables resection in 15–30% of patients.[12] However, the 5-year survival rates following resection after systemic chemotherapy are still around 30%,[12] and there are circumstances that prohibit the usage of current regimens, such as drug toxicity and refractory disease.

Therefore, despite being technically demanding, hepatic arterial infusion (HAI) chemotherapy has a certain role in the treatment of unresectable liver metastases. HAI has the advantage of bringing a high concentration of cytotoxic

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agents to the liver with a minimal systemic toxicity[13] and thus provides high response rates of up to 83%.[13] However, HAI alone cannot cure such patients.[14–17] Indeed, there were at best only one or two 5-year survivors in each HAI trial.[15–17]

To overcome this problem, we had conducted a pilot study of multimodality therapy with hepatic resection after HAI and portal vein embolization for unresectable hepatic metastases and reported the feasibility and potential benefit for selected patients.[18] The purpose of the present study was to evaluate the long-term efficacy of HAI and hepatic resection after HAI for patients with initially unresectable liver metastases from colorectal carcinoma.

Patients and Methods

Between 1988 and 1999, 72 patients with synchronous or metachronous unresectable hepatic colorectal metastases received HAI. Of them, nine patients received HAI after resection of two liver segments or more and ten after resection of one liver segment or less. Informed consent was obtained from each patient. All patients had multiple liver metastases involving three or four hepatic segments (Table 1), which were detected by computed tomography (CT) and ultrasonography (US) and/or confirmed by intraoperative US and biopsy. These metastases were considered unresectable because the remaining functional parenchymal volume of the liver after resection was estimated to be too small to maintain normal liver function or the tumors were contiguous to essential intrahepatic vascular structures. If hepatic metastases became resectable after HAI, resection was performed. All patients were followed up for at least 5 years or until death. Retrospective analysis of clinicopathologic data from the prospective database and medical records of these patients was conducted.

All patients underwent hepatic arterial catheterization and placement of an implantable reservoir[19] or an Infusaid model 400 pump (Infusaid, Norwood, MA, USA)[18] with or without a laparotomy. In the laparotomy group, the gall bladder was removed and the right gastric and gastroduodenal arteries and small branches supplying the stomach and duodenum were ligated. An arterial catheter was placed into the gastroduodenal artery, with the tip placed at the junction of the proper hepatic artery and gastroduodenal artery. In the non-laparotomy group, the gastroduodenal and right gastric arteries were occluded with steel coils. A catheter was placed into the proper hepatic artery via the subclavian or femoral artery. After the catheter was connected to the reservoir or the pump, fluorescein dye or indigo carmine was injected through the catheter to confirm complete perfusion of the liver.[18,19]

Table 1 Patient Characteristics

	No. of patients
Patient	
Sex	
Male	50
Female	22
Age (years)	59 (range 32–78)[a]
Primary tumor	
Site	
Colon	39
Rectum	32
Unknown	1
Histological grade[b]	
Well-differentiated	28
Moderately differentiated	41
Poorly differentiated	3
Transmural invasion depth (pT)[b]	
T2	3
T3	63
T4	4
Unknown	2
Regional lymph node metastasis (pN)[b]	
N0	10
N1	19
N2	30
Unknown	3
Pathologic stage[b]	
I	1
II	3
III	14
IV	52
Unknown	2
Liver metastasis	
Appearance	
Synchronous	52
Metachronous	20
No. of tumors[c]	
2	2 (2)
3	3 (2)
4	4 (1)
5–9	25 (4)
≥10	38
Sum of tumor diameters (cm)[c]	
5–9	27 (8)
10–14	30 (1)
15–19	8
≥20	7
Number of involved segments	
3	10
4	62
CEA levels (ng/ml)	61.3 (range 1.6–6,000)[a]

CEA carcinoembryonic antigen

[a] Numbers are median and range

[b] UICC TNM classification (6th edition)

[c] Numbers in parenthesis represent the number of patients who underwent resection of two liver segments or more before hepatic arterial infusion

HAI was initiated 2–3 weeks after recovery from simultaneous colorectal resection or the next day after catheter placement alone. The protocols for HAI were as follows:

Protocol 1 The initial dose of 360 mg/m^2 per day of 5-fluorouracil (FU) was infused for 7 days by using an extracorporeal continuous infusion pump (CADD-1, Pharmacia, St. Paul, MN, USA), followed by 180 mg/m^2 per day of 5-FU for 21 days. After a 7-day interval without infusion, 180 mg/m^2 per day of 5-FU was infused for 7 days. This 7-day infusion/7-day no infusion cycle was repeated.[19]

Protocol 2 The initial dose of 360 mg/m^2 per day of 5-FU was infused for 14 days by the same pump. After a 7-day interval without infusion, 180 mg/m^2 per day of 5-FU was infused for 7 days. This 7-day infusion/7-day no infusion cycle was repeated.

Protocol 3 The initial dose of 1,000 mg/m^2 of 5-FU was administered over 5 h once a week by the same pump, and this therapy was repeated as long as possible.

Protocol 4 The starting doses of 120 mg/m^2 per day of 5-FU was administered by continuous infusion through the Infusaid pump for 21 days, alternating with normal saline for 7 days, and 4 mg/m^2 per day of mitomycin C was given by injection through the side port of the pump once a month. This treatment cycle was repeated as many times as possible.[18]

We used 5-FU instead of the floxuridine (FUDR) because FUDR was not permitted in Japan. The patients underwent a physical examination, complete blood count, and blood biochemistry profile every 2 weeks. When abdominal symptoms or abnormal values in the blood test attributable to HAI were noted, HAI was discontinued until the complications were resolved. After resolution of the complications, subsequent doses were administered at half of the starting dose. Upper gastrointestinal endoscopy and angiography via the implanted reservoir were performed when symptoms of epigastric pain and/or vomiting were observed. When severe complications such as bleeding from a duodenal ulcer, sclerosing cholangitis, occlusion of the hepatic artery or extravasation, appearance of extrahepatic metastases, and regrowth of hepatic tumors occurred, HAI was terminated. Treatment was continued for as long as the liver tumors were evaluated to have either decreased in size or remained unchanged.[18]

All of the patients were examined before the initiation of HAI and every 2 months thereafter with CT and US of the abdomen and chest X-ray. The tumor response was evaluated with CT and US and was defined according to the World Health Organization criteria.[20] A complete response (CR) denoted the disappearance of all liver tumors for more than 4 weeks by CT and/or US. A partial response (PR) indicated a reduction of more than 50% in the sum of the largest diameters of all tumors for more than 4 weeks by CT. Progressive disease (PD) was defined as an increase in tumor size of greater than 25% or an appearance of new liver tumors. The patients with other response were considered to have stable disease (NC). The duration of the response was measured from the onset of a tumor reduction of more than 50% to disease progression.

Survival curves were estimated with the Kaplan–Meier method and differences in survival were evaluated with the log-rank test. All statistical analyses were performed using SPSS for Windows, version 11.0J (SPSS-Japan Inc., Tokyo, Japan). All P values were two-sided and a P value of less than 0.05 was considered to be statistically significant.

Results

The characteristics of the patients are shown in Table 1 and treatment results in Table 2. The overall response rate was 38% (eight patients with CR, 19 with PR; Table 2). NC was found in 20 patients and PD in 25. The response rates for the protocols 1, 2, 3, and 4 were 50% (one patient with CR, five with PR), 67% (two CR, four PR), 20% (two CR, six PR), and 64% (three CR, four PR), respectively. Minor complications including epigastric pain, nausea, vomiting, and back pain were observed in 44 patients (61%). Of eight patients (11%) with severe complications, six patients had duodenal ulcers, one sclerosing cholangitis, and one both duodenal ulcer and sclerosing cholangitis. Among the seven patients with duodenal ulcers, six suffered bleeding and four underwent emergency surgery. The two patients with sclerosing cholangitis developed liver abscesses and received US-guided drainage, but died at 40 and 82 months after the initiation of HAI, respectively.

All patients were followed for at least 5 years or until death. At the last follow-up, three patients (4%) undergoing hepatectomy after HAI were alive. Two patients (3%) died of liver abscess due to sclerosing cholangitis without recurrence and 67 patients (93%) died of the disease. Extrahepatic recurrences appeared in 45 patients (62%), including lung metastases in 41 patients, bone metastases in nine, local recurrence in five, lymph node metastases in three, and brain metastases in two.

The median survival of the 72 patients after the initiation of HAI was 18 (range, 3–167) months. Seven patients (10%) survived more than 58 months. The 1-, 2-, 3-, 4-, and 5-year survival rates were 72%, 32%, 18%, 10%, and 7%, respectively (Fig. 1). The survival of the responders (CR

Table 2 Treatment Results

Protocol no.	No. of patients	Response rate (%)	CR rate (%)	Complication rate (%)	Rate of severe complication[a] (%)	Resection rate (%)
1	12	50	8	75	8	0
2	9	67	22	77	11	33
3	40	20	5	65	5	5
4	11	64	27	90	36	18
Total	72	38	11	72	11	10

CR complete response

[a] Sever complications were sclerosing cholangitis and duodenal ulcer

plus PR) was better than that of the non-responders (NC plus PD; $P<0.001$). The median survival time was 26 months for the responders versus 12 months for the non-responders.

Table 3 shows details of the eight patients with CR. Of them, seven patients developed liver and/or lung metastases afterward, and only one patient maintained CR who died of liver abscess due to sclerosing cholangitis at 40 months. Of the seven patients with relapses, one patient undergoing resection of metastases confined to the liver was alive at 118 months. Another patient received HAI again, but died at 27 months. The remaining five patients received systemic chemotherapy because of extrahepatic disease or occlusion of the hepatic artery.

Owing to shrinkage of liver metastases after HAI, seven patients (10%) could undergo hepatectomy. Details of these patients are shown in Table 4. Of the three patients with PR whose remaining metastases were confined to the right lobe, one patient could undergo right lobectomy and two extended right lobectomy after portal vein embolization. Another patient could undergo left lobectomy and wedge resection after portal vein embolization. The other three patients underwent wedge resection. Postoperative complications included bile leakage in two patients and liver abscesses in two. One patient died of liver abscesses due to sclerosing cholangitis at 82 months, and three patients died of liver and/or lung metastases. The median survival of these patients was 63 months, whereas it was 17 months for those who could not undergo hepatectomy ($P<0.001$; Fig. 2). The 1-, 3-, and 5-year survival rates of the patients with hepatectomy after HAI were 100%, 86%, and 71%, respectively, and five patients (7%) survived more than 5 years.

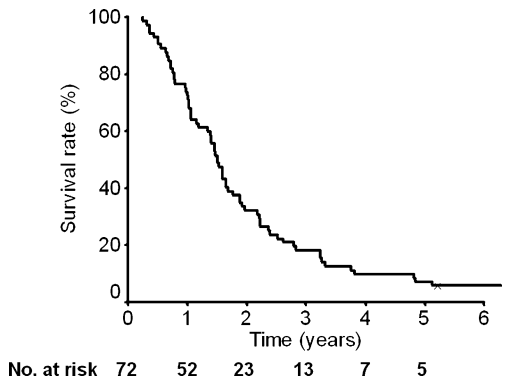

Figure 1 Survival curve of the overall patients who received hepatic arterial infusion chemotherapy for unresectable hepatic colorectal metastases ($n=72$). Time is from the initiation of hepatic arterial infusion.

Discussion

Complete surgical resection is currently the only treatment that can provide long-term survival and cure for patients with hepatic colorectal metastases.[4–10] Although only 10–25% of the patients can undergo complete resection,[2,3,12,21] the resection rate may be improved if chemotherapy sufficiently reduces the size and number of the tumors.[3,12,18,21]

The current systemic regimens consisting of 5-FU, leucovorin, oxaliplatin, irinotecan, bevacizumab, and cetuximab bring about response rates of 70% or more so that they are regarded as standard therapy for unresectable metastatic colorectal cancer.[11,12] However, the median survival after such chemotherapy alone is up to 20 months.[22] Although the systemic chemotherapy also enables resection in 15–30% of patients with disease limited to the liver,[12] the 5-year survival rates following such resection are still around 33%.[12,21] In addition, the current regimens cannot be used for patients who suffer toxicity or refractory disease after the current systemic therapy.

On the other hand, the response rates of HAI with FUDR are reported to be 42–62% and the median survival after HAI have ranged from 13 to 17 months.[13,15,16,23,24] In our previous study, the median survival of eight patients with unresectable liver metastases, who had undergone resection of the primary tumor and received HAI with 5-FU, was 30 months with a response rate of 75%.[18] Therefore,

Table 3 Details of the Patients with Complete Response

Case no.	Age (years)/sex	No. of tumors	Sum of tumor diameters (cm)	Protocol no.	Duration of CR (months)	Site of relapse	Treatment after relapse	Survival (months)[a]	Outcome
1	78/M	10	7.3	P-4	28	None	None	40	Dead[b]
2	62/M	7	5.6	P-4	15	Liver	SCT	46	DOD
3	44/M	5	11.4	P-2	10	Liver	Resection	118	ANED
4	65/M	11	10	P-4	9	Liver, Lung	SCT	58	DOD
5	57/M	7	7.2	P-3	7	Liver, Lung	SCT	45	DOD
6[c]	66/F	2	2	P-1	4	Liver	SCT	26	DOD
7	61/F	12	9.7	P-2	4	Liver	SCT	21	DOD
8	59/F	11	9	P-3	3	Liver	HAI	27	DOD

CR complete response, *SCT* systemic chemotherapy, *HAI* hepatic arterial infusion, *DOD* dead of disease, *ANED* alive with no evidence of disease

[a] Survival from initiation of hepatic arterial infusion

[b] The patient died of liver abscess due to sclerosing cholangitis

[c] The patient underwent resection of eight liver metastases before HAI

although HAI is not effective for extrahepatic diseases and has some technical difficulties, HAI seems to have a certain role for selected patients with disease limited to the liver.

In this study, the response rate was 38% overall, but ranged from 20% to 67% according to the protocols. Reflecting these response rates, the median survival time was 18 months. These results are comparable to those following HAI with FUDR and are approaching those with the current systemic regimens. Although this was not a randomized controlled study and the number of patients was limited, protocol 2 showed the highest response rate of 67%, the highest resection rate, the moderate rate of severe complications, and seemed to be the best among our protocols. However, 62% of our patients developed extrahepatic relapses, mostly lung metastases, for which HAI has limitations.

The median survival of our patients with CR was 42 months and the survival of the responders was significantly better than the non-responders in line with previous reports.[19] However, most patients showing CR had relapses eventually as reported before.[12] Actually, of the eight patients with CR, seven had relapses and only one patient who underwent hepatectomy for relapsed liver metastases has been free of disease. Therefore, as is recommended in the Expert Consensus Statement,[12] hepatic metastases should be resected when they become resectable.

Although there have been many studies on hepatectomy following systemic chemotherapy,[12,21,25] the number of studies on hepatectomy after HAI is limited,[18,26,27,28,29] particularly with a few long-term follow-up studies.[18,26,27,28,29] Elias et al.[26] reported that liver tumors in 6% of 239 patients who received HAI with 5-FU and other

Table 4 Details of Seven Patients Who Underwent Hepatectomy After Hepatic Arterial Infusion Chemotherapy

Case no.	Age (years)/sex	No. of tumors	Sum of tumor diameters (cm)	Protocol no./response	PVE	Type of surgery	Complication after surgery	Site of relapse	Survival (months)[a]	Outcome
1	40/M	5	12.8	P-4/PR	Yes	RL	Bile leakage	None	167	ANED
2	44/M	5	11.4	P-2/CR	No	W	None	None	118	ANED
3	46/M	14	13	P-4/PR	Yes	ERL	None	None	82	Dead[b]
4	56/F	7	11.4	P-3/PR	Yes	LL+W	None	Lung	63	ANED[c]
5	35/F	8	20	P-2/PR	Yes	ERL	Bile leakage	Liver	62	DOD[d]
6	67/M	8	8.1	P-3/PR	No	W	Liver abscess	Lung	58	DOD[d]
7	62/M	5	10.4	P-2/PR	No	W	Liver abscess	Liver	22	DOD[d]

PVE portal vein embolization, *PR* partial response, *CR* complete response, *RL* right lobectomy, *W* wedge resection, *ERL* extended right lobectomy, *LL* left lobectomy, *ANED* alive with no evidence of disease, *DOD* dead of disease

[a] Survival from initiation of hepatic arterial infusion

[b] The patient died of liver abscess due to sclerosing cholangitis

[c] The patient is still alive after hepatectomy and after partial resection of the lung for lung metastasis

[d] The patient died of lung and/or liver metastases

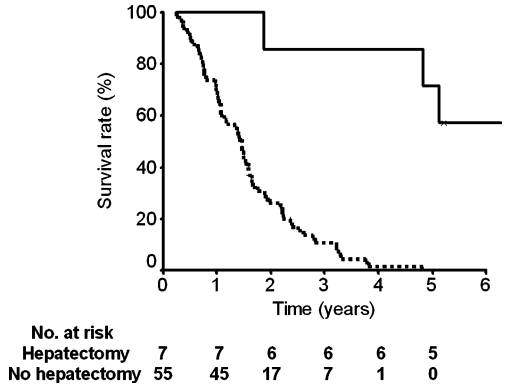

Figure 2 Survival curves according to the additional hepatectomy after hepatic arterial infusion chemotherapy for unresectable hepatic colorectal metastases. Survival of the patients with additional hepatectomy (n=7, *solid line*) was significantly better than that of those without hepatectomy (n=65, *broken line*; P<0.001). Time is from the initiation of hepatic arterial infusion.

agents for unresectable hepatic tumors subsequently became resectable, and five of the nine patients with hepatic colorectal metastases had been free of disease, with a mean follow-up time of 36 months. Link et al.[27] evaluated 168 patients with unresectable hepatic colorectal metastases treated with HAI with FUDR and others. The overall resection rate was 5%, and seven patients were alive 2–58 months after resection. Meric et al.[28] reported that 18 of 383 patients (5%) treated with HAI with FUDR or 5-FU and others for unresectable hepatic colorectal metastases could undergo resection. Of them, 15 patients developed recurrence at a median follow-up of 17 months and three died of other causes within 7 months. Clavien et al.[29] used HAI with FUDR and induced resectability in six of 23 previously treated patients (26%) with unresectable hepatic colorectal metastases (including 20 previously treated with irinotecan). The actuarial survival rate at 3 years was 50%.

In the present study, although the resection rate was 10%, the median survival of the seven patients with hepatectomy was 63 months and six patients survived more than 58 months. In terms of resection rate and survival, our results seem to be preferable to those of the previous HAI series[26,27,28] and almost similar to the recent results with FUDR.[29] In addition, our survival results appear to approach those with the current systemic regimens.[12,21,25] In resection rate, however, ours are worse than those with the systemic regimens. Moreover, in spite of long-term survival, 43% of our patients eventually died of the disease. Therefore, the current HAI are not sufficiently effective for unresectable colorectal liver metastases in terms of long-term survival.

Integration of targeted agents such as cetuximab and bevacizumab into the current systemic regimens has been shown to raise response rates up to 70% or more[12] and may improve the resection rate and survival. Another possible option is a combination of HAI and systemic therapy, which simultaneously utilizes a high drug concentration in the liver brought about by HAI and the suppression of extrahepatic disease by systemic therapy. A third possibility is postoperative adjuvant chemotherapy. Portier et al.[30] conducted a randomized controlled trial and showed that postoperative 5-FU plus leucovorin improved disease-free survival of the patients who underwent liver resection for colorectal metastases. All these options and their combinations seem to be promising and warrant further investigation.

Timing of hepatectomy is another important issue for improving the outcomes. If we had performed hepatectomy for the seven patients with CR, the resection rate would have been 19% (14/72) and they might have avoided relapses. Therefore, as is recommended in the Expert Consensus Statement,[12] resection should be performed as soon as hepatic metastases become technically resectable. Also, resection should encompass the segments involved based on pre-chemotherapy imaging.[12]

In this study, four patients (57%) suffered postoperative complications consisting of bile leakage and liver abscess. This morbidity is higher than expected in hepatectomy without neoadjuvant chemotherapy. Indeed, we have seldom experienced liver abscess in surgery alone. Elias et al.[26] reported that postoperative complications were significantly more frequent after hepatectomy following HAI than after hepatectomy alone (57% versus 18%). The rates of complications directly associated with hepatectomy, including hemorrhage, biliary fistula, abscess, and atelectasis, were 29% in the HAI group versus 11% in the non-HAI group. HAI with 5-FU or FUDR is known to cause nodular regenerative hyperplasia, steatohepatitis, chemical hepatitis, and biliary sclerosis.[11,13] Although their pathogenesis has not been well established,[11,13] these high complication rates are attributable to such hepatobiliary toxicity. In this aspect, early resection has an advantage of shortening the duration of HAI and thus reducing damage to the liver.

During HAI in our series, two patients developed liver abscesses due to sclerosing cholangitis and four had bleeding duodenal ulcers, both of which were life-threatening and necessitated emergency intervention. The etiology of sclerosing cholangitis is not well understood, but is mainly attributable to a combination of ischemia and inflammation.[13] The incidence of sclerosing cholangitis with FUDR HAI was reported to rise with an increase in the infusion dose[16] and the duration of infusion.[15] Therefore, we should reduce dosage and shorten duration as less as possible. The addition of dexamethasone to HAI regimens, circadian modification, and drug alternation also have been attempted[13] and may be beneficial. Gastrointestinal toxicity, mainly gastroduodenal inflammation and ulceration, is directly related to extrahepatic perfusion.[13] This can be

avoided by careful hepatic artery dissection, including ligation of the right gastric artery and all the small branches in the hepatoduodenal and hepatogastric ligaments, during catheter placement.[13] Oral histamine receptor blockers may decrease the severity of gastric toxicity.[13] Early detection of toxicity and discontinuation of HAI are also important to prevent the occurrence of severe complications. We should pay careful attention to elevations of aspartate aminotransferase, alkaline phosphatase, and bilirubin in addition to gastrointestinal symptoms.[13]

In conclusion, the present study showed that almost all patients showing CR or PR after HAI for unresectable hepatic colorectal metastases had relapses, but overall long-term survival of patients undergoing hepatectomy after HAI was favorable. Therefore, when HAI makes liver metastases resectable, they should be resected. This approach appears helpful for patients with unresectable colorectal metastases limited to the liver who suffered toxicity or refractory disease after the current systemic therapy. Although the standard drug for HAI is FUDR, efficacy of the current HAI regimen with 5-FU appears almost similar. To improve survival further, measures to increase candidates for resection, reduce liver and lung relapses, and reduce complications are necessary.

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ORIGINAL ARTICLE

Post-cholecystectomy Quality of Life: A Prospective Multicenter Cohort Study of Its Associations with Preoperative Functional Status and Patient Demographics

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Abstract
Purpose This study analyzed patient demographics and preoperative functional status for associations with post-cholecystectomy quality of life (QOL).
Methods This prospective study analyzed 159 cholecystectomy patients at two tertiary academic hospitals. All patients completed the SF-36 and the gastrointestinal quality of life index (GIQLI) at baseline and at 3 and 6 months postoperatively. The 95% confidence intervals for differences in responsiveness estimates were derived by bootstrap estimation. Scores derived by these instruments were interpreted by generalized estimating equation (GEE) before and after cholecystectomy.
Results The examined population significantly ($p<0.05$) improved in both SF-36 subscales and GIQLI subscales. After adjusting for time effects (time, and time^2) and baseline predictors, GEE approaches revealed the following explanatory variables for QOL: time, time^2, age, gender, preoperative GIQLI score, body mass index, and number of comorbidities.
Conclusion The data revealed dramatically improved post-cholecystectomy QOL. However, QOL change was simultaneously associated with preoperative functional status and demographic characteristics.

Keywords SF-36 · GIQLI · Cholecystectomy · Bootstrapping · GEE

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Introduction

Cholecystectomy is commonly performed for symptomatic cholelithiasis or cholecystitis.[1,2] Accurately predicting quality of life (QOL), a standard outcome measure,[3,4] after cholecystectomy is important when selecting treatment modality and for allocating scarce medical resources.

Cholecystectomy outcome is reportedly affected by hospital size and various patient characteristics.[5–7] Few studies of cholecystectomy outcome have analyzed longitudinal data over more than two time points, and few have explored the relationships between demographics, preoperative functional status, and QOL over periods exceeding 3 months.[4,6] Secondly, most have described US or European populations, so their results may not be applicable to populations elsewhere.[8–10] Thirdly, no longitudinal studies have applied statistical methodology to control for right censoring and inter-correlation resulting from repeated measures obtained from the same patient pool.[11]

We previously analyzed 145 laparoscopic cholecystectomies (LC) and 14 open cholecystectomies (OC) to compare responsiveness and minimal clinically important differences between the gastrointestinal quality of life (GIQLI) and the SF-36.[12] However, in this study, we included more OC procedures and extended our surveys for 6 months. This study therefore examined whether QOL (in individual patients) trends are linear and whether patient demographics and preoperative functional status are longitudinally associated with post-cholecystectomy QOL.

Methods

Study Design and Sample

All patients who had undergone cholecystectomy performed between May 2007 and June 2008 by any one of three senior surgeons (KT, HH, YH) practicing at two tertiary academic hospitals in southern Taiwan were surveyed by the SF-36 and the GIQLI. Twenty-two cholecystectomies performed by low-volume surgeons (defined as surgeons who had performed four or fewer surgeries within the previous year) were excluded from analysis. All involved institutions approved this study of human subjects. As Fig. 1 shows, 164 subjects were eligible for the study. Patients with cognitive impairment (n=1), severe organ diseases (n=1), or psychiatric diseases (n=1) were excluded. Of the 161 eligible subjects who gave written consent and were enrolled in the study at baseline, two were excluded due to the conversion of LC to OC, and two were excluded because they did not undergo postoperative assessments. The remaining 122 LC subjects and 32 OC subjects all completed preoperative and 3- and 6-month postoperative assessments.

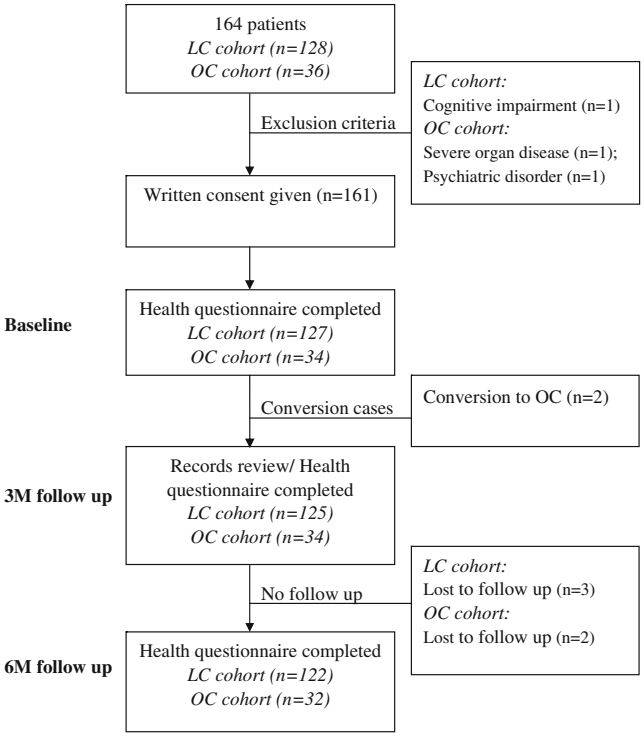

Figure 1 Changes in population size during the study. The *flow chart* shows numbers of subjects meeting initial exclusion criteria, those who voluntarily withdrew during the study, and those lost to follow-up.

Instruments and Measurements

In this study, each SF-36 subscale (Chinese version) was administered to measure QOL outcomes and each served as a dependent variable. As described in the literature, the physical component summary scale (PCS) and mental component summary scale (MCS) were calculated using norm-based scoring methods to compare QOL in the study population with that of the general Taiwan population.[13,14] A PCS or MCS value of 50 was considered average for the general Taiwan population. Both the PCS and MCS have been widely adopted and were used in the present study to provide an overall index of QOL and to further evaluate the longitudinal changes in generic measures as a whole.[15]

The GIQLI is recognized as a valid and reliable instrument for measuring functional status, especially in patients undergoing cholecystectomy.[12] Each of its 36 items is scored from 0 to 4, with a higher score indicating better health status, and the total GIQLI score ranges from 0 to 144. A Chinese version of the GIQLI has demonstrated validity.[16]

The following patient data obtained by records review and questionnaire interview were tested as independent variables in this study: age, gender, body mass index (BMI), current comorbidities, alcohol and tobacco use, preoperative functional status (GIQLI subscale), operating time, ASA score, average length of stay, and re-hospitalization within 30 days.

Statistical Analysis

The unit of analysis in this study was the individual cholecystectomy patient. After determining the distribution of observed subjects and those lost to follow-up at different time points, descriptive statistical data were compared between the LC and OC cohorts.

The relative magnitude of change between two time intervals was assessed by calculating effect size, which is the difference between the mean scores for two time intervals divided by the standard deviation of the previous (or formal) time interval score.[17] This method standardizes the extent of change measured by an instrument to allow comparisons between instruments. Effect sizes of 0.2, 0.5, and 0.8 are typically regarded as indicating small, medium, and large changes, respectively.[17] Due to the skewed distribution, bias-corrected and accelerated bootstrapping was performed with 1,000 replications to calculate effect size, difference in effect size, and 95% confidence intervals.[18]

Longitudinal data were characterized by repeated observations of the same subjects with high between-subject variability but low within-subject variability.[11,12] Firstly, trends in QOL outcomes over time were determined. A variable time (in months) was introduced into the generalized estimating equations (GEE) model with the PCS and MCS as the outcome variable to determine average monthly score improvements. Since QOL improvements apparently decreased over time, a quadratic time variable was also introduced.

Univariate models were then used to assess effective predictors of change in QOL at different time points when using the baseline preoperative measures. These effective predictive variables were included as covariates in the GEE approach because they were statistically significant in the multivariate models and are recognized in the literature as valid QOL predictors.[4–6] Restated, the intent was to model the dependent variable (mean PCS and mean MCS) as a function of time, time^2, age, gender, BMI, number of comorbidities, baseline emotional score, and baseline physical score. The Stata Statistical Package, version 9.0 (Stata Corp., College Station, TX, USA) was used for all statistical analyses, and a p value<0.05 was considered statistically significant.

Results

The age and gender distributions in the study sample were consistent with those observed in the national population (data not shown). At baseline, the LC and OC cohorts did not significantly differ in age, gender, BMI, current comorbidities, alcohol or tobacco use, operating time, ASA score, 30-day re-hospitalization, or preoperative functional status. Average

Table 1 Patient Characteristics

Items	LC cohort (n=125)	OC cohort (n=34)
Age (years), mean	55.48 (15.12)	62.21 (13.68)
Gender		
Female	52	20
Male	73	14
Body mass index (kg/m^2)	24.24 (4.17)	24.86 (4.60)
Current comorbidities, mean	0.54 (0.89)	0.78 (1.42)
Current alcohol use		
Yes	20	7
No	105	27
Current tobacco use		
Yes	22	10
No	104	24
Operation time (min), mean	80.41 (39.23)	137.86 (69.08)
ASA score	2.08 (0.47)	2.21 (0.43)
Length of stay (days), mean[a]	4.90 (3.92)	9.15 (4.74)
Re-hospitalization within 30 days		
Yes	121	34
No	4	0
Preoperative GIQLI, mean		
Symptoms	55.38 (14.68)	55.22 (16.31)
Emotional dysfunction	11.97 (7.46)	12.93 (3.87)
Physical dysfunction	17.69 (6.27)	16.64 (6.08)
Social dysfunction	11.77 (3.90)	11.93 (3.63)

LC laparoscopic cholecystectomy, *OC* open cholecystectomy

[a] Other than average length of stay, patient characteristics did not statistically differ (p<0.05) between LC and OC cohorts. For each item, standard deviations are given in parentheses

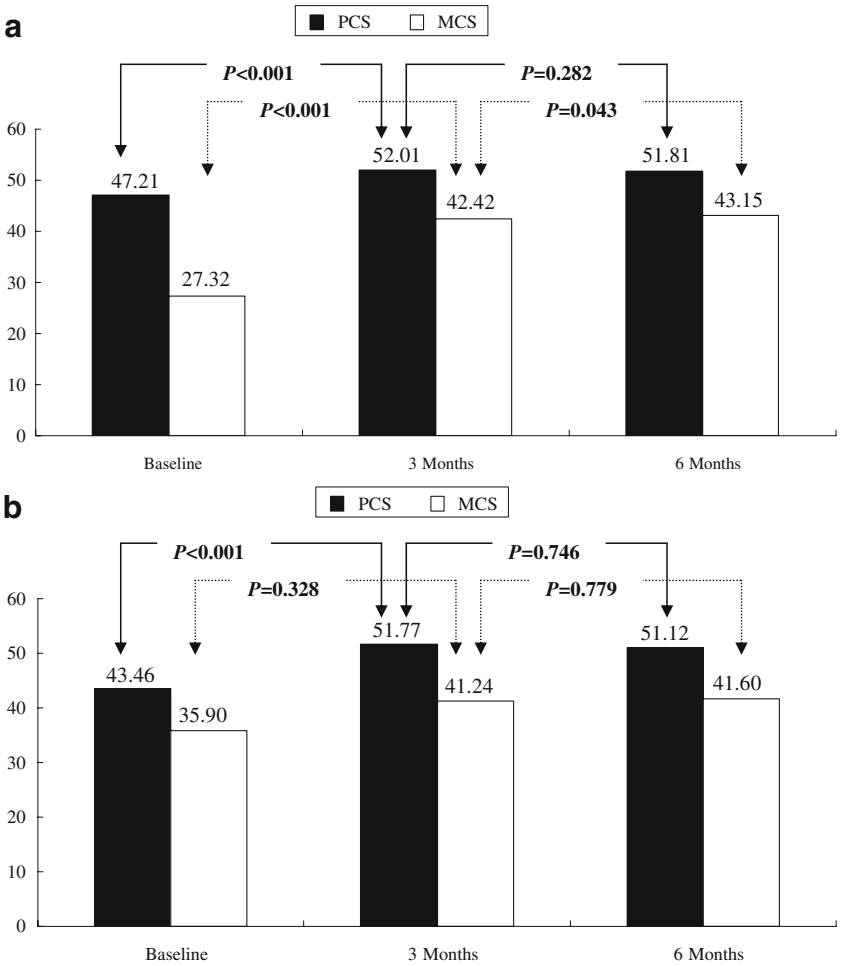

Figure 2 **a** Quality of life outcomes before and after laparoscopic cholecystectomy; *p* value denotes the significance of differences between each time interval and baseline. *PCS* physical component scale, *MCS* mental component scale. **b** Quality of life outcomes before and after open cholecystectomy; *p* value denotes significance of differences between each time interval and baseline. *PCS* physical component scale, *MCS* mental component scale.

hospital stay was significantly longer in the OC cohort than in the LC cohort (9.15 vs. 4.90 days, respectively, $p<0.05$; Table 1).

Figure 2 shows the mean values and *p* values for PCS and MCS at each time point before and after cholecystectomy. In the LC cohort, PCS and MCS improved significantly ($p<0.05$) between the preoperative and third month postoperative periods. If the third month after discharge is considered baseline, MCS had significantly ($p<0.05$) improved by the sixth month after discharge, but PCS had not ($p=0.282$). In the OC cohort, PCS had significantly ($p<0.05$) improved between the preoperative period and the third month after discharge. However, if the third month after discharge is considered baseline, the change in PCS did not significantly differ (third month vs. sixth month=51.77 vs. 51.12, $p=0.746$). The MCS did not significantly improve between the preoperative period and the third or sixth months after discharge. Interestingly, post-cholecystectomy PCS and MCS were above and below the norm, respectively.

Table 2 compares the effect sizes between the LC cohort and the OC cohort at different time intervals throughout the

Table 2 Effect Size for Quality of Life Outcomes: Comparison of LC and OC Cohorts

Items	LC cohort Effect size (3months vs. baseline)	OC cohort Effect size (3months vs. baseline)	LC–OC Mean difference [estimate (95% CI)][a]	LC cohort Effect size (6 vs. 3months)	OC cohort Effect size (6 vs. 3months)	LC–OC Mean difference [estimate (95% CI)][a]
Physical component scale (PCS)	0.39	1.11	−0.72 (−1.02, −0.42)	−0.03	−0.09	0.06 (−0.05, 0.17)
Mental component scale (MCS)	0.67	0.22	0.45 (0.24, 0.67)	0.04	0.02	0.02 (−0.07, 0.10)

LC laparoscopic cholecystectomy, *OC* open cholecystectomy

[a] Mean difference is presented as effect size (95% confidence intervals obtained by bootstrapping)

Table 3 Univariate Models of Relationship Between Demographics, Preoperative Functional Status, and Quality of Life after Cholecystectomy

Variables	LC cohort (n=125)				OC cohort (n=34)			
	PCS		MCS		PCS		MCS	
	β	p	β	P	β	P	β	p
Age	−0.19	0.034	−0.18	0.040	0.45	0.013	0.35	0.061
Gender (female vs. male)	23.96	0.734	78.15	0.419	9.02	0.531	30.00	0.058
Body mass index	0.23	0.010	0.21	0.016	0.76	<0.001	0.51	0.003
Current comorbidities	−0.17	0.043	−0.18	0.039	−0.37	0.043	−0.39	0.040
Current alcohol use (positive vs. negative)	16.47	0.971	84.91	0.230	12.33	0.063	23.18	0.236
Current tobacco use (positive vs. negative)	30.03	0.410	89.31	0.142	17.25	0.072	24.00	0.200
Baseline symptom score	−0.03	0.777	−0.08	0.310	−0.17	0.362	−0.32	0.054
Baseline emotional score	−0.20	0.012	−0.32	<0.001	−0.67	<0.001	−0.66	<0.001
Baseline physical score	−0.30	<0.001	−0.36	<0.001	−0.35	0.031	−0.54	0.003
Baseline social score	−0.01	0.887	0.03	0.796	−0.12	0.513	−0.10	0.604
Operation time	0.01	0.965	0.08	0.396	0.08	0.665	0.10	0.609
ASA score	−0.08	0.364	−0.09	0.314	−0.11	0.564	−0.28	0.137
Average length of stay	−0.01	0.935	0.01	0.945	−0.01	0.975	−0.21	0.273
Re-hospitalization in 30 days (positive vs. negative)	29.52	0.417	93.25	0.099	–	–	–	–

Coefficients of chi-square or Pearson correlation

LC laparoscopic cholecystectomy, *OC* open cholecystectomy, *PCS* physical component scale, *MCS* mental component scale

6-month survey. The MCS effect size for the periods between the preoperative and 3-month survey and between the 3- and 6-month surveys was much larger in the LC cohort than in the OC cohort. However, the PCS effect size for the same period was much larger in the OC cohort than in the LC cohort. Differences were considered statistically significant at the 0.05 level if confidence intervals excluded zero. As of the preoperative and 3-month surveys, the LC cohort were more responsive than the OC cohort, and MCS significantly differed (0.45, 95% CI 0.24–0.67). However, the OC cohort revealed a relatively stronger response than the LC cohort did between 3 months and baseline in PCS (0.72, 95% CI 0.42–1.02).

Table 3 shows the univariate models describing the relationship between demographics, preoperative functional status, and post-cholecystectomy QOL. In both the LC and OC cohorts, baseline age, BMI, current comorbidities, and preoperative functional status (GIQLI emotional and physical subscales) were significantly related ($p<0.05$) to PCS and MCS.

Table 4 summarizes the results of all of relevant GEE analyses. The first model, which compares trends in QOL between the two cohorts over time, indicated that QOL outcomes in the LC cohort varied but gradually decreased. In the OC cohort, the regression coefficient for variable time and variable time^2 in the PCS were 6.88 ($p<0.001$) and −0.71 ($p<0.001$), respectively; those in the MCS were 7.30 ($p<0.001$) and −0.76 ($p<0.001$), respectively.

The second model, which describes the relationships between known baseline demographics and their associations with time and QOL, revealed that in both cohorts, BMI was significantly and positively related to PCS and MCS. However, age and current comorbidities were significantly and negatively related to PCS and MCS, which indicates the high frequency of PCS and MCS in patients who are young, have high BMI, and have few comorbidities. All observed effects of baseline demographics varied over time.

The third model describes the longitudinal relationship between preoperative functional status and QOL after adjustment for time, baseline demographics, and their interactions with time. In both the LC and OC cohorts, baseline emotional score was significantly and negatively related to PCS, but baseline emotional score and baseline physical score were significantly and positively related to PCS and MCS. Again, all associations with baseline demographics and preoperative functional status varied over time.

Discussion

This follow-up study compared the longitudinal relationship between demographics, preoperative functional status, and post-cholecystectomy QOL between two entirely independent cohorts. Although they substantially differed

Table 4 Longitudinal Relationship Between Demographics, Preoperative Functional Status, and Quality of Life After Cholecystectomy

Model	Variables	LC cohort				OC cohort			
		PCS		MCS		PCS		MCS	
		β	P	β	P	β	P	β	p
1	Intercept	47.21	<0.001	43.46	<0.001	28.08	<0.001	27.33	<0.001
	Time	2.48	<0.001	3.99	0.004	6.88	<0.001	7.30	<0.001
	Time^2	−0.24	<0.001	−0.41	0.008	−0.71	<0.001	−0.76	<0.001
2	Intercept	45.80	<0.001	45.50	<0.001	26.64	0.006	19.76	0.002
	Time	4.86	<0.001	5.17	<0.001	12.87	<0.001	13.57	<0.001
	Time^2	−0.24	<0.001	−0.25	<0.001	−0.72	<0.001	−0.76	<0.001
	Age	−0.13	0.042	−0.12	0.027	−0.06	0.046	−0.07	0.036
	Gender (male vs. female)	−0.02	0.781	−0.04	0.405	−0.03	0.573	−0.05	0.052
	Body mass index	2.23	<0.001	3.79	<0.001	2.11	<0.001	1.65	0.009
	Body mass index × time	−0.90	0.021	−1.02	0.001	−0.68	0.020	−0.55	0.036
	Current comorbidities	−1.99	0.012	−2.19	<0.001	−0.27	0.029	−0.50	0.035
	Current comorbidities × time	0.11	0.029	0.53	0.004	0.08	0.042	0.07	0.011
3	Intercept	45.44	<0.001	38.80	<0.001	16.77	0.024	17.87	<0.001
	Time	4.86	<0.001	7.96	<0.001	12.06	<0.001	13.59	<0.001
	Time^2	−0.24	<0.001	−0.41	0.008	−0.71	<0.001	−0.76	<0.001
	Age	−0.09	0.037	−0.10	0.046	−0.06	0.037	−0.08	0.023
	Gender (male vs. female)	−0.01	0.703	−0.02	0.301	−0.02	0.063	−0.03	0.057
	Body mass index	2.23	<0.001	2.79	<0.001	5.11	<0.001	3.65	<0.001
	Body mass index × time	−0.90	0.021	−1.02	0.001	−1.68	<0.001	−0.25	0.013
	Current comorbidities	−1.08	0.012	−1.90	<0.001	−0.27	0.029	−0.30	0.035
	Current comorbidities × time	0.22	0.041	0.53	0.004	0.08	0.022	0.07	0.011
	Baseline emotional score	−0.59	0.008	0.26	0.006	−1.87	<0.001	1.91	<0.001
	Baseline emotional score × time	0.09	0.042	−0.09	0.040	0.15	0.010	−0.14	0.022
	Baseline physical score	0.58	0.009	1.51	0.007	0.81	0.024	1.01	0.005
	Baseline physical score × time	−0.08	0.042	−0.15	0.034	−0.04	0.046	−0.02	0.047

Model 1 describes quality of life changes over time; model 2 describes associations between demographics and quality of life; model 3 describes associations between demographics, preoperative functional status, and quality of life (see Table 1 for other definitions)

in average length of stay, their remarkably similar data strongly support the validity of the results.

To clarify trends in PCS and MCS over time, survey data were analyzed using the categorical time variable before and after cholecystectomy. The results indicated that PCS and MCS improved significantly during the first 3 months after discharge ($p<0.001$) then stabilized during the next 6 months. These results reveal that change trends for PCS and MCS may reflect the added complexity of lower extremity involvement.[12]

For MCS, effect size for the period between the preoperative and 3-month surveys was significantly larger in the LC cohort than in the OC cohort, indicating that compared to improvement in overall physical function, the magnitude of improvement in overall mental functioning was larger in the LC cohort than in the OC cohort. However, the change in effect size was significantly larger in the OC cohort than in the LC cohort. This finding was not unexpected since pain relief and improved symptoms are directly related to cholecystectomy outcome.[4,12] Before surgery, the LC cohort scored lower in emotional dysfunction but higher in physical dysfunction score than the OC cohort did. Consequently, improved pain relief and symptom function may improve both physical and emotional function as well as overall QOL. This improvement may explain why the effect size for PCS was larger in the OC cohort than in the LC cohort whereas the effect size for MCS was larger in the LC cohort than in the OC cohort immediately after cholecystectomy.

Additionally, the similar PCS and MCS between the LC and OC cohorts as of the 3- and 6-month surveys indicate that QOL outcomes in cholecystectomy patients are not entirely linear at the group level, which is consistent with the literature.[19] Studies of QOL outcomes over time[4,19,20] suggest that linear models of PCS and MCS progression constructed by curve fitting of individual longitudinal data

may be oversimplified. Although linear modeling may be useful for comparing group means in short-term randomized clinical trials, they clearly do not reflect clinical reality.[21]

This study confirmed previous findings that QOL improvement is inversely related to age.[6,20] Although the literature indicates that patients in advanced stages of a disease tend to have more comorbidities and less social support than patients in early stages do, the number of comorbidities and social support variables in the present study were controlled in the GEE models. Therefore, the observed QOL improvements may reflect selection bias caused by more stringent application of selection criteria by referring physicians based upon patient demographics, suggesting greater likelihood of improvement. Alternatively, because alleviating pain and other symptoms are the main goals of cholecystectomy, surgeons treating younger patients may tend to focus on QOL. However, the questions raised by these caveats require further study.

The literature on the influence of BMI on post-cholecystectomy QOL is sparse. In this study, the significant positive relationships between BMI and QOL outcomes observed in both the LC and OC cohorts indicate that BMI is positively associated with PCS and MCS. Before cholecystectomy, the mean scores for the role limitation domains due to physical functioning and emotional problems were relatively lower in patients with high BMI than in those with low BMI, probably because roles are severely limited by physical function and emotional status (data not shown). Such patients often regain satisfactory QOL once their physical limitations and emotional problems are reduced or eliminated by surgery. Consequently, alleviating role limitations can increase scores in other QOL dimensions, which would then increase PCS and MCS.

Notably, the number of comorbidities was inversely related to QOL in terms of overall physical and mental function, which is consistent with the reported association between increased comorbidity and poor post-cholecystectomy PCS and MCS.[4,6,8]

Finally, the single best predictor of PCS and MCS throughout the 6-month study was preoperative functional status, which is consistent with reports[4,20] that the best predictors of postoperative QOL are preoperative emotional and physical function scores. Therefore, effective counseling is essential for apprising patients of expected post-cholecystectomy impairments. If QOL outcomes are considered benchmarks, then preoperative functional status, which is a major predictor of postoperative outcome, is crucial.

Although all research questions were satisfactorily addressed, one limitation should be noted. Prospective data were collected for a cohort in which the earliest patients were enrolled in 2007. Therefore, varying follow-up periods may have caused selection bias.[22] Nonetheless, PCS and MCS did not significantly differ between patients who did and did not complete the entire 6-month study (data not shown).

In conclusion, factors other than surgical outcome should be considered when evaluating post-cholecystectomy QOL. All the significant factors identified in this study can be addressed in preoperative consultations to educate cholecystectomy candidates regarding the expected course of recovery and functional outcomes. Patients should also be advised that postoperative QOL depends on preoperative functional status and demographic profile. The results of this study can be generalized to other Taiwan hospitals as well as to other countries with similar social and cultural practices.

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ORIGINAL ARTICLE

A Central Pancreatectomy for Benign or Low-Grade Malignant Neoplasms

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Abstract
Inctroduction A central pancreatectomy is a parenchyma-sparing procedure that is performed to reduce long-term endocrine and exocrine insufficiency.
Method In this study, we analyzed the perioperative course, the frequency of postoperative onset of diabetes mellitus, and long-term change of body weight in patients undergoing a central pancreatectomy, in comparison to the patients undergoing a distal pancreatectomy for low-grade neoplasms including cystic neoplasms and neuroendocrine tumors.
Results and Discussion The rate of postoperative complications including grade B/C pancreatic fistula was no different between both groups. Only one patient undergoing a central pancreatectomy (4.7%) developed new onset of mild diabetes, whereas 35% in the distal pancreatectomy group developed new onset or worsening diabetes (p=0.0129). The body weight in the distal pancreatectomy group was significant lower than that in the central pancreatectomy group at 1 and 2 years after surgery (1 year; P<0.0001, 2 years; P=0.0055), and the body weight in the patients undergoing a central pancreatectomy improved to preoperative values within 2 years after surgery.
Conclusion A central pancreatectomy is a safe procedure for the treatment of low-grade malignant neoplasms in the pancreatic body; the rate of onset of diabetes is minimal, and the body weight improves early in the postoperative course.

Keywords Central pancreatectomy · Postoperative complication · Diabetes mellitus · Body weight change

Introduction

In recent years, the incidental discovery rate of benign or low-grade malignant neoplasms of the pancreas has increased with the advance of diagnostic imaging system.[1,2] The resection of neoplasms located in the pancreatic body traditionally has been accomplished by a distal pancreatectomy (DP) as a standard operation.[3–5] However, the use of a DP for isolated, small, and low-grade malignant neoplasms in the pancreatic body, such as noninvasive intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), benign neuroendocrine tumor (NET), and pancreatic metastases from other tumors, results in the removal of unaffected normal pancreatic tissue, increasing the risk of endocrine and exocrine malfunction. Whereas tumor enucleation, which is considered an indication for benign neoplasm such as an insulinoma, should be avoided when the main pancreatic duct may be injured or the margins are not defined.[6] Under these circumstances, a central pancreatectomy (CP) has been proposed as an alternative technique in the patients with isolated and small neoplasms in the pancreatic body, not required with lymph node dissection, for preserving the pancreatic parenchyma and reducing the risk of exocrine and endocrine insufficiency.[7–9]

In 1957, Guillemin and Bessot[10] first performed a central segmental pancreatic resection for a patient with pancreatitis, and 2 years later, Letton and Wilson[11] performed in two cases of severe traumatic injury of the pancreatic body. The first CP for a neoplasm was done by Dagradi and Serio[12] in 1984 for benign insulinoma. Since then, several institutions have reported perioperative

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course and postoperative complications of this technique using the following terminology: CP,[7–9] middle pancreatectomy,[13] or middle segmental pancreatectomy.[14]

Most reports revealed higher pancreatic fistula rates of CP, as opposed to standard pancreatic resection.[9,15,16] These reports are convinced because a CP requires handling two divided edges of the pancreas, creating two opportunities for pancreatic fistula. Regarding pancreatic function, a few reports revealed preservation of endocrine and exocrine functions in the patients undergoing a CP, in comparison to those undergoing a DP.[6,13,14] However, the DP group in the previous studies enrolled the patients with pancreatic ductal carcinoma, requiring lymph node dissection and adjuvant therapy, and chronic pancreatitis.[3,17] Indeed, these patients may have impaired pancreatic function after surgery; therefore, the comparison of both surgical techniques may not be suitable for patients with high-grade malignancies or chronic pancreatitis.

In the present study, evaluating the benefit of a CP more accurately, we analyzed the patients with benign or low-grade malignant neoplasms in terms of postoperative complications, onset of diabetes mellitus, and body weight change.

Material and Methods

Patients

Data were prospectively collected in a database from October 1999 through September 2008 for the patients undergoing a CP at Wakayama Medical University Hospital (WMUH). The indication for surgery was a symptomatic or an asymptomatic localized neoplasm in the pancreatic body of unknown histology. The potential suitability for a CP was determined by preoperative imaging in all cases, such as ultrasonography (US) and computed tomography (CT), with most patients undergoing magnetic resonance imaging, or endoscopic US, or endoscopic retrograde pancreatography.

To evaluate perioperative and long-term functional outcomes for a CP, we compared a CP and a DP for only patients with benign or low-grade malignant neoplasms during the same time. Informed consent was obtained from all patients, and this clinical study was conducted according to the guidelines of the Ethical Committee of WMUH.

Surgical Procedure for a CP

After a midline upper abdominal laparotomy, the lesser sac was opened by division of the gastrocolic ligament preserving the gastroepiploic vessels. The anterior aspect of the pancreas was exposed by dividing the adhesions between the posterior surface of the stomach and the pancreas. Intraoperative US of the pancreas was used to detect the tumor and determine the relationship of the tumor to the vascular structure and the main pancreatic duct. The superior mesenteric, portal, and splenic veins were dissected free from the posterior aspect of the pancreas, with care taken to ligate multiple small side branches to the pancreas. The lesion, localized in the body of the pancreas, was resected with a margin of at least 1 cm to both cut pancreatic ends. Both cut ends were submitted for an intraoperative frozen section analysis in all patients. No anastomoses were performed in the proximal pancreatic remnant. Reconstruction of the distal pancreatic remnant was performed by a duct-to-mucosal, an endo-to-side pancreaticojejunostomy in 21 patients, and a pancreaticogastrostomy in three patients. External suture rows were performed as a single suture between the remnant pancreatic capsule, parenchyma, and jejunal or gastric seromuscular. Internal suture rows, duct-to-mucosa, were performed between the pancreatic ductal and jejunal or gastric mucosa.[18] A 5-French polyethylene

Table 1 Characteristics of 52 Patients with Benign or Low-Malignant Neoplasms of the Pancreatic Body

Characteristics	Central pancreatectomy (n=24)	Distal pancreatectomy (n=28)	P value
Median age [year (range)]	69.0 (26–81)	68.5 (20–78)	0.7550
Gender ratio, (male/female)	10/14	9/19	0.4771
Pathology			
IPMN (%)	16 (66)	13 (46)	0.1430
Minimally invasive carcinoma	1	1	
Carcinoma in situ	2	2	
Adenoma	13	10	
Mucinous cystic neoplasm (%)	2 (8)	3 (10)	0.7716
Carcinoma in situ	0	1	
Adenoma	2	2	
Serous cystic adenoma	2 (8)	4 (14)	0.5030
Solid pseudopapillary tumor	1 (4)	1 (3)	0.9114
Benign neuroendocrine tumor	2 (8)	5 (17)	0.3150
RCC metastasis	1 (4)	0 (0)	0.2754
Lymphoepithelial cyst	0 (0)	1 (3)	0.3499
Accessory spleen	0 (0)	1 (3)	0.3499
Mean size of tumor (cm)	3.0±1.0	3.5±2.0	0.0191

IPMN intraductal papillary mucinous neoplasm, *RCC* renal cell carcinoma

pancreatic duct drainage tube (Sumitomo Bakelite Co., Japan) was used in 12 patients and no stent in 12 patients. One 10-mm Penrose drain was routinely placed near the pancreatic anastomosis.[19]

Perioperative Course and Postoperative Complications

Perioperative mortality, defined as in-hospital death after surgery, and postoperative complications were evaluated. The pancreatic fistula definition was retrospectively assessed according to the International Study Group on Pancreatic Fistula (ISGPF) recommendations.[20] Intra-abdominal abscess was defined as intra-abdominal fluid collection with positive cultures identified by US or CT associated with persistent fever and elevations of white blood cells.[18,19] Delayed gastric emptying was defined as prolonged aspiration of 500 ml/day from a nasogastric tube left in place for ≧10 days after surgery, the need for reinsertion of a nasogastric tube, or the failure to maintain oral intake by postoperative 14th postoperative day.[18,19]

Onset of Diabetes Mellitus and Change of Body Weight

The follow-up was based on clinical, radiologic, and laboratory assessments every 6 to 12 months, to evaluate tumor recurrence as well as the endocrine and exocrine function.

The onset of diabetes was evaluated by monitoring the fasting glucose blood level and HbA1c levels. Patients suspected of having diabetes were diagnosed using an oral glucose tolerance test and thereafter were treated by diabetes specialists. New-onset diabetes was defined as diabetes with requirement of diet and/or medical treatment. Worsening diabetes was defined as deterioration in the metabolic control of previously diagnosed diabetes, thus requiring a modification of the medical treatment.

Percent change in body weight (%BW) and the presence of severe diarrhea (loose bowel movements more than ten times per day) were assessed as the exocrine function in both groups (CP and DP).

Table 2 Perioperative Course and Postoperative Complications

Variable	Central pancreatectomy (n=24)	Distal pancreatectomy (n=28)	P value
Operative median time [min (range)]	279 (205–399)	155 (100–401)	<0.0001
Blood loss median volume [ml (range)]	355 (20–4070)	425 (20–1630)	0.5882
Blood transfusion (%)	3 (13)	2 (7)	0.5136
Median size of remnant pancreatic tail [cm (range)]	5.6 (1.5–9.8)	–	
Comorbid pancreatitis	0 (0)	0 (0)	–
Reconstruction			
Pancreaticogastrostomy (%)	3 (12)	–	
Pancreaticojejunostomy (%)	21 (88)	–	
Overall morbidity (%)[a]	7 (29)	5 (18)	0.3346
Surgical complication (%)			
Pancreatic fistula[b]			
Grade A	12 (50)	6 (21)	0.0309
Grade B	3 (13)	4 (14)	0.8505
Grade C	0 (0)	0 (0)	–
Intra-abdominal abscess	1 (4)	2 (7)	0.6463
Delayed gastric emptying	1 (4)	0 (0)	0.2754
Wound infection	1 (4)	1 (3)	0.9114
Hemorrhage	0 (0)	0 (0)	–
Need of reoperation (%)	0 (0)	0 (0)	–
Need of interventional procedure (%)	3 (13)	5 (18)	0.5935
Nonsurgical complication (%)			
Pneumonia (%)	1 (4)	0 (0)	0.2754
Hepatic failure (%)	1 (4)	0 (0)	0.2754
Postoperative hospital stay [day (range)]	21.5 (11–58)	14.5 (8–57)	0.0362
Mortality			
During 30 postoperative days	0 (0)	0 (0)	–
During hospital stay	1 (4)	0 (0)	0.2754

[a] Overall morbidity is represented as morbidity other than grade A pancreatic fistula

[b] The pancreatic is defined according to the International Study Group on Pancreatic Fistula recommendation.

Statistical Analysis

Continuous variables were expressed as the mean±standard deviation. Comparison between two groups was performed with the Mann–Whitney *U* test, while categorical variables were compared by the χ^2 test and Fisher exact test when cell counts were less than five. A *P* value of <0.05 was considered to be statistically significant.

Results

Clinical Characteristics

Table 1 shows the clinical characteristics of the two groups (CP and DP). Twenty-four patients (ten men and 14 women) underwent a CP and 28 (nine men and 19 women) underwent a DP. The median age was 69.0 (range, 26–81 years) in the CP group and 68.5 years (range, 20–78 years) in the DP group. The definitive histology of the resected neoplasms in the CP group were 16 IPMN (13 branch type and three mixed type), two MCN, two serous cystadenoma, one solid pseudopapillary tumor, two benign NET, and one pancreatic metastasis from renal cell carcinoma, whereas that in the DP group included 13 IPMN (four branch type, three mixed type, and six main-duct type), three MCN, four serous cystadenoma, one solid pseudopapillary tumor, and five benign NET. Regarding IPMN, the incidence of main-duct type in the DP group was higher than that in the CP group (46% vs. 0%, *P*=0.0138). No differences were found between the two groups regarding age, gender, and incidence of each disease; however, the patients undergoing a DP had a larger neoplasm than the patients undergoing a CP (3.0±1.0 vs. 3.5±2.0 cm, *P*=0.0191; Table 1).

Surgical Resections and Perioperative Data

In addition to a pancreatic resection, one patient underwent cholecystectomy due to cholecystolithiasis in the CP group and 26 (93%) splenectomy, four cholecystectomy due to

Table 3 Onset of Diabetes Mellitus and Body Weight Change During More than 6 Months Follow-up After Surgery in Patients Undergoing Central Pancreatectomy and Distal Pancreatectomy

	Central pancreatectomy	Distal pancreatectomy	*P* value
Median follow-up [month (range)]	33.5 (3–111)	26.5 (3–110)	
Endocrine function			
New onset or worsening diabetes (%)	1/21 (5)	9/26 (35)	0.0129
New diabetes	1	6	
Diet treatment	1	2	
Oral drug	0	2	
Insulin	0	2	
Worsening diabetes[a]	0	3	
Diet treatment→oral drug	0	1	
Oral drug→insulin	0	2	
Body weight change			
Body weight change at 6 months after surgery			
Available for follow-up	21	26	
Median %BW	97.2 (91.8–110.3)	93.0 (80.0–103.1)	0.0003
Decreasing %BW <95%, n (%)	4 (19)	18 (69)	0.0006
Decreasing %BW <90%, n (%)	0 (0)	6 (23)	0.0184
Body weight change at 1 year after surgery			
Available for follow-up	20	26	
Median %BW	99.5 (92.1–113.2)	92.5 (76.9–102.1)	<0.0001
Decreasing %BW <95%, *n* (%)	2 (10)	19 (73)	<0.0001
Decreasing %BW <90%, *n* (%)	0 (0)	8 (31)	0.0063
Body weight change at 2 years after surgery			
Available for follow-up	17	19	
Median %BW	100.0 (92.1–117.6)	92.9 (76.9–108.9)	0.0055
Decreasing %BW <95%, *n* (%)	2 (12)	12 (63)	0.0016
Decreasing %BW <90%, *n* (%)	0 (0)	5 (26)	0.0164
Postoperative severe diarrhea (%)	0 (0)	0 (0)	–

[a] Worsening diabetes is defined as a deterioration in the metabolic control of previously diagnosed diabetes, requiring a modification of the medical treatment

%BW percent change of body weight compared to the preoperative body weight

cholecystolithiasis, and one left nephrectomy due to renal cell carcinoma in the DP group. In the CP group, the median size of distant remnant was 5.6 cm (range, 1.5–9.8 cm). The pathological findings of stump in all resected specimens revealed no evidence of chronic pancreatitis, such as stromal fibrosis or lymphoplasmacytic infiltration, associated with primary disease including IPMN. Although the CP group required a longer operative time than the DP group (median; 279 vs. 155 min, $P<0.0001$), the operative blood loss volume (median, 355 vs. 425 ml, $P=0.5880$) and the percentage of patients needing blood transfusions (13% vs. 7%, $P=0.5136$) were not significantly different between both groups (Table 2).

Perioperative Course and Complications

The mortality during the first 30 postoperative days was zero in both groups, and one patient of IPMN with severe liver cirrhosis undergoing a CP died 55 days after surgery due to hepatic failure, uncontrollable ascites, icterus, and gastrointestinal bleeding. Although the incidence of grade A pancreatic fistula (transient fistula without any clinical impact) in the CP group was 50%, the rate of clinically significant fistula (grade B and C by the ISGPF)[20] was only 13%, which was not a significantly different incidence in the DP group (14%, $P=0.8505$). The rate of overall morbidity excluding grade A pancreatic fistula was not significantly different between the two groups (CP vs. DP; 29% vs. 18%, $P=0.3346$), and no differences were found between the two groups regarding the need for interventional procedures (CP vs. DP; 13% vs. 18%, $P=0.5935$). The postoperative hospital stay in the DP group was shorter than that in the CP group (median; 21.5 days vs. 14.5 days, $P=0.0362$).

Postoperative Onset of Diabetes Mellitus and Change of Body Weight

The pancreatic function was analyzed in the 21 patients undergoing a CP and 26 undergoing a DP with more than 6 months follow-up after surgery. The median follow-up was 33.5 months (range, 3–111 months) for the CP group and 26.5 months (range, 3–110 months) for the DP group.

No patient had preoperative diabetes in the CP group, whereas three patients had preoperative diabetes in the DP group. Only one patient (4.7%) developed new onset of mild diabetes treated with diet alone in the CP group, in comparison to nine (35%) patients in the DP group ($P=0.0129$) who developed new onset diabetes or worsening diabetes (Table 3).

The ratios of patients with decreasing %BW at 6 months, 1 year, and 2 years after surgery in the DP group were higher than that in the CP group (Table 3). However, the rate of patients taking pancreatic enzyme supplementation was not significantly different (CP vs. DP; 43% vs. 42%, $P=0.9698$). Furthermore, the body weight in the patients undergoing a CP had recovered to preoperative body weight within 2 year after surgery, whereas patients undergoing a DP remained at %BW of 93% at 2 years after surgery (Fig. 1).

No patient in the both groups had continued postoperative severe diarrhea (Table 3).

No patient in either group showed any evidence of either local recurrence or distant metastases during the follow-up.

Discussion

A CP is a procedure for localized tumor in the pancreatic body to avoid the extended loss of functional unaffected pancreatic parenchyma and is accepted as a method of choice for benign and low-grade malignant neoplasms or pancreatic metastases from other carcinomas, not requiring lymph node clearance.[7,8,13,14] In the present study, the final pathologic examination after a CP showed that 16 patients had IPMN, including one minimally invasive carcinoma, two carcinoma in situ, and 13 adenoma, two MCN, two

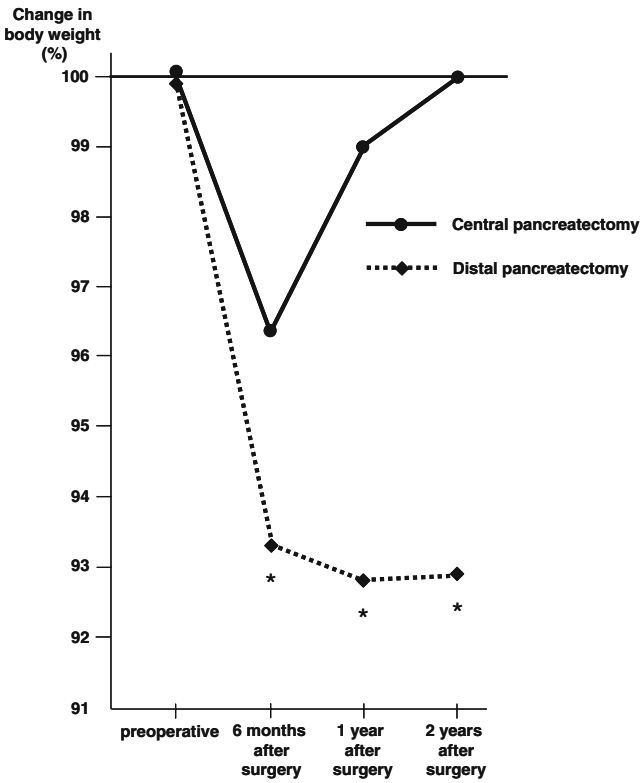

Figure 1 Percent change of body weight in patients with a central pancreatectomy and distal pancreatectomy. The preoperative body weight is defined as 100%. A significant difference is found between the patients with a central pancreatectomy and a distal pancreatectomy at 6 months, 1 year, and 2 years after surgery (*$P<0.05$).

serous cystadenoma, one solid pseudopapillary tumor, two benign NET, and one metastasis from renal cell carcinoma. Regarding IPMN, a few reports revealed the recurrence of remnant parenchyma after a CP.[13,14,16,21] Our data showed that three patients had malignant IPMN with negative resection margins, and these patients have to be followed up strictly, although no patients have recurrence including local recurrence or distant metastasis.[1,22] Intraoperative frozen section analysis of the two resection margins (pathological findings of cut ends of duodenal site and splenic site) is essential for avoiding recurrence of remnant pancreas in patients undergoing a CP. In addition, preoperative and intraoperative diagnosis of define negative margins is difficult in main-duct type IPMN; therefore, main-duct type IPMN may not be indicated for a CP.

The aim of this study is to assess the advantage and disadvantage of CP, concerning perioperative course, postoperative complication, and long-term pancreatic function, in comparison to the patients undergoing a DP as a control group. To compare both surgical procedures, only patients with benign or low-grade malignant neoplasms were selected as a DP group, excluding patients with high malignancies requiring extended surgery and adjuvant therapy and chronic pancreatitis because postoperative pancreatic function of these patients are often getting poor.[3,17]

Our data showed that surgery-related mortality was zero in both groups, and the incidence of overall morbidity was no different between the two groups (CP vs. DP; 29% vs. 18%, P=0.3346). The rate of clinically significant pancreatic fistula (grade B and C) was no different between the CP and DP groups (13% vs. 14%, P=0.8505), and these results are consistent with other reports following a CP.[13,14,21] The data of our present study indicate that a CP is a safe procedure with acceptable morbidity and mortality rates.

In the literature, most reports have stressed the good endocrine function after a CP.[6,13,14,21] In this study, only one patient undergoing a CP developed new onset of mild diabetes, receiving diet counseling and requiring no medical therapy. However, six patients (23%) developed new onset of diabetes (two diet therapy, two taking oral drug, and two insulin treatment), and three (12%) developed worsening diabetes in the DP group. The most important reason for high endocrine insufficiency in patients undergoing a DP may be extended resected volume of normal parenchyma.[23–25]

The assessment of exocrine function is difficult because of nonexistence of objective and easy examination for exocrine function.[13,14,16] In this study, we follow up the postoperative body weight and evaluate the %BW compared to the preoperative values as an exocrine function. The median %BW in the DP group was significantly lower than that in the CP group at 6 months, 1 year, and 2 year after surgery, and the median %BW in patients undergoing a CP improved at 2 years after surgery, whereas that of the DP group remained low at 2 years. The differences in body weight between after a CP and a DP are significant, suggesting that CP preserves and improves the pancreatic exocrine function within at least 2 years after surgery.

Conclusion

Our data show that CP is a safe technique for the treatment of benign or low-grade malignant neoplasms. Furthermore, the rate of new onset of diabetes mellitus was minimal after a CP, and the body weight improved within 2 years after a CP, suggesting that CP is an effective procedure for selected patients.

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ORIGINAL ARTICLE

Is Blind Pancreaticoduodenectomy Justified for Patients with Ampullary Neoplasms?

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Abstract
Background Many specialists justify pancreaticoduodenectomy (PD) for pancreatic head neoplasms with suspected but unproven malignance (blind-PD). Our aim in this study was to determine whether blind-PD is also justified for ampullary neoplasms.
Methods We retrospectively reviewed the records of all patients with presumed resectable ampullary neoplasms treated at the National Taiwan University Hospital from 1998 to 2008.
Results Of the 84 patients without a preoperative tissue diagnosis of malignance, 64 had blind-PD and 20 had ampullectomy (AMP) with intraoperative frozen section. Patients with jaundice, gastrointestinal bleeding, imaging findings showing tumor invasion, and larger tumor size were significantly more frequently treated by blind-PD. Final pathological diagnosis was benign in ten of 64 blind-PD-treated patients.
Conclusions Our data support a selective use of blind-PD because (1) a significant portion (65%) of benign ampullary neoplasms can be safely and effectively treated by AMP, (2) blind-PD does not treat ampullary cancer at earlier stage, and (3) blind-PD is associated with significantly more complications and significantly longer hospital stay than AMP. However, blind-PD is strongly recommended for patients with large ampullary neoplasms (>3 cm in diameter), with jaundice, or with malignant endoscopic appearance.

Keywords Blind pancreaticoduodenectomy · Ampullary neoplasm · Ampullectomy

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Introduction

Many specialists justify pancreaticoduodenectomy (PD) for pancreatic head neoplasms with suspected but unproven malignance (blind-PD) because: (1) preoperative diagnostic procedures may complicate the management or delay surgery, and delaying surgery may increase the likelihood that a tumor is unresectable or has metastasized; (2) a negative biopsy does not rule out cancer; (3) blind-PD can be performed with a low morbidity and mortality and there is a low incidence of benign diagnoses; and (4) quality of life usually improves after blind-PD for benign periampullary noplasms.[1–3] However, this may not be true for ampullary neoplasms because: (1) endoscopic biopsy of ampullary neoplasms can be more easily and safely performed than fine needle aspiration biopsy of a pancreatic head tumor; (2) small benign ampullary neoplasms can be easily and safely treated by ampullectomy,[4–7] but limited resection of benign neoplasms at the pancreatic head or

distal common bile duct (CBD) are more difficult and risky to perform; and (3) there is a higher reported proportion of benign tumors at the ampulla (~27%) than at the pancreatic head (10%).[5,8,9]

Although endoscopic biopsy can be safely and repeatedly performed without the risk of cancer spreading, the diagnostic rate ranges from 40% to 70%.[10–14] A positive tissue diagnosis supports performing a PD and justifies the increased possibility of complications. On the other hand, a persistent negative endoscopic biopsy does not confirm a benign diagnosis.

Some authors suggest ampullectomy (AMP) and intraoperative frozen section evaluation for presumed benign ampullary neoplasms.[5] However, AMP with intraoperative frozen section is reported to have a 10% to 25% false-negative rate.[5,9,15–17] Therefore, in those cases where a preoperative endoscopic biopsy is benign, the burden lies with the surgeon as to whether to (1) perform a blind-PD, (2) base his decision on an intraoperative frozen section of ampullectomy specimen, or (3) repeat endoscopic biopsies and delay the eventual surgery. In clinical practice, blind-PD has been performed for a certain population of patients with ampullary neoplasms.[8,9] But whether blind-PD is justified for patients with ampullary neoplasms has not been addressed. To address this issue, we retrospectively reviewed all patients with presumed resectable ampullary neoplasms treated at the National Taiwan University Hospital (NTUH) from 1998 to 2008. We sought to determine (1) the proportion of ampullary neoplasms treated by blind-PD, (2) the proportion of benign ampullary neoplasms treated by blind-PD, (3) the safety of blind-PD when compared to AMP, and (4) if blind-PD treated ampullary cancer at an earlier tumor stage.

Patients and Methods

The records of all patients who underwent an operation to treat an ampullary tumor at the Department of Surgery, National Taiwan University Hospital from January 1998 to August 2008, were retrospectively reviewed. All patients with a diagnosis of familial adenomatous polyposis and non-adenocarcinoma histopathology (i.e., sarcomas, neuroendocrine/carcinoid tumors, and metastatic lesions) were excluded from further analysis. Patient, radiographic, endoscopic, treatment-related, and pathologic variables were reviewed. Patient variables included age, gender, and presenting symptoms. The radiographic and endoscopic studies used in diagnosis were recorded. These included ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI), and endoscopy biopsy. PD with suspected but unproven malignance was defined as blind-PD and PD after tissue diagnosis of malignance was defined as targeted-PD.

To perform an AMP, a Kocher maneuver was used to mobilize the duodenum and the head of the pancreas. A longitudinal duodenotomy was made in the lateral aspect of the duodenum just opposite to the tumor. The tumor was inspected to determine whether an AMP could be performed with adequate margins and safe reconstruction. In general, the tumor had to be <3 cm in diameter and without long CBD extension to be considered a candidate for AMP. To begin, the duodenal mucosa was infiltrated with 0.001% epinephrine and incised circumferentially approximately 5 mm from the edge of the tumor. The dissection was initially carried beneath the tumor at the bile duct (upstream) margin and the bile duct wall was transected with the electrocautery. If gross tumor was seen at the cut bile duct margin, a complete resection was not possible without converting to a PD. If the bile duct margin was visibly uninvolved, the resection was continued and the tumor separated from the underlying duodenal muscle and pancreatic duct. The specimen was removed and oriented for the pathologist, who was asked to perform frozen section examinations of the duodenal and bile duct margins and determine whether the tumor was benign or malignant. Once the resection was complete, the common bile duct and pancreatic duct orifices were sutured to the edges of the duodenal wall. The duodenotomy was closed and a drain was placed in the area. If the frozen section indicated malignancy, AMP was immediately converted to PD. PD was performed as described before.[18]

In those cases where a preoperative endoscopic biopsy was benign, the choice of AMP with intraoperative frozen section, blind-PD, and repeated endoscopic biopsy was at the discretion of the operating surgeon. All ampullary endoscopic biopsies were performed with endoscopic forceps, without the use of endoscopic US (EUS).

Patient and disease characteristics for each surgical group were compared by chi-square, Fisher's exact, and Mann–Whitney *U* tests as appropriate using the Statistical Package for Social Science for Windows (SPSS), version 10.0 (SPSS, Chicago, IL, USA). The tests were two sided, and $p<05$ was considered statistically significant.

Results

From January 1998 to August 2008, 202 consecutive patients received treatment for ampullary neoplasms at NTUH. Ten patients underwent endoscopic ampullectomy after EUS indicated no tumor infiltration into the bile and pancreatic ducts, and the tumor was confined to the mucosa; seven with small tumors (<3 cm in diameter) had snare polypectomy; three with large tumors (>3 cm in diameter) had piecemeal polypectomy combined with thermal ablation and required two or more endoscopic sessions for complete removal of the

tumor. The pathological diagnosis of the initial ampullectomy specimens was adenoma in nine and adenocarcinoma in one. The patient with adenocarcinoma was converted to PD. Three (33%) of the nine patients with initial pathology consistent with adenoma had a recurrence and a second endoscopic ampullectomy was performed. Pathological diagnosis of the second ampullectomy specimens was adenoma in two and adenocarcinoma in one. The patient with adenocarcinoma was converted to PD. Thus, endoscopic false-negative results occurred in one of ten patients (10%).

Of the 202 patients, 194 underwent surgery to treat ampullary neoplasms. Ten received biliary and/or gastrojejunostomy bypass only because of old age (one patient), comorbidity (one patient), or multiple liver metastases (eight patients). The remaining 184 patients received a surgical resection. Three patients with a final pathological diagnosis of carcinoid or neuroendocrine tumor were excluded, and the remaining 181 patients (mean age, 62.2 years; 81 women and 100 men) were included in the analysis. Twenty of the 181 did not have a preoperative endoscopic biopsy because of large tumor size (>3 cm) identified on CT (12), pancreatic invasion identified on CT (5), and patients' refusal of endoscopy (3). Blind-PD was performed for 12 patients with large (>3 cm) tumors and five patients with imaging studies indicating tumor invasion into the pancreas, and AMP with intraoperative frozen section was performed for three patients (Fig. 1). All three frozen sections indicated no malignance and AMP was completed. Of the 17 blind-PD-treated patients, the final pathological diagnosis was adenocarcinoma in 15 and adenoma in two. The final pathological diagnosis of the three AMP-treated patients was adenoma in all three.

Results of the 161 first preoperative endoscopic biopsies were adenocarcinoma in 88 patients and benign in 73 patients. Of the 88 patients with a first preoperative endoscopic biopsy consistent with adenocarcinoma, 87 had targeted-PD and one had AMP because of advanced age (88 years old) (Fig. 1). Of the 73 patients with a benign

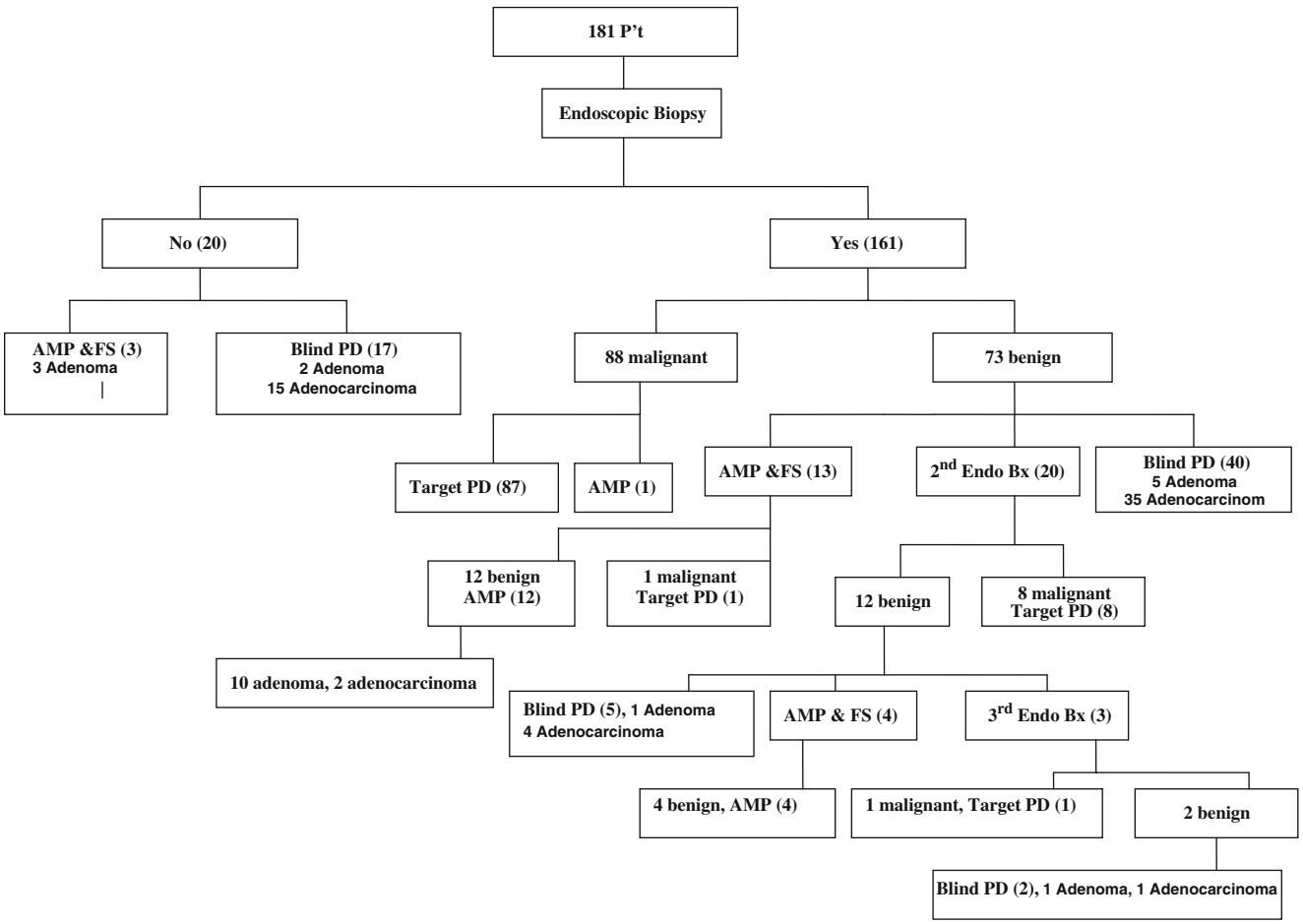

Figure 1 Preoperative endoscopic biopsy, intraoperative frozen section, and definite operative procedures in 181 studied patients. *Endo Bx* endoscopic biopsy, *AMP* ampullectomy, *FS* frozen section, *PD* pancreaticoduodenectomy, *Blind PD* pancreaticoduodenectomy without preoperative tissue diagnosis of malignance.

first endoscopic biopsy, 40 patients had blind-PDs, 13 patients had AMP with intraoperative frozen section, and 20 patients had a second endoscopic biopsy. Of the 40 patients who received blind-PD, the final pathological diagnosis was adenocarcinoma in 35 and adenoma in five. Intraoperative frozen section of ampullectomy specimens indicated malignancy in one patient (converted to PD) and benign lesions in 12 patients (AMP only in all 12 patients). Of the 12 patients who received an AMP whose frozen section examinations were benign, the final pathological diagnosis was adenocarcinoma in two and adenoma in ten.

Of the 20 patients who received a second endoscopic biopsy, eight (40%) biopsies were consistent with malignancy and the patients underwent targeted-PD. Of the 12 patients with benign results of the second endoscopic biopsy, five had blind-PD, four had AMP after benign frozen section results, and three had a third endoscopic biopsy (Fig. 1). Of the five patients who underwent blind-PD, the final pathological diagnosis was adenocarcinoma in four and adenoma in one. The final pathological diagnosis was adenoma in all four AMP-treated patients.

The third endoscopic biopsy was malignant in one patient (targeted-PD) and benign in two patients. Blind-PD was performed for the two patients with benign results of the third endoscopic biopsy and the final pathological diagnosis was adenocarcinoma in one and adenoma in one (Fig. 1).

Of the 181 studied patients, the final pathological diagnosis was consistent with malignancy in 155 (85.6%) and benign in 26 (14.4%). An analysis of preoperative clinical data revealed symptomatic patients (either presenting with jaundice or bleeding) were significantly more likely to have malignant final pathology than asymptomatic patients (Table 1). The likelihood of malignancy in symptomatic patients, jaundiced patients, patients with gastrointestinal bleeding, patients with a dilated common bile duct, and patients with a large tumor (diameter >3 cm) was 89.4%, 92.5%, 91.5%, 96.2%, 91.2%, and 93.5%, respectively.

The final pathological diagnosis was adenocarcinoma in 141 of 161 patients having a first endoscopic biopsy. Therefore, first endoscopic biopsy detected malignancy in 88 (63.1%) of 141 patients with ampullary carcinoma (Table 2). The final pathological diagnosis was consistent with malignancy in 14 of 20 patients who had a second endoscopic biopsy. Therefore, second endoscopic biopsy detected malignancy in eight (57.1%) of 14 patients with ampullary carcinoma (Table 2). The final pathological diagnosis was adenocarcinoma in two of three patients who had a third endoscopic biopsy. Therefore, a third endoscopic biopsy detected malignancy in one (50%) of two patients with ampullary carcinoma (Table 2).

Twenty patients had AMP with intraoperative frozen sections. Frozen sections were consistent with carcinoma in one patient and benign in 19 patients (Table 2). All 19 patients with benign frozen sections had AMP; however, the final pathological diagnosis was adenocarcinoma in two (10.5%). Therefore, frozen section had an 11% false-negative rate. Both patients refused salvage PD and died of recurrence at 9 months (multiple bone metastases and local recurrence) and at 27 months (multiple lung metastases) after AMP. In contrast, no tumor recurrence was noted in the 17 AMP-treated patients with benign ampullary neoplasms.

Of the 84 patients without a preoperative tissue diagnosis of malignancy, 64 had blind-PD and 20 had ampullectomy with intraoperative frozen section (19 patients with benign frozen sections underwent 19 AMP; one patient with malignancy identified on frozen section was converted to targeted-PD). A comparison of demographics between the 64 blind-PD-treated patients and the 20 AMP-treated patients showed no significant differences in age or gender (Table 3). However, patients in whom the endoscopic appearance of the tumor favored cancer (ulceration, nodularity, hard in consistence), were jaundiced, and who had a large tumor (diameter >3 cm) significantly more frequently had blind-PD (Table 3). Of the 84 patients, 44 (30 with malignant and 14 with benign

Table 1 Comparison of Preoperative Clinical Data Between Patients with Malignant and Benign Final Pathology

	Malignant n=155	Benign n=26	p value
Age, years	62.3±11.1	62.5±12.2	0.96
Gender (male/female)	86/69	13/13	0.6
Incidental/symptomatic	3/152	8/18	<0.001
Jaundice	124/31	10/16	<0.001
Bile duct dilatation	129/26	12/14	<0.001
Endoscopic diagnosis of malignancy	126 (82%)	5 (19%)	<0.001
Bleeding	33/122	3/23	0.25
Tumor size ≥3 cm	43 (27.7%)	3 (11.5%)	0.08

Table 2 Histology Results According to Preoperative Endoscopic Biopsy, CT, EUS, Intraoperative Frozen Section, and Final Pathology

	1st endoscopic Bx (n=161)	2nd endoscopic Bx (n=20)	3rd endoscopic Bx (n=3)	CT (n=77)	EUS (n=44)	Frozen section (n=20)
Result of test						
Benign	73	12	2	69	30	19
Malignant	88	8	1	8	14	1
Final pathology						
Benign	20	6	1	23	30	17
Malignant	141	14	2	54	14	3
Sensitivity	62%	57%	50%	15%	80%	33%
Specificity	100%	100%	100%	100%	57%	100%
Positive predictive value	100%	100%	100%	100%	80%	100%
Negative predictive value	27.4%	50%	50%	29.8%	57%	89.5%

CT computed tomography, *EUS* endoscopic ultrasound, *Bx* biopsy

final pathology) had EUS and 77 (54 with malignant and 23 with benign final pathology) had preoperative CT. CT diagnoses were periampullary cancer in eight, dilated common and/or pancreatic duct with periampullar soft tissue density in 34, dilated common and/or pancreatic duct but no identified tumor in 28, and distal common bile duct stone in seven. The sensitivity and specificity of CT to detect malignancy was 15% and 100%, respectively, in our series (Table 2).

Of the 84 patients not diagnosed with malignancy by endoscopic forceps biopsy, 44 (30 with malignant and 14 with benign ampullary neoplasms) had endoscopic US. Invasion of the tumor into the duodenal wall, common bile duct, or pancreas (signs of malignancy) was detected by EUS in 30 patients (24 with malignant and six with benign final pathology). In contrast, no tumor invasion was detected by EUS in 14 patients (six with malignant and eight with benign final pathology). Therefore, accuracy, sensitivity, and specificity of EUS to detect malignancy in our series were 73%, 80%, and 57%, respectively (Table 2).

Perioperative death occurred in two patients after blind-PD, but in no patient after AMP. Perioperative morbidities were significantly more common in patients who underwent blind-PD than those who underwent AMP (Table 3). The mean length of hospital stay was 13±4 days (median, 13 days; range, 8–23 days) after AMP and 24.2±17.7 days (median, 18 days; range, 11–65 days) after blind-PD ($p<$ 0.001, Table 3). The final pathological diagnosis was benign in ten (15.6%) of the 64 blind-PD-treated ampullary neoplasm patients and malignant in two (11%) of the 19 AMP-treated ampullary neoplasm patients.

Of the 98 patients with a preoperative tissue diagnosis (97 by endoscopic biopsy and one by intraoperative frozen section), 97 had targeted-PD and one had AMP (old age). A comparison of final pathological data between the 97 targeted-PD-treated and 54 blind-PD-treated adenocarcino-

Table 3 Comparison of Demographics Between Blind Pancreaticoduodenectomy and Ampullectomy-Treated Patients

	Blind-PD (n=64)	Ampullectomy (n=20)	p value
Mean age (range)	63.1±11.5 (30–82)	65.2±11.7 (45–86)	0.37
Gender (male/female)	38/26	8/12	0.13
No. of patients with jaundice	45/19	8/12	0.014
No. of patients with gastrointestinal bleeding	18/46	2/18	0.097
No. of patients with elevated tumor marker	12/52	1/19	0.138
Endoscopic appearance (malignant[a]/benign)	40/7	2/15	<0.001
Tumor size, cm, mean (range)	2.47±1.28 (0.3–8)	1.6±0.65 (0.6–2.9)	<0.001
Perioperative morbidity	25 (39%)	2 (5%)	0.015
Perioperative mortality	2 (3.1%)	0 (0%)	0.42
Length of hospital stay after operation (days)	24.2±17.7 (11–57)	13±4 (8–23)	<0.001

[a] Malignant endoscopic appearance: ulcerations, nodular, firm consistency

Table 4 Comparison of Pathologic Data Between Patients Treated by Targeted and Blind Pancreaticoduodenectomy

	Blind-PD (n=54)	Targeted-PD (n=97)	p value
Number of preoperative endoscopic biopsies	0.8±0.67 (0–3)	1.12±0.37 (1–3)	0.003
Tumor diameter, cm	2.47±1.28 (0.3–8)	2.33±1.21 (0.5–8.6)	0.48
Depth of invasion (T1, T2, T3, T4)	6, 25, 22, 1	20, 30, 45, 2	0.23
Node status (positive/negative)	14/40	40/57	0.06
Stage (AJCC, 2002)			0.22
Stage IA [n (%)]	6 (11.1%)	17 (17.5%)	
Stage IB [n (%)]	19 (35.2%)	21 (21.7%)	
Stage IIA [n (%)]	14 (25.9%)	19 (19.6%)	
Stage IIB [n (%)]	14 (25.9%)	38 (39.1%)	
Stage III [n (%)]	1 (1.9%)	2 (2.1%)	

PD pancreaticoduodenectomy, *AJCC* American Joint Commission on Cancer

mas showed no significant differences in tumor diameter, depth of tumor invasion, nodal status, and American Joint Committee on Cancer (AJCC) TNM stage (Table 4). Blind-PD did not treat patients at an earlier tumor stage than targeted-PD (Table 4).

Discussion

Uniform indications for AMP have not been widely accepted. Rattner et al.[17] proposed that small (<3 cm) benign ampullary lesions, neuroendocrine tumors, and even early-stage (T1) ampullary invasive cancers could all be effectively treated by AMP. However, several recent studies stressed that nodal metastases could be found in a significant portion of T1 or even Tis tumors and concluded that few ampullary adenocarcinoma can be curatively treated by ampullectomy.[5,9,19,20] Therefore, it has become apparent that all surgically suitable patients with malignant ampullary tumors should be treated by PD. However, it is often not easy to differentiate malignant from benign ampullary neoplasms before or even during surgery. As shown in our study, as well as others, there are no clinical or imaging findings that reliably predict malignancy, and sensitivity of preoperative endoscopic biopsy to detect malignancy ranges from 40% to 70%.[10–14] In clinical practice, options for patients in whom the results of the first endoscopic biopsy are benign include (1) repeat endoscopic biopsy, (2) blind-PD, and (3) AMP with intraoperative frozen section.

In the present study, the chance to detect malignancy became less and less with repeated endoscopic biopsy (first, 62.4%; second, 57.1%; third, 50%). Additionally, repeated endoscopic biopsy is associated with increased medical costs, increased patient discomfort, and a delay of a definitive therapy. For patients in whom a diagnosis of malignancy is not made by endoscopic biopsy, CT and EUS can provide additional information regarding the size of the tumor, depth of invasion, and status of local lymph nodes, which can often be helpful in determining to do local resection or PD. In our study, CT was useful to exclude liver metastases and vascular involvement, but rather insensitive (sensitivity, 15%) in detecting malignancy. In contrast, EUS is accurate, sensitive, and specific in detecting tumor invasion into the duodenum, CBD, or pancreas in 73% of malignant neoplasms.

Recently, there have been an increased number of reports discussing endoscopic ampullectomy as a means to improve the diagnosis accuracy of endoscopically guided biopsies, and even as a treatment for ampullary neoplasms.[21] Biopsies done through a snare resection approach were shown to improve sensitivity, but are associated with increased rates of complications such as hemorrhage, pancreatitis, and papillary stenosis.[21,22] Additionally, snare resection can only be performed for small ampullary tumors (<3 cm) that do not exhibit infiltration to the bile and pancreatic ducts. Large tumors require piecemeal excision, with or without thermal ablation, for complete removal when approached endoscopically, require two or more endoscopic sessions for complete removal, and their endoscopic removal is associated with high complication (around 25%) and recurrence rates (between 10% and 40%).[23–28] However, as shown in our study, endoscopic ampullectomy may be falsely negative for malignancy due to the difficulty in the pathological interpretation of cauterized tissue.

Thus, in clinical practice, many patients with benign endoscopic biopsy results received blind-PD or AMP with intraoperative frozen section instead of repeated endoscopic biopsies.[9] Blind-PD assures that no ampullary adenocarcinoma will be left, but it exposes patients with benign lesions to higher operative risks (Table 2) with unclear benefit. In contrast, AMP can be performed with lower operative risks (no operative mortality and only two minor complications in 20 ampullectomies in our series), but it cannot guarantee that a malignancy will not be missed. Additionally, not every benign ampullary lesion is eligible for ampullectomy. It is difficult to achieve a clear margin

and safe reconstruction after AMP for large tumors, tumors with surrounding duodenal diverticulum, and tumors with long segment CBD extension. In the present data, we performed AMP for 19 small (<3 cm) ampullary neoplasms with benign endoscopic appearance and benign endoscopic biopsy results. However, in spite of the benign results of intraoperative frozen sections, the final pathological diagnosis was carcinoma in two (10.5%) patients, which is also consistent with many recent reports that frozen sections have a 10% to 25% false-negative rate.[6]

If blind-PD had been routinely performed for all studied patients, there would be 26 (14.4%) benign ampullary neoplasms treated by PD. Instead, 17 of 26 benign ampullary neoplasms were safely and effectively treated by AMP, and there were only nine (4.3%) benign ampullary neoplasms treated by PD (p=0.003). A comparison of pathologic data for ampullary adenocarcinoma between patients treated by blind- and targeted-PD showed no significant differences in tumor size, depth of invasion, nodal status, and AJCC TNM staging. Blind-PD did not treat ampullary cancer at earlier stage.

Our current approach to the management of ampullary neoplasms is summarized in a management algorithm (Fig. 2). After a comprehensive history and physical examination, periampullary neoplasms are initially investigated by CT or MRI, and then invasive endoscopy with EUS and biopsy if the neoplasm can be visualized is performed. If endoscopically directed biopsies are consistent with carcinoma, and CT indicates no extrapancreatic disease or tumor invasion to local vessels, targeted-PD will be performed. If endoscopically directed biopsies are benign (likelihood of missed malignance is 38%) and EUS shows tumor invasion to the duodenum, CBD, or pancreas, blind-PD will be performed. If endoscopically directed biopsies are benign and EUS shows a small tumor (<3 cm) without tumor invasion, endoscopic ampullectomy will be performed. If endoscopically directed biopsies are benign and EUS shows a large tumor (≥3 cm) without tumor invasion, open ampullectomy and frozen section will be performed.

In conclusion, our results do not justify the routine use of blind-PD for all ampullary neoplasms because (1) a significant portion (65%) of benign ampullary neoplasms can be safely and effectively treated by AMP, (2) blind-PD does not treat ampullary cancer at earlier stage, and (3) blind-PD is associated with significantly more complications and significantly longer hospital stay than AMP. However, blind-PD is strongly recommended for patients with large ampullary neoplasms (>3 cm in diameter), with jaundice, or with malignant endoscopic appearance because (1) the chance to detect malignancy is reduced with an increasing number of endoscopic biopsies and (2) intraoperative frozen section has 10% to 25% false-negative rate.

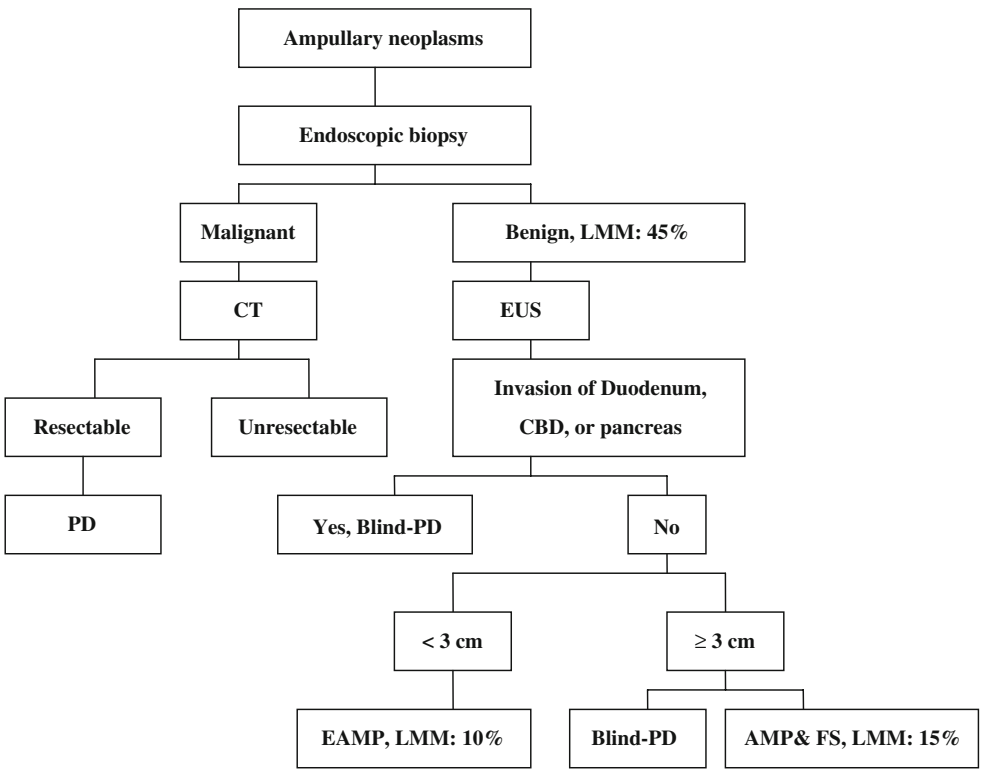

Figure 2 Decision tree for choice of resection method of ampullary neoplasms. *CT* computed tomography, *EUS* endoscopic ultrasound, *CBD* common bile duct, *PD* pancreaticoduodenectomy, *EAMP* endoscopic ampullectomy, *AMP & FS* ampullectomy and frozen section, *LMM* likelihood of missed malignancy.

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ORIGINAL ARTICLE

A Reduction in Delayed Gastric Emptying by Classic Pancreaticoduodenectomy with an Antecolic Gastrojejunal Anastomosis and a Retrogastric Omental Patch

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Abstract
Background Delayed gastric emptying (DGE) continues to be a major cause of morbidity following pancreaticoduodenectomy (PD). A change in the method of reconstruction following PD was instituted in an attempt to reduce the incidence DGE.
Methods Patients undergoing PD from January 2002 to December 2008 were reviewed and outcomes determined. Pylorus-preserving pancreaticoduodenectomy (PPPD) with a retrocolic duodenojejunal anastomosis (n=79) or a classic PD with a retrocolic gastrojejunostomy (n=36) was performed prior to January 2008. Thereafter, a classic PD with an antecolic gastrojejunal anastomosis and placement of a retrogastric vascular omental patch was undertaken (n=36).
Results A statistically significant decrease in DGE was noted in the antecolic group compared to the entire retrocolic group (14% vs 40%; p=0.004) and compared to patients treated by classic PD with a retrocolic anastomosis alone (14% vs 39%; p=0.016). On multivariate analysis, the only modifiable factor associated with reduced DGE was the antecolic technique with an omental patch, odds ratio (OR) 0.3 (confidence interval (CI) 0.1–0.8) p=0.022. Male gender was associated with an increased risk of DGE with OR 2.3 (CI 1.1–4.8) p=0.026.
Conclusion A classic PD combined with an antecolic anastomosis and retrogastric vascular omental patch results in a significant reduction in DGE.

Keywords Pancreaticoduodenectomy · Delayed gastric emptying · Complication · Antecolic anastomosis · Retrocolic anastomosis

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Introduction

Despite substantial reductions in mortality associated with pancreaticoduodenectomy (PD), the morbidity associated with this procedure remains significant.[1,2] In high-volume centers, the morbidity associated with PD continues to range from 30% to 60%, even with improvements in intensive care management and overall perioperative care.[3–7] Delayed gastric emptying (DGE) and pancreatic fistula are the two most common complications associated with PD.

The reported incidence of DGE varies according to the definition used. It is only recently that a consensus definition for DGE has been suggested.[8] As per the International Study Group of Pancreatic Surgery (ISGPS), DGE has been defined as an inability to return to standard diet by the end of the first post-operative week following pancreatic resection. DGE occurs in approximately 19% to

57% of patients undergoing pancreaticoduodenal resection, with various theories regarding its etiology.[9–15]

The cause of DGE following PD is probably multifactorial.[9,13,16–19] Changes in neuro-hormonal pathways related to duodenal and jejunal resection and regional ileus due to subclinical sepsis are two of several theories concerning the pathogenesis of DGE.[20] In all cases of DGE, gastric coordination eventually improves and symptoms resolve. Numerous attempts have been made to prevent DGE without convincing evidence of improved outcomes. In a review of all randomized trials, it was concluded that, due to a lack of homogeneity in the definition DGE and design of studies, definite opinions regarding DGE and variables that influence it could not be derived.[21]

Based on the various theories concerning DGE, a change of technique in gastric reconstruction following pancreaticoduodenal resection was undertaken to reduce the incidence of DGE. Patients that had reconstruction with the new technique were compared to the preceding cases and factors influencing DGE were determined. Recent consensus definitions were used to define DGE.

Patients and Methods

Patient Population

All patients undergoing PD on the liver, pancreas, and foregut unit at Penn State Milton S. Hershey Medical Center from January 2002 to December 2008 were included in this study. Patients were identified from a prospective operative registry. Patient review and assessment was performed with institutional review board (IRB) approval.

Preoperative Assessment

Demographic data and indications for surgery were recorded for all patients.

Operative Procedures

Operative intervention and complications were identified. The extent of resection and the type of reconstruction was recorded. All surgical resections were performed using standard techniques. Pancreatic reconstruction was performed by two-layer duct-to-mucosa anastomosis and the bile duct reconstruction by single-layer interrupted sutures. In all cases, the jejunum was brought up to these anastomoses in a retrocolic manner through a defect created in the colon mesentery. Prophylactic jejunostomy tubes were utilized only in severely malnourished patients, when extra nutritional requirements were anticipated.

Between January 2002 and January 2008, a pylorus-preserving pancreaticoduodenectomy (PPPD) was the procedure of choice. Classic PD was performed with gastric antral excision when there was tumor infiltration into the proximal duodenum or inflammatory changes in this region. Anastomoses to the stomach or duodenum were constructed in a retrocolic, two-layer, hand-sewn fashion. Drains were placed posterior to the biliary and pancreatic anastomoses. A nasogastric tube was positioned during the case.

A change in technique was instituted after January 2008 due to concerns of consistently high DGE rates. The technique employed was based on theoretical concepts considered to reduce DGE and results of previously published clinical studies. In 36 consecutive cases, a classic PD was undertaken regardless of the pathology. While the pancreatic and bile duct anastomoses were constructed in a retrocolic fashion as before, the gastrojejunal anastomosis was now completed in an antecolic fashion by standard two-layer, hand-sewn techniques (Fig. 1). In all cases, a tongue of vascularized omentum was fashioned from the greater curve of the stomach to lie behind the gastrojejunal anastomosis to further separate the stomach from the underlying pancreaticojejunal anastomosis.

Post-operatively, all patients were managed in a surgical intensive care unit (SICU) setting for only the first 12 to 24 h, unless further monitoring was required. Nasogastric tubes were routinely removed day 1 post-operatively. A liquid diet was commenced day 2 post-operatively, with progression to soft diet as tolerated. The right and left drains were checked for amylase and bilirubin after day 4 and were removed sequentially over 2 days if there was no evidence of any pancreatic or biliary leakage. Patients were discharged home on day 6 or 7 unless there was an indication for more prolonged hospital stay. In all cases, erythromycin was given intravenously at 200 mg every 8 h until the time of discharge starting on day 2 post-operatively. A proton pump inhibitor was administered intravenously following surgery and converted to an oral dosage once a diet was tolerated. Pancreatic enzyme supplements were prescribed once a soft diet was commenced. Tight serum glucose control was maintained post-operatively by use of an insulin sliding scale.

Complications

Length of intensive care stay and hospital stay were recorded for all patients. Perioperative mortality was defined as death within 30 days of surgery. Complications were defined according to internationally accepted criteria.[22] DGE was defined according to the ISGPS as the inability to return to a standard diet by day 7 post-operatively or reinsertion of a nasogastric tube prior to this period.[8] Pancreatic fistula was also defined, according to

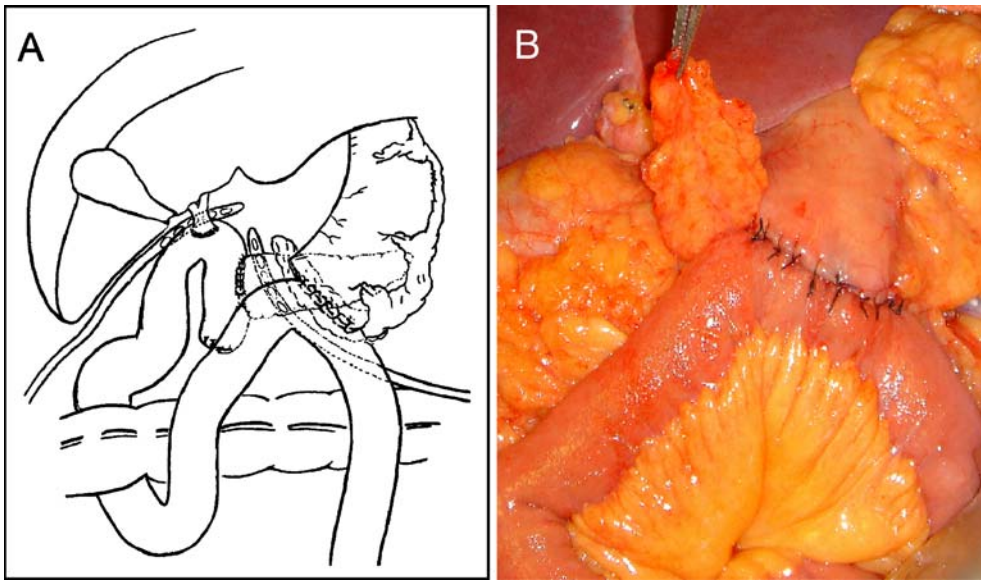

Figure 1 **a** Schematic diagram of antecolic reconstruction and vascular omental patch after PD. **b** Operative photo showing the layout of the gastrojejunal anastomosis with a well-vascularized omental tongue forming a patch positioned behind the stomach and gastrojejunostomy.

ISGPS criteria, as any measurable amount of fluid after post-operative day 3 with an amylase level three or greater times the serum amylase.[23] Patients in whom intra-abdominal collections required drainage in the perioperative period were considered to have high-impact pancreatic fistula, unless another explanation was clearly available.

All patients not tolerating a diet by day 7 post-operatively were defined as having DGE. Total parentral nutrition (TPN) was instituted in the majority of the cases and hospital discharge initiated in those patients that were otherwise well. The severity of DGE was not graded. Once TPN was instituted, there was generally no attempt at early reintroduction of a solid diet.

Statistical Analysis

Results were expressed as median (range) unless otherwise stated. Comparisons between categorical variables were determined by χ^2 and Fisher's exact test as appropriate. Non-categorical variables were assessed by the Mann–Whitney U test. To test the independence of risk factors for DGE, significant variables ($p<0.150$) in univariate analysis were entered into a multivariable logistic regression model with likelihood ratio forward selection. A statistical software package (SPSS version 11.5, Chicago, IL, USA) was used for statistical analysis, with $p<0.05$ considered as statistically significant.

Results

Patient Characteristics

There were 151 consecutive patients undergoing PD during the study period, with the last 36 performed by classic non-pylorus-preserving resection with an antecolic gastrojejunal anastomosis and retrogastric omental patch. The characteristics of the two groups of patients are shown in Table 1. There were significantly more American Society of Anesthesiologists (ASA) class IV patients in the antecolic group than in the retrocolic group ($p<0.001$). There was also a trend toward a higher rate of pre-existing diabetes in the antecolic group compared to the retrocolic group (31% vs 17%; $p=0.066$). The operative times in the antecolic group were significantly longer than in the retrocolic group (10 h vs 9 h; $p<0.001$). All patients in the antecolic group had a classic PD, compared to 36 of 115 (31%) cases in the retrocolic group.

Complications

Complications

There was no operative mortality in this series. Complications are shown in Table 2. In the retrocolic group, pancreatic fistula occurred in 20 (17%) patients, consisting of 11 (55%) grade A, four (20%) grade B, and five (25%) grade C. In the antecolic group, pancreatic fistula occurred in eight (22%) patients, consisting of five (63%) in grade A and three (38%) in grade C classes. There was no difference in pancreatic fistula rate between the groups ($p=0.515$). Wound infections were noted in 20 (12%) patients with no significant differences between the retrocolic and antecolic groups (10% vs 23%; $p=0.069$).

The only statistically significant difference in complication was a decrease in DGE in the antecolic group (14% vs 40%; $p=0.004$). Five patients in the antecolic group developed DGE. Two of these patients had manipulation or repair of large paraesophageal hernia

Table 1 Demographics, Indications and Operative Details of Patients Undergoing Pancreaticoduodenal Resection by Different Techniques of Reconstruction

	Overall (n=151)	Retrocolic (n=115)	Antecolic (n=36)	Difference (p value)
Patient characteristics				
Male	81(54%)	61(53%)	20(56%)	0.792
Age	67 (21–88)	67(29–88)	67(21–88)	0.577
BMI	26(17–45)	25(17–45)	27(20–42)	0.036
ASA class II	19(13%)	13(11%)	6(17%)	
III	124(82%)	101(88%)	23(64%)	<0.001*
IV	8(5%)	1(1%)	7(20%)	
Biliary stent	44(29%)	36(31%)	8(22%)	0.295
Diabetes	30(20%)	19(17%)	11(31%)	0.066
Pathology				
Pancreatic cancer	69(46%)	51(44%)	18(50%)	
Ampullary, duodenal, bile duct malignancy	21(14%)	13(10%)	8(16%)	0.599
Other	61(40%)	51(44%)	10(28%)	
Operative				
Estimated blood loss (ml)	400(100–2,500)	400(100–2,000)	500(100–2,500)	0.067
Blood transfusions	19(13%)	12(10%)	7(19%)	0.155
Operative time (h)	9 (4–21)	9(4–21)	10(7–20)	<0.001*
Pylorus preserving	79(52%)	79(69%)	0(0%)	NA
Feeding jejunostomy	10(7%)	10(9%)	0(0%)	0.118
Post-operative				
Days in SICU	1(1–22)	1(1–6)	1(1–22)	0.302
Length of stay (days)	7(5–34)	8(5–30)	7(6–34)	0.996

BMI body mass index, *SICU* surgical intensive care unit, *NA* not applicable

*p value<0.05

Table 2 Complications of Pancreaticoduodenal Resection According to Technique

	Overall (n=151)	Retrocolic (n=115)	Antecolic (n=36)	Difference (p value)
Patients with complications	89(59%)	70(61%)	19(53%)	0.389
Complications excluding DGE	64(42%)	48(42%)	16(44%)	0.774
DGE	51(34%)	46(40%)	5(14%)	0.004*
Pancreatic fistula	28(19%)	20(17%)	8(22%)	0.515
Wound infections	20(13%)	12(10%)	8(22%)	0.069
Post operative bleeding	5(3%)	4(4%)	1(3%)	1.0
Intra-abdominal abscess	8(5%)	4(4%)	4(11%)	0.93
Pneumonia	4(3%)	4(4%)	0(0%)	0.573
Urinary tract infection	8(5%)	5(5%)	3(8%)	0.397
Thromboembolic	10(7%)	8(7%)	2(6%)	1.0
Other	7(5%)	5(4%)	2(6%)	0.672
Reoperation	3(2%)	3(3%)	0(0%)	1.0
Readmission	41(27%)	34(30%)	7(20%)	0.233
DGE	20(13%)	20(17%)	0(0%)	0.004*
Infective complication	19(13%)	14(12%)	5(14%)	0.787
Other	5(3%)	3(3%)	2(6%)	0.593

*$p \leq 0.05$ Chi-Square/Fisher's exact test

during the PD. Another patient in the antecolic group had symptoms of a small bowel obstruction 1 week post-operatively requiring nasogastric tube reinsertion, which resolved after removal of her abdominal drain tube. She was classified as having DGE based on the strict definition set by the ISGPS.

Readmissions

There were 41 (27%) readmissions overall related to one or more complications in this series. The major reason for readmission was DGE (20 (13%)), followed by infective complications (19 (13%)). DGE was treated by intravenous rehydration and initiation of TPN in cases of readmission. Infective complications were mainly in the form of collections caused by pancreatic leaks, requiring drainage. In these cases, patients were generally admitted to hospital for 12 to 24 h of observation following percutaneous interventions. The overall readmission rates were similar in the antecolic and retrocolic groups (20% vs 30% $p=0.233$). There was, however, a significant reduction in readmissions related to DGE in the antecolic group (0% vs 17%; $p=0.004$). Readmissions due to infective complication were similar between the antecolic and retrocolic groups (14% vs 12% $p=0.787$).

Classic Pancreaticoduodenectomy

Comparison of 36 patients undergoing classic PD in the retrocolic group to the 36 patients in the antecolic group is shown (Table 3). The patients in the antecolic group had higher ASA IV classification than the retrocolic group ($p=0.047$). There was significantly reduced DGE in the antecolic group compared to the retrocolic classic PD group (14% vs 39%; $p=0.016$). No other significant differences were noted. Comparison of all 72 patients treated by classic PD compared to PPPD only showed a trend towards reduced DGE (37% vs 63%; $p=0.067$). When excluding the patients in the antecolic group, the rate of DGE between PPPD and classic PD with a retrocolic gastrojejunal anastomosis were similar (41% vs 39%; $p=0.870$).

Factors Associated with Delayed Gastric Emptying

The overall effects of various factors on DGE based on univariate analysis is shown in Table 4. Classic PD with

Table 3 Comparison of Classic PD with Retrocolic Gastrojejunal Anastomoses to Antecolic Gastrojejunal Anastomoses and Retrogastric Omental Patch

	Classic PD retrocolic ($n=36$)	Classic PD antecolic & patch ($n=36$)	p value
Patient characteristics			
Male	20(56%)	20(56%)	1.0
Age	67(46–84)	67(21–88)	0.714
BMI	26(18–39)	27(20–42)	0.350
ASA class II	4(11%)	6(17%)	
III	31(86%)	23(64%)	0.047*
IV	1(3%)	7(19%)	
Biliary stent	10(28%)	8(22%)	0.586
Diabetes	7(19%)	11(31%)	0.276
Pathology			
Pancreatic cancer	15(42%)	18(50%)	0.478
Operative			
Estimated blood loss (ml)	375(100–2,000)	500(100–2,500)	0.072
Blood transfusions	7(50%)	7(50%)	1.0
Operative time (h)	9(4–21)	9(6–20)	0.189
Feeding jejunostomy	3(8%)	0(0%)	0.239
Post-operative			
Days in SICU	1(1–4)	1(1–22)	0.662
Length of stay (days)	8(6–34)	8(5–30)	0.694
Complications	22(61%)	19(53%)	0.475
DGE	14(39%)	5(14%)	0.016*
Other	14(39%)	16(44%)	0.633

BMI body mass, *SICU* surgical intensive care unit

*p value<0.05

Table 4 Factors Associated with DGE

	No DGE (n=100)	DGE (n=51)	OR (CI)	Difference (p value)
Demographics				
Male gender	48(48%)	33(65%)	2.0(1.0–4.0)	0.052
BMI ≥30	19(19%)	9(17%)	0.9(0.4–2.2)	0.840
Age ≥70	40(40%)	26(39%)	1.6(0.8–3.1)	0.198
Preoperative				
Diabetes	18(18%)	12(24%)	1.4(0.6–3.2)	0.421
ASA III/IV	88(88%)	44(86%)	0.9(0.3–2.3)	0.762
Biliary stent	29(29%)	15(29%)	1.0(0.5–2.1)	0.958
Pathology				
Pancreatic cancer	50(50%)	19(37%)	0.6(0.3–1.2)	0.137
Operative details				
Time ≥10 h	37(37%)	18(35%)	0.9(0.5–1.9)	0.837
Blood loss ≥500 ml	39(39%)	20(39%)	1.0(0.5–2.0)	0.98
Blood transfusion	12(12%)	7(14%)	1.2(0.4–3.2)	0.762
Feeding jejunostomy	6(6%)	4(8%)	1.3(0.4–5.0)	0.667
Pylorus preserving	47(47%)	32(63%)	1.9(1.0–3.8)	0.067
Antecolic technique	31(31%)	5(10%)	0.2(0.1–0.9)	0.004*
Post-operative details				
Pancreatic fistula	17(17%)	11(22%)	1.3(0.6–3.1)	0.496
Non-DGE complications	41(41%)	23(45%)	1.2(0.6–2.3)	0.630

BMI body mass index, *SICU* surgical intensive care unit

*$p<0.05$ Chi-Square/Fisher's exact test

antecolic gastrojejunal anastomosis and retrogastric omental patch was the only modifiable factor associated with decreased DGE with an odds ratio (OR) of 0.2 (confidence interval (CI) 0.1–0.9) p=0.004. There was a strong trend towards higher DGE in male patients, OR 2.0 (CI 1.0–4.0) p=0.052.

Overall, the presence of complications was not associated with increased DGE. Specifically, pancreatic fistula was not associated with increased DGE. When analyzed as separate groups, in patients treated by classic PD or PPPD with a retrocolic anastomosis or those with a classic PD and antecolic gastrojejunal anastomosis and omental patch, there was still no statistically significant association between pancreatic fistula and DGE. Overall, a trend toward decreased DGE was noted in patients with pancreatic cancer pathology (p=0.137), and in patients treated by classic PD, rather than PPPD (p=0.067).

On multivariate analysis, two independent factors significantly influenced DGE. An antecolic anastomosis with a retrogastric omental patch significantly reduced DGE, OR 0.3 (CI 0.1–0.8) p=0.022, whereas male gender was associated with increased DGE, OR 2.3 (CI 1.1–4.8) p=0.026.

Discussion

Multiple theories regarding the etiology of DGE have been proposed. Disruption of hormone and neuronal homeostasis;[20,21,24] diminished hormonal stimulation;[17,19,25–29] gastroparesis due to intra-abdominal complications;[9,17,30–34] post-operative pancreatitis;[35] pyloric, antral, and duodenal ischemia;[36,37] denervation of the stomach;[17,38] post-operative pylorospasm;[39] and torsion and angulation of reconstruction[36,40] are all proposed theories concerning the pathogenesis of DGE.

The reported incidence of DGE is highly variable, and ranges from 0% to 57% in randomized controlled trials.[21,41–43] This may reflect the variability in the definition of DGE. Some previous studies defined DGE as an inability to tolerate a diet by 10 days post-operatively.[21,43] This definition is not applicable to contemporary series, in which median hospital stay following PD is generally between 7 and 10 days. The incidence of DGE in our series prior to the institution of a change in technique was 40% according to strict consensus statement definitions.

A change in technique of gastric reconstruction was instituted in an attempt to reduce DGE rates. The change undertaken reflected possible theoretic benefits of one or more techniques over another and findings of previously reported studies. Antral resection was performed based on a meta-analysis showing a trend towards reduced DGE with classic PD.[44] It was also based on the theory that DGE relates to pylorospasm, duodenal ischemia, and alterations of neurohormonal factors that control antral and pyloric contraction.[36,37,39] We acknowledge that there are some reports of long-term advantages of PDDD over standard PD.[45] This is, however, controversial, with advocates of

both procedures.[46] Our primary goal was to significantly reduce DGE by a change in operative technique. Long-term gastro-intestinal function was not examined.

An antecolic gastrojejunal anastomosis was performed to maximally distance this anastomosis from the pancreas, minimize possible jejunal kinking or angulation, and allow greater mobility of the stomach and jejunum. We created a vascularized omental tongue as a patch to further separate the gastrojejunal anastomosis from the pancreaticojejunostomy and any associated pancreatic leaks. In addition, we avoided gastrostomy and feeding jejunostomy tubes to minimize other factors that may slow gastric emptying and intestinal motility. All patients in this series were given erythromycin based on theoretical benefits of improved gastric emptying and positive results of previous randomized controlled trials.[19,42,43]

A reduction in DGE from 40% to 14% was noted with institution of a change in technique, despite inclusion of sicker patients according to ASA classifications and a trend towards a higher number of diabetics in the antecolic group. We expect to be criticized for a high rate of DGE in the retrocolic group. This, however, reflects strict use of the ISGPS criteria to define DGE. A change in our technique virtually eliminated hospital readmissions due to DGE. The reduced DGE rate noted is unlikely to be related to changes in peri-operative care during the different time periods examined. We specifically confined our study to patients treated after 2002, during a period when all patients had similar peri-operative management. Increased referral of complex patients to our institution with significant co-morbidities may explain the differences in ASA classification and longer operating times seen in the latter antecolic group.

Warshaw was the first to define the concept of DGE and associated it with pylorus-preserving pancreaticoduodenal resection.[47] Several studies have suggested decreased DGE or earlier return of gastric function after standard PD.[41,48,49] One randomized trial of 33 patients had zero cases of DGE after standard PD resection compared to 43% after PPPD ($p< 0.05$).[41] This study, however, was conducted over an 8-year period with small number of patients. The reverse was shown in a randomized trial of classic PD, including extended lymph node dissection compared to PPPD, with 16% DGE compared to 6% ($p=0.006$).[50] Most series indicate no difference in DGE between classic PD and PDDD.[51] In our own series, there was no only a trend towards reduced DGE in the 72 patients treated by classic PD compared to the 79 patients undergoing PPPD. The trend was lost with exclusion of the antecolic classic PD patients.

The effect of an antecolic anastomoses in reducing DGE is supported by several publications.[37,52–55] Theoretically, antecolic anastomosis avoids any mechanical problems by allowing increased mobility of the duodenojejunal or gastrojejunal anastomosis and avoiding torsion that may negatively affect gastric emptying.[32,40,56] There are also arguments that decreased blood flow may occur due to venous congestion following retromesenteric passage of the afferent limb.[57] In addition, such an anastomosis provides an anatomical barrier from the pancreas, minimizing possible negative effects of a pancreatic leak. In a recent trial of 40 patients undergoing PPPD randomized to either antecolic or retrocolic anastomosis, the rate of DGE in the antecolic group was 5% compared to 50% in the retrocolic group.[53] Similar results were shown in a prospective study of 100 patients with retrocolic duodenojejunal anastomosis undergoing PPPD compared to 100 patients with an antecolic duodenojejunal anastomosis.[52] The DGE rate was 5% in the antecolic group compared to 24% in the retrocolic cases. However, patients in the retrocolic group had greater operative blood loss and had a higher rate of medical complications than the antecolic group. In a recent study consisting of a small number of patients undergoing standard PD, an antecolic gastric anastomosis and undivided Roux-en-Y with a Braun enteroenterostomy resulted in less DGE that a standard reconstruction.[58] It is possible that an antecolic method of reconstruction rather than creation of an enteroenterostomy was the cause of reduced DGE. In our study, the only modifiable factor resulting in reduced DGE on multivariate analysis was our change of technique, performing a classic PD with an antecolic anastomosis and retrogastric omental patch. Our patients appeared well-matched, with the only differences being higher ASA IV classification and longer operating times in the antecolic group. There was also a trend towards more patients with diabetes in the antecolic group. Intuitively, these differences would be considered to be more likely to increase DGE rates than to decrease them. We also noted that male gender was associated with higher risk of DGE. Although the pathophysiologic basis of this is undermined, this is in keeping with the findings of other studies.[52,59]

Post-operative complications were shown in several studies to be associated with DGE.[9,32,33,59,60]. In a study of 51 patients undergoing PPPD, DGE did not occur when there were no other complications, whereas 43% of patients with severe complications also had DGE.[32] Pancreatic fistula is the most common complication associated with DGE based on several large series.[61,62] Although not demonstrated in our study, it is possible that an antecolic anastomosis with the addition of a retroanastomotic omental patch reduces the effects of a clinical or subclinical pancreatic leak on gastric, intestinal, and anstomotic functioning. In our series, overall complications and pancreatic fistula rates were similar in the retrocolic and antecolic treatment groups and were not associated with increased DGE.

We can conclude from this study that a classic PD with an antecolic anastomosis and retrogastric omental patch results in significant reductions in DGE and related hospital

readmissions. Further randomized studies are required to fully confirm these findings and to determine the role of antecolic anastomosis and vascularized omental patch in the setting of both classic PD and PPPD.

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ORIGINAL ARTICLE

Methylene Blue Attenuates Pancreas Ischemia–Reperfusion (IR)-Induced Lung Injury: A Dose Response Study in a Rat Model

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Abstract
Background Oxidants (and their generator, xanthine oxidase [XO]) play a role in inducing acute lung injury (ALI) expressed both structurally and functionally. Such damage has recently been demonstrated in the presence of pancreas ischemia–reperfusion (IR). We now investigated whether methylene blue (MB), a clinically used coloring agent and antioxidant in itself, protected the lung exposed to pancreas IR.
Materials and Methods Isolated pancreata (eight replicates/group) were (1) continuously perfused (controls), (2) made ischemic (IR-0) for 40 min and reperfused without treatment, (3) organs procured from allopurinol-treated rats made ischemic and reperfused with allopurinol, and (4) made ischemic and treated upon reperfusion with three different doses of MB contained in the perfusate. All perfusate solutions were directed into the isolated lungs' circulation whereby they were perfused for 60 min.
Results Pancreas injury was documented in all IR organs by abnormally high reperfusion pressure, wet-to-dry ratio, amylase and lipase concentrations, and abnormal XO activity and reduced glutathione in the circulation. Lungs paired with IR-0 pancreata developed ~60% increase in ventilatory plateau pressure and final Po_2/Fio_2 decrease by 35%. Their weight during reperfusion and bronchoalveolar lavage (BAL) volume and contents increased 1.5–2.5 times the normal values; XO and reduced glutathione values were abnormal both in the BAL and in the lung tissues. Lungs exposed to IR effluents containing allopurinol or 68 μM MB were minimally damaged, whereas perfusion solutions containing 42 or 128 μM MB were ineffective in preventing lung injury.
Conclusions Ex vivo pancreas IR-induced ALI is preventable by MB, although at a narrow dose range.

Keywords Pancreas · Ischemia–reperfusion · Lung · Injury · Oxidants · Methylene blue

Introduction

Ischemia–reperfusion (IR) is a complex set of events frequently encountered during circulatory disturbances.[1] Warm IR of the pancreas is associated with microcirculatory derangements, e.g., increased vascular permeability, arterial constriction, stasis of capillary system, and increased level of circulating pancreatic enzymes.[2–4] The systemic consequences of acute pancreatitis might resemble those reported after hepatic or intestinal IR.[5] This contention is supported by clinical observations of acute lung injury (ALI) or multiple organ dysfunction syndromes that frequently accompany pancreatitis, even at an early stage.[4,6]

We have previously documented oxidants' participation in the processes of ALI.[4,5,7,8] Xanthine oxidase (XO) was demonstrated to be a significant source of stress oxidants: XO activity increases after bowel, hind limb, or hepatic IR or hemorrhage and resuscitation, both in animals and in humans.[4,5,7–9] The role of XO in inducing remote ALI was demonstrated for pancreas IR as it had been for other organs,

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using XO oxidoreductase inhibitors (e.g., allopurinol, sodium tungsten).[4,5,7–10]

MB is a dye that competes with molecular oxygen for the transfer of electrons from flavo-enzymes. The shunting of electrons to and from the colorless reduced leukomethylene blue diverts their flow from the enzyme's metal–sulfur center where molecular oxygen is normally converted into superoxide radicals and thus the generation of cytotoxic mediators is attenuated.[11,12] The presence of MB would ultimately block at least part of the XO-dependent detrimental effects. MB was shown to be beneficial in preventing aortal dysfunction after exposure to post ischemic liver reperfusate in ex vivo conditions.[13] Unlike sodium tungsten, MB is a relatively safe clinical compound.

On the basis of the above accumulated data regarding remote ALI, and the potentials of MB to protect organs from damage, we now evaluated the efficacy of increasing doses of MB in protecting the normal, isolated–perfused rat lung from the damaging effects of an IR pancreas. We also used allopurinol, a specific inhibitor of XO, as a reference for the beneficial effect of MB.

Materials and Methods

This study was performed in accordance with the Public Health Service policy on Humane Care and Use of Laboratory Animals, the National Institute of Health (NIH) Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act and was approved by the Institutional Animal Care and Use Committee of Tel Aviv Sourasky Medical Center.

Organ Preparation and the Double-Organ System

Adult male Wistar rats (n=96), weighing 350–420 g, were anesthetized with intraperitoneal barbiturate. One-half of the animal cohorts donated the pancreata and another—the lungs. Following laparotomy, the pancreata were exposed and separated from adjacent tissues and perfused according to Fujimoto et al's method.[14] After separate animals underwent a tracheotomy, their lungs were ventilated with 95% air–5% CO_2 with a piston-type rodent ventilator (10 ml kg^{-1} tidal volume at a rate of 40 breaths min^{-1}) and a thoracotomy was performed. The lungs were isolated and perfused as reported elsewhere[5,7–9] with hemoglobin-free, modified, 5% (weight $volume^{-1}$) bovine serum albumin (BSA)-enriched Krebs–Henseleit (Krebs) solution (in mM=118 NaCl, 4.7 KCl, 27 $NaHCO_3$, 2.5 $CaCl_2$, 1.2 $MgSO_4$, 1.2 KH_2PO_4, 0.05 EDTA, 11 α-D-glucose). Lungs were then suspended from a force displacement transducer (Grass Instruments Co., Quincy, MA, USA). The double-organ perfusion system used in this study is shown in Fig. 1 and was described in detail elsewhere.[5,7] Two separate peristaltic pumps were used to perfuse the pancreas and the paired lung. Pre- and post-organ perfusate always passed through an in-line warmer and membrane oxygenator as well as thermometers. All physiological parameters

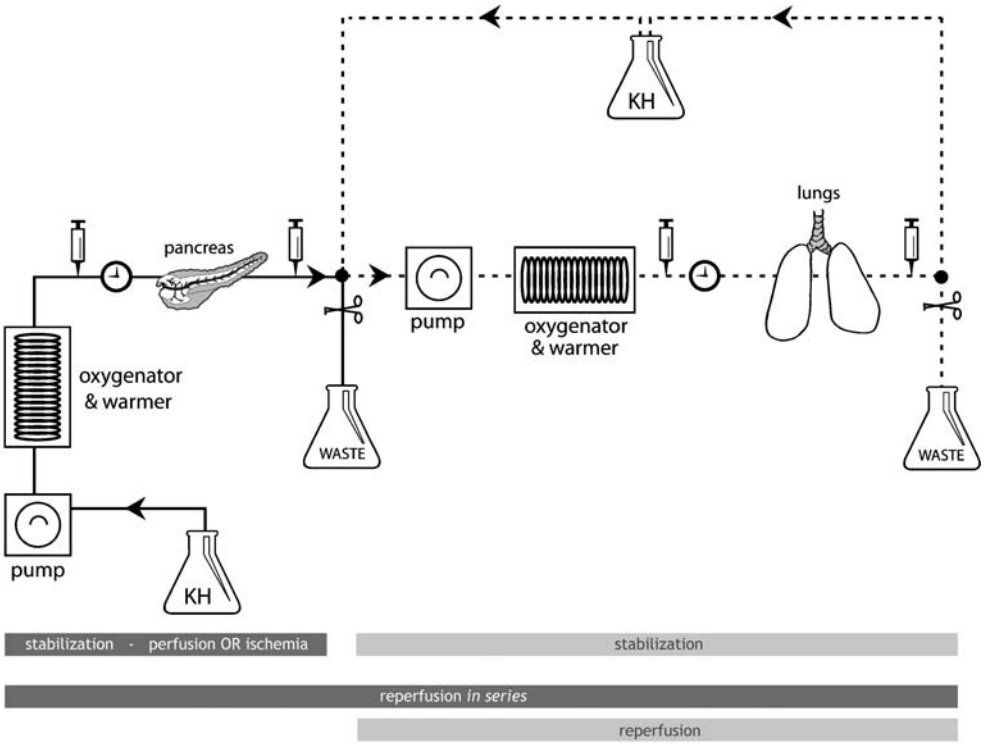

Figure 1 Scheme of the double-organ perfusion system.

were continuously recorded (Statham Medical P132284™ pressure transducer, Mennen Medical®, Clarence, NY, USA) positioned at the level of the perfusate entering/exiting the organs or the main bronchi. The data were logged onto a hemodynamic monitor (CS/3™, Datex-Ohmeda®, Helsinki, Finland).

The pancreata were always perfused with Krebs in a single-pass mode, while the lungs were perfused either in a single-pass (during the conjoint phase) or in a closed-loop recirculation mode (during stabilization and after the conjoint perfusion, see below). The isolated organs were put in an environmental chamber designed to control temperature and minimize water evaporation.

Drug and Experimental Protocol

Methylene blue (MB) 1% (Hope Pharmaceutics, St. Ana, USA) was added to the Krebs, making respective concentrations of 42, 68, and 128 μM solutions in three IR groups. The administration of MB took place at the time of pancreas+lung serial reperfusion (see below), passing via either organ and aiming to counteract the production of ROS, as would be done clinically.[15]

Allopurinol, a XO oxidoreductase inhibitor and a classic antioxidant standard, was shown to block XO production in the IR liver.[16] Allopurinol (Sigma-Aldrich, Rehovot, Israel, 50 mg kg^{-1}) was injected 6 h before the experiment intraperitoneally in animals whose pancreata were later treated with a 1 mM allopurinol Krebs solution that perfused one group of organs[13] (see below).

Pancreata were divided into six groups ($n=8$ replicates/group). Their paired lungs were never subjected to ischemia. One pancreas group served as non-ischemia control and another group was subjected to ischemia without treatment upon reperfusion (IR-0). A third IR group was treated with allopurinol (IR-A, see above), and three additional IR groups had pancreata reperfused with 42, 68, or 128 μM MB–Krebs solution (IR-42, IR-68, and IR-128, respectively).

After 30 min of pancreas stabilization, all IR pancreata were rendered ischemic by stopping the flow for 40 min;[4] the control organs were continually perfused during that time. In the meantime, isolated lungs were stabilized so that, when pancreas ischemia terminated, the pancreas reperfusate (including the controls') was shuttled into the pulmonary circulation. After 15 min of in-series pancreas+lung reperfusion (with or without treatment), the pancreas was removed from the circuit and the accumulated effluent was circulated through the only lung in a closed-loop manner for another 45 min. The pancreas was reperfused for 15 min because the vast majority of the endocellular enzymes and other compounds that indicate organ damage and are capable of inducing local and remote organ damage are released into the circulation during this period.[4,5] The 45-min lung reperfusion[4,5,7,8] is a time lag during which the slow build-up of lung damage can be recognized. Finally, since the pancreas flow rate is two to three times lower than that of the lung, additional fresh Krebs (the missing volume between the lung and the pancreas flow rates) was added during the 15-min in-series period to fill in for the larger pre-determined lung perfusion volume.

Determination of Organ Parameters

Organ viability vs. damage was assessed as previously reported,[4] recording changes in pancreas perfusion pressure, exiting perfusate content, and post-experimental wet weight-to-dry weight ratio (WDR). Lung perfusion pressure, plateau ventilatory pressure, and changes in lung weight during the experiment were continuously recorded. Po_2/Fio_2 was calculated as well. We have previously demonstrated[4,5] that pulmonary capillary pressure and airway compliance closely and directly correlate with perfusion pressure and ventilatory plateau pressure, respectively; the former were thus omitted in the present report.

At the end of each experiment, lung airways were gently flushed three times with 1 ml of warm saline through the trachea, and the fluid was gently sucked out. Markers of altered bronchoalveolar lavage (BAL), e.g., increased regained volume and/or content, indicate abnormal alveolocapillary permeability.[4,5]

Biochemical Analyses

Aliquots of 1.0 ml of effluent were collected for laboratory analyses every 15 min throughout the experiment, with additional time points at 1, 5, and 10 min during the in-series reperfusion phase. Samples were processed in duplicate within 24 h from the experiment. Tissues were also assayed. The addition of MB to the Krebs did not interfere with any biochemical analyses.[4,17]

Abnormal amylase or lipase concentrations in the pancreas-exiting perfusate indicate pancreatic damage.[18] They were determined by standard methods and kits for automated analyses (Roche-Böehringer Mannheim GmbH Diagnostics, Mannheim, Germany and Hitachi 747 Analyzer, Tokyo, Japan).

The total activity of XO plus its reduced form, xanthine dehydrogenase (XDH), was assessed following Hashimoto's method[19] (with modifications). After the tissue was washed in an ice-cold sucrose and bottled on a filter paper, it was homogenized with a micro-homogenizer with 0.25 M sucrose solution. After overnight dialysis against 200 ml of 0.25 M sucrose solution at 0°C, the fresh solution thus obtained was used to measure XO activity; overnight dialysis was proven not to cause any

change in the activity. The activity was quantified spectrophotometrically by monitoring the formation of uric acid from xanthine through the increase in absorbance at 292 nm. One unit of activity was defined as 1 μmol min^{-1} of uric acid formed at 37°C, at pH 7.5. Activity was expressed in mU g^{-1} wet weight for tissues.

Reduced glutathione (GSH) is an intracellular low molecular weight thiol that exerts protective activities, primarily intracellularly.[20] In case of glutathione deficiency, brain mitochondria may be damaged due to the accumulation of hydrogen peroxide and the lack of the protective glutathione activity.[21] GSH was analyzed in fluids and in fresh organ specimens (Calbiochem #354102 kit, San Diego, CA, USA) and expressed as mM and μmol g^{-1} dry weight tissue, respectively.

All organs were weighed at the completion of the experiments. Portions were maintained in an oven at 70°C for 5 days and then reweighed to calculate their WDR.

Statistical Analyses

The data variables are summarized as means±SD. A post hoc analysis was done at each time point after the analysis of variance (ANOVA), with comparisons between group means using the Student–Newman–Keuls' test. Trends in each group were compared by ANOVA with repeated measures, followed by Tukey's multiple comparison tests. The significance level was set at $P \leq 0.05$.

Results

Pancreas Data

During stabilization, pancreas perfusion pressure was similar among all groups (39–46 mmHg) and remained unchanged in the control group throughout the experiments. It increased in all the IR organs within <3 min of reperfusion, reaching maximum values of 56–68 mmHg. IR also produced edema, as expressed by the 50–78% increase in pancreas WDR compared to the corresponding controls (Table 1).

The biochemical profiles of the various pancreatic effluents are displayed in Table 2. Amylase and lipase activities increased 2–4-fold in the IR groups, starting at 2 min of reperfusion and remained elevated throughout reperfusion, compared to control values. The total XO activity increased and the GSH content decreased during this phase in all IR pancreata except for the control, IR-A, and the IR-68 groups. There was a slight tendency of all abnormal values to decrease at 15 min of reperfusion.

The post-experimental XO activity and GSH content in the pancreas tissues are reported in Fig. 2. The XO activity in all IR-treated pancreata was 2–3-fold lower than those in the controls, reflecting loss of cell components, except for the IR-68 where XO activity was similar to the control's and for the IR-A where XO was very low because its generation was inhibited by allopurinol. GSH concentration in the IR-0 tissues was multi-fold lower than in the controls, IR-68, or IR-A. This represents GSH pool being consumed due to oxidant/antioxidant misbalance, and lost from the disrupted cells as well.

Lung Ventilatory Data

Ventilatory plateau pressure, an important index of lung damage, was similar among all lungs during the stabilization period (Fig. 3, upper plane). During reperfusion, it did not change significantly in the controls, IR-A, and in the IR-68 groups, but it did in the IR-0>IR-42>IR-128 groups. The final P_{O_2}/Fi_{O_2} values were the lowest in the IR-0-attached lungs compared to all other groups of lungs, including the IR-treated ones (Table 3).

Lung Circulatory Data

Pulmonary perfusion pressure is reported in Fig. 3 (lower plane): it was similar in all lungs during stabilization and remained unchanged in the control and changed minimally in the lungs that were attached to the IR-A and the IR-68 pancreata. The lungs that were reperfused with the IR-0, the IR-42, and the IR-128-MB effluents showed 2–4-fold increase in the perfusion pressure by the end of reperfusion.

Table 1 Wet Weight to Dry Weight Ratio (WDR) (mean±SD)

Group	Pancreases	Lungs
Control	1.35±0.42	4.31±0.56
Ischemia–reperfused, untreated (IR-0)	2.45±0.78*, **	10.17±1.34*, **
Ischemia–reperfused, allopurinol treated (IR-A)	2.40±0.51*	4.17±0.34
Ischemia–reperfused, MB 42 μM treated (IR-42)	2.31±0.52*, **	7.13±1.0*, **
Ischemia–reperfused, MB 68 μM treated (IR-68)	2.03±0.6*	4.67±0.79
Ischemia–reperfused, MB 128 μM treated (IR-128)	2.23±0.54*, **	5.57±1.11*, **

*$p<0.01$ vs. the corresponding controls and IR-A, **$p<0.05$ vs. the IR-68 group

Table 2 Contents of Pancreas Effluents (Mean ± SD)

Time points and groups	Amylase (U l^{-1})	Lipase (U l^{-1})	Total XO (mU ml^{-1})	GSH (mM)
Stabilization 30 min				
Control	365±47	260±50	0.13±0.01	0.03±0.004
Ischemia–reperfused, untreated (IR-0)	346±37	255±42	0.12±0.012	0.03±0.002
Ischemia–reperfused, allopurinol treated (IR-A)	358±40	256±46	0.12±0.01	0.028±0.004
Ischemia–reperfused, MB 42 μM treated (IR-42)	345±39	255±42	0.14±0.01	0.025±0.01
Ischemia–reperfused, MB 68 μM treated (IR-68)	359±55	261±39	0.13±0.01	0.03±0.005
Ischemia–reperfused, MB 128 μM treated (IR-128)	355±64	267±36	0.13±0.01	0.04±0.003
Reperfusion 2 min				
Control	401±60	268±57	0.15±0.09	0.02±0.01
Ischemia–reperfused, untreated (IR-0)	878±67*	1401±123*	0.41±0.1*	0.15±0.08*
Ischemia–reperfused, allopurinol treated (IR-A)	798±77*	1340±163*	0.11±0.1	0.018±0.01
Ischemia–reperfused, MB 42 μM treated (IR-42)	767±69*	1319±109*	0.33±0.07****	0.18±0.09*
Ischemia–reperfused, MB 68 μM treated (IR-68)	775±87*	1288±96*	0.39±0.04****	0.014±0.02
Ischemia–reperfused, MB 128 μM treated (IR-128)	743±96*	1248±71*	0.34±0.05*	0.17±0.01*, ***
Reperfusion 15 min				
Control	372±36	261±39	0.15±0.09	0.02±0.001
Ischemia–reperfused, untreated (IR-0)	532±47*, **, ***	981±95*, ***	0.22±0.047**, ***, ****	0.1±0.01*, **, ***
Ischemia–reperfused, allopurinol treated (IR-A)	352±67*, **	342±52***	0.13±0.07	0.017±0.002
Ischemia–reperfused, MB 42 μM treated (IR-42)	478±53*, **, ***	919±69*, **, ***	0.21±0.06***, ****	0.08±0.008*, **
Ischemia-reperfused, MB 68 μM treated (IR-68)	340±61**	681±64*, **	0.16±0.04****	0.06±0.004**
Ischemia–reperfused, MB 128 μM treated (IR-128)	388±54*, **	714±55*, **, ***	0.18±0.07****	0.06±0.005*, **

Abbreviations: *XO* xanthine oxidase plus xanthine dehydrogenase, *GSH* reduced glutathione, *IR* ischemia–reperfused organs, *MB* methylene blue, *A* allopurinol

*$p<0.01$ vs. controls, **$p<0.01$ vs. the 2-min reperfusion values, ***$p<0.01$ vs. IR-68 organs, ****$p<0.05$ compared to the control organs

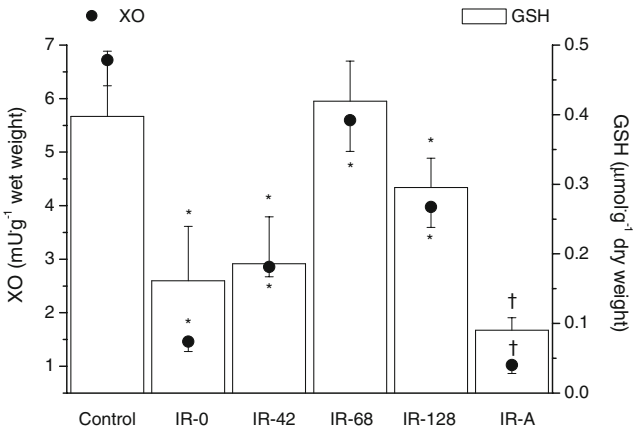

Figure 2 Post-experimental pancreas tissue total xanthine oxidase (XO+ XDH) and reduced glutathione (GSH) data. *$p<0.01$ vs. controls, IR-A and IR-68 organs; †$p\leq0.02$ vs. all groups. Abbreviations: *IR-0* ischemia–reperfused, untreated pancreata; *IR-42* ischemia-reperfused, MB 42 μM-treated organs; *IR-68* ischemia-reperfused, MB 68 μM-treated organs; *IR-128* ischemia–reperfused, MB 128 μM-treated organs; *IR-A* ischemia-reperfused, allopurinol-treated pancreata.

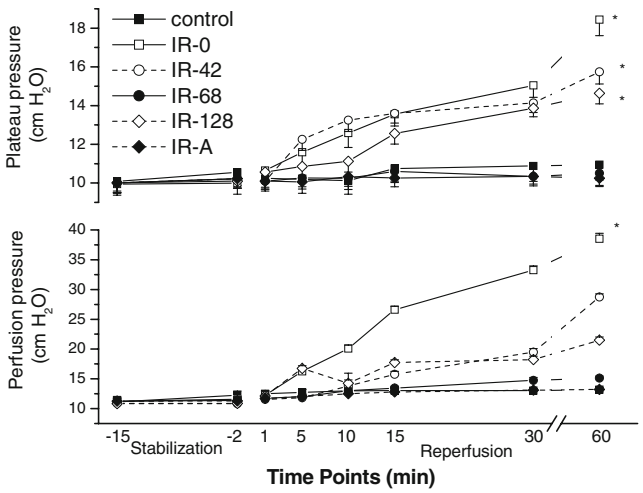

Figure 3 Lung ventilatory plateau pressure (*upper plane*) and perfusion pressure (*lower plane*) values. *$p<0.05$ vs. control, IR-A and IR-68 groups. Abbreviations: *IR-0*, lungs attached to ischemia–reperfused, untreated pancreata; *IR-42* lungs attached to ischemia–reperfused, MB 42 μM-treated organs; *IR-68* lungs attached to ischemia–reperfused, MB 68 μM-treated organs; *IR-128* lungs attached to ischemia–reperfused, MB 128 μM-treated organs; *IR-A* lungs attached to ischemia–reperfused, allopurinol-treated pancreata.

Table 3 Final Po_2/Fio_2 and Bronchoalveolar Lavage (BAL) Data (Mean±SD)

Groups	Po_2/Fio_2	Bronchoalveolar lavage			
		Volume (ml)	Amylase (U l^{-1})	Total XO (mU ml^{-1})	GSH (mM)
Control	675±65	0.56±0.04	15±3	0.1±0.01	0.01±0.003
Ischemia–reperfused, untreated (IR-0)	445±69*	0.88±0.05*	44±8*	0.3±0.02*	0.005±0.001*
Ischemia–reperfused, allopurinol treated (IR-A)	641±61	0.50±0.05	16±2	0.11±0.01	0.011±0.003
Ischemia–reperfused, MB 42 μM treated (IR-42)	567±61*	0.71±0.1*	35±7*	0.18±0.02**	0.008±0.002**
Ischemia–reperfused, MB 68 μM treated (IR-68)	603±59	0.50±0.06	21±6	0.11±0.02	0.012±0.002
Ischemia–reperfused, MB 128 μM-treated (IR-128)	596±43**	0.59±0.07*	32±5*	0.10±0.03**	0.01±0.001**

Abbreviations: *XO* xanthine oxidase plus xanthine dehydrogenase, *GSH* reduced glutathione, *IR* ischemia–reperfused organs, *MB* methylene blue, *A* allopurinol

*$p<0.01$, **$p<0.05$ compared to the corresponding control, IR-A- and IR-68-treated groups

All lungs remained isogravimetric during stabilization; the control, the IR-A, and the IR-68 lungs did not gain much weight during the entire experiments (Fig. 4). In contrast, the IR-0 and the IR-42, and less so the IR-128, lungs progressively gained weight, starting at 5 min of reperfusion: they ultimately reached ~4 times the IR-A and controls' weight gain. This picture paralleled lungs' WDRs (Table 1): IR-0 lungs recorded the highest values while IR-A and IR-68s values changed minimally comparably.

Analysis of IR-0s BAL volumes and contents proved abnormal as well. High BAL amylase concentration indicates disrupted alveolocapillary barrier. Amylase in the IR-0, the IR-42, and the 128-MB BALs was two to three times higher compared to the corresponding controls, IR-A and IR-68s (Table 3). The total XO activity, also adjusted to the total BAL volume, was low in most IR-treated lungs compared to the IR-0-attached lungs, as were the trends of the retrieved volumes; it was minimal in the IR-A lungs. The GSH profiles were rather high in the controls and in the IR-68s and slightly lower in the IR-As, compared to the IRs (Table 3).

Lung Tissue XO and GSH

The post-experimental total XO activity in the lung tissues is displayed in Fig. 5. The IR-0 lungs' XO was ~75% higher than in the controls; XO activity in the IR-A lungs was minimal and that of the IR-68 group was the lowest

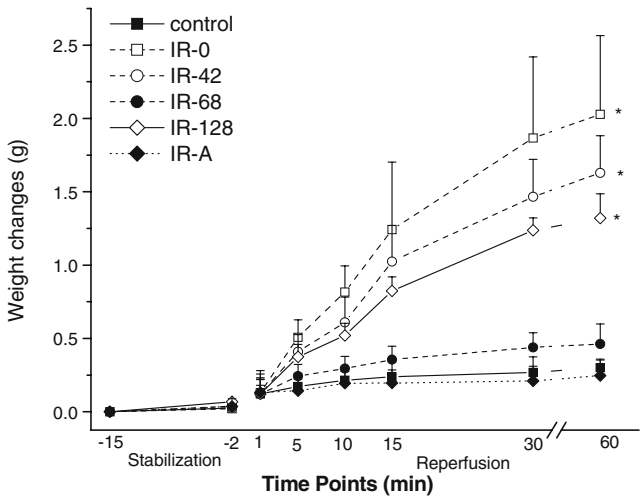

Figure 4 Intra-experimental lung weight gain. *$p\leq0.05$ vs. control, IR-A and IR-68 groups. Abbreviations: *IR-0* lungs attached to ischemia–reperfused, untreated pancreata; *IR-42* lungs attached to ischemia–reperfused, MB 42 μM-treated organs; *IR-68* lungs attached to ischemia–reperfused, MB 68 μM-treated organs; *IR-128* lungs attached to ischemia–reperfused, MB 128 μM-treated organs; *IR-A* lungs attached to ischemia–reperfused, allopurinol-treated pancreata.

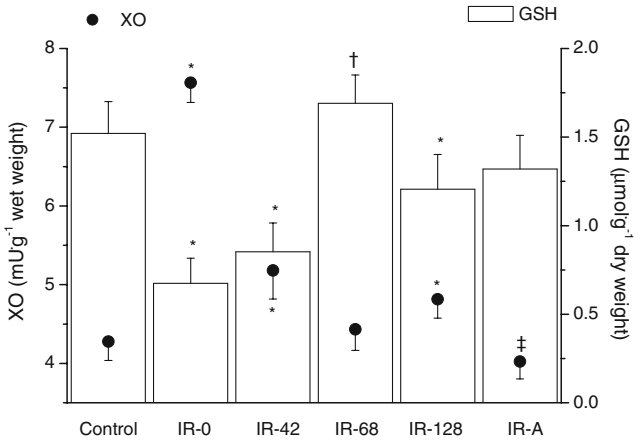

Figure 5 Post-experimental lung tissue total xanthine oxidase (XO+XDH) and reduced glutathione (GSH) data. *$p<0.01$ vs. the controls, IR-A- and IR-68-treated organs; †$p<0.05$ vs. control, IR-A- and IR-MB-treated groups; ‡$p<0.05$ vs. all groups. Abbreviations: *IR-0* lungs attached to ischemia–reperfused, untreated pancreata; *IR-42* lungs attached to ischemia–reperfused, MB 42 μM-treated organs; *IR-68* lungs attached to ischemia–reperfused, MB 68 μM-treated organs; *IR-128* lungs attached to ischemia–reperfused, MB 128 μM-treated organs; *IR-A* lungs attached to ischemia–reperfused, allopurinol-treated pancreata.

among all IR-MB-treated groups. Contrarily, GSH contents in the control and in the IR-68 and the IR-128 lungs were higher by a mean of 60–80% compared to the IR-0- and the IR-42-attached organs (Fig. 5). They were also higher than the content detected in the IR-A lungs.

Discussion

This study reiterates our previous report that ALI may be induced soon after a normal rat lung is exposed to the effects of warm ischemia of the pancreas.[4] The present double-organ model investigated clinical characteristics of ALI, e.g., pulmonary permeability abnormality and relative hypoxia that had previously been associated with pancreatitis.[22] The present blood-free protocol further establishes one of our group's initial suspicions: that all organs that undergo IR would probably "talk the same language" but would also "respond with the same phrase": they will transmit remote damage by the same pathological code, XO and ROS, and these can be withheld by drugs such as allopurinol and MB.

The results of the present study confirm the long-standing hypothesis that the oxidant/antioxidant misbalance, i.e., XO increase and GSH decrease, is associated with pulmonary vascular and ventilatory injury.[4,13] This occurred despite the ~2 times lower total XO activity recorded in the pancreas compared to those found in the liver, for example[4,5,7,9] and the pancreatic effluent being diluted before entering the pulmonary circulation. The potentials of XO to induce ALI following pancreas IR is strongly supported by the data gathered from the IR-treated (both allopurinol and MB) organs. Amylase and lipase leaked out of all pancreata during reperfusion at similar magnitudes in all IR organs, because of the IR-induced cellular lyses. Nevertheless, the exposure of the normal lungs to the 68-MB-treated and the IR-A organs' reperfusates did not conclude in ALI, despite the presence of high amylase and lipase. Only the presence of abnormally high XO activity and a relatively reduced GSH content in the circuit, without sufficient antioxidant (allopurinol or MB) counter-activity, was associated with lung damage.

MB, a low molecular weight and partially liposoluble vital dye, competes with oxygen for electrons that are transferable from flavo-enzymes.[11,12] Some authors suggested that MB inhibits the production of superoxides by competing with molecular oxygen at the metal–sulfur centers of XO, enabling anaerobic oxidation of purine substrates.[12,23] Others contended that MB acts as a "parasitic" electron acceptor, shunting electron flow from the normal pathway to the colorless, reduced form of MB, leukomethylene blue, and thus effectively bypassing the generation of ROS.[11] In the presence of NO, MB can also act as an antioxidant by eliminating the superoxide that reacts with NO to produce peroxynitrite.[24] The efficacy of MB in protecting the rat-isolated aorta from reperfusion-induced dysfunction was demonstrated in a similar isolated perfused double-organ model where MB was used in similar dose regimens.[17] The selective protection that was obtained with MB in this study is similar to that of allopurinol, a specific anti-XO compound, and substantiates the role of XO and ROS in the generation of such damage.

The effect of MB is likely to be in a bell-shaped manner. It is difficult to explain why MB is beneficial in ALI at a 68 μM regimen but is ineffective when 42 and 128 μM solutions are applied. The therapeutic range is narrow, especially considering the inhibition of guanylate cyclase[17] and NADH cytochrome c reductase[23] by MB. Indeed, the relative ineffectiveness of the MB 128 μM solution in protecting lung parameters could originate by the excessive MB-dependent blocking effect on the guanylate cyclase. It was previously concluded that the inhibition of NO could become disadvantageous to the epithelial–endothelial alveolocapillary integrity of the lung, which could outweigh the protective benefits of MB. Under such circumstances, the hypoxia in our 42 >128 μM groups could have further down-regulated the effects of MB as previously documented.[25] Together with ROS endothelial-damaging potentials,[10] which would ultimately lead to vascular tone impairment, rather high MB dose could generate a vicious cycle of edema, hypoxia, and therapeutic disappointment, as was herein demonstrated.

The BAL data that were retrieved from the IR-coupled lungs, both treated or not, further support our results that MB selectively but beneficially protected the gas-exchanging components of the lung, including the vascular phase. The pancreas-originated enzymatic load and the total XO activity in the various perfusates, mainly in the IR-0 and the IR-42 BALs, indicate that the fluid and the enzymes traversed the alveolocapillary membrane from the vascular bed and scattered within the tissue to be later detected.[26] The findings of low XO in the IR-68 and IR-128 BALs, and the lower retrieved volumes, represent limited solutes scattering and fluid permeability through the less damaged alveolocapillary barrier in the presence of effective antioxidant activity of the MB-68 and the MB-128 regimens.[5,26] Another explanation for the low XO in the BAL content of the two high MB groups, which would illustrate an integration of the two separate phase activities, may be that these concentrations—but not the MB-42—inhibited ROS production within the lung tissue after inducing initial membrane damage. This is supported by the significantly higher amylase activity detected in the IR-128 group's BAL compared to those of the IR-MB-68 and the MB-42 groups.

GSH is an essential component in tissue oxidants-antioxidants balance.[21,26] Remotely induced damaged lungs pretreated with *N*-acetyl-L-cysteine were least damaged.[26] GSH affords direct scavenging potentials, such as trapping H_2O_2 and consequently decreasing the production of the highly reactive hydroxyl radical.[27] It is also a natural scavenger of the superoxide anion, protecting the cellular protein thiol groups, which are essential for protein function and cellular integrity.[20,27,28] The data that emerged from the present study, regarding GSH relationship with XO in the pancreas, support the primary contention described previously,[4,29] i.e., that the oxidant/antioxidant misbalance associated or not with the loss of intra- and extracellular GSH that follows remote organ IR may lead to lung edema, hypoxia, and increased vascular permeability in an otherwise normal lung. In the IR-0, IR-42, and the IR-128 lungs, the pancreatas' and lungs' GSH leaked out of the organs, and was low in the same groups' BAL, probably because it also had been consumed in the circuit as an antioxidant, as was shown earlier.[26] Contrarily, the higher GSH contents in the IR-68 lungs indicate a proportionately lesser antioxidant consumption because of the low oxidative activity in the circuit as a result of adequate activity of MB. This explanation is supported by our previous demonstrations of MB's dose-dependent organ protection[17,26] and by the data retrieved from the IR-A group of lungs. In addition, the prophylactic use of MB was recently proven in reducing the neurological injury while improving clinical outcome in a rabbit spinal cord IR model.[30] These authors found higher GSH levels in the MB-treated group, concluding, as did we, that MB is efficacious because of its antioxidant properties.

The findings of this study may be relevant to the prevention of clinical lung injuries associated with IR conditions. The present model could mimic clinical syndromes such as shock,[1] aortic aneurysm repair,[29,31,32] and liver or pancreas transplantation,[33,34] all of which are no flow–reflow events that affect the function of large areas, and may damage remote organs upon reperfusion. Better definition of species- and dose-specific characteristics of MB's efficacy may lead to its consideration as a possible therapeutic tool in such conditions. Both in this and in previous studies,[4,5,7,26] indices of ALI (e.g., disturbed P_{O_2}/F_{iO_2} ratio or alveolar transudate) would stand for MB's efficacy. "Wet lung" is indeed one of the therapeutic objectives and telling early signs of ALI; it would represent non-distensible or fluid-filled alveoli, disruption of the ultra thin physiologic barrier between the air and the vascular compartment that is at the basis of normal oxygen transport from the alveoli to the pulmonary venous circuit. In our IR-68-MB-treated group, the alveoli were presumably empty and compliant enough to contain larger lavage volumes, resulting in lower retrieved fluid volumes as was in the controls and the appropriately protected lungs.[5]

Furthermore, clinical acute pancreatitis is diagnosed mainly by acute abdominal pain associated with a concomitant increase in the serum amylase and lipase levels.[18] Even though injury is usually mild, severe pancreatic damage develops in 20% of the patients, of whom 15–25% will die, many critically ill and those suffering from ARDS.[6,35] Since this study documented tissue edema, abnormal BAL indices, and hypoxia in association with post-ischemia pancreatitis, and since all these phenomena were attenuated when XO and ROS damaging activities were controlled by MB (and comparably by allopurinol), these findings support our primary hypothesis—and now report—of reducing lung injury by the use of various antioxidants: mannitol, *N*-acetyl-L-cysteine, and now MB, at the first signs of ALI, thus preventing their deterioration into full blown ALI.[4,5,7,9,26,36] Finally, while this manuscript was edited for publication, others have demonstrated the possible role of MB in protecting the lung from the effects of rat mesenteric artery-induced IR.[37] This report both follows our previous data in animals[17,38] and further supports the present promising clinical findings.

In summary, acute lung injury is a frequent complication of pancreatitis. An early increase in alveolocapillary membrane permeability can ensue, leading to lung functional deterioration and hypoxia. While the precise pathophysiology of post-pancreatitis clinical ALI is incompletely understood, this experimental work in an isolated, double-organ animal model points to clinically feasible therapeutic strategies, such as a non-toxic antioxidant, MB, that is currently in use for other indications, and that is potentially capable of attenuating remotely induced ALI.

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ORIGINAL ARTICLE

Small Pancreatic and Periampullary Neuroendocrine Tumors: Resect or Enucleate?

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Abstract
Objective The aim of this study was to compare the outcomes of enucleation versus resection in patients with small pancreatic, ampullary, and duodenal neuroendocrine tumors (NETs).
Methods Multi-institutional retrospective review identified all patients with pancreatic and peri-pancreatic NETs who underwent surgery from January 1990 to October 2008. Patients with tumors ≤3 cm and without nodal or metastatic disease were included.
Results Of the 271 patients identified, 122 (45%) met the inclusion criteria and had either an enucleation (n=37) and/or a resection (n=87). Enucleated tumors were more likely to be in the pancreatic head (P=0.003) or functioning (P<0.0001) and, when applicable, less likely to result in splenectomy (P=0.0003). The rate of pancreatic fistula formation was higher after enucleation (P<0.01), but the fistula severity tended to be worse following resection (P=0.07). The enucleation and resection patients had similar operative times, blood loss, overall morbidity, mortality, hospital stay, and 5-year survival. However, for pancreatic head tumors, enucleation resulted in decreased blood loss, operative time, and length of stay compared to pancreaticoduodenectomy (P<0.05).
Conclusion These data suggest that most outcomes of enucleation and resection for small pancreatic and peri-pancreatic NETs are comparable. However, enucleation has better outcomes than pancreaticoduodenectomy for head lesions and the advantage of preserving splenic function for tail lesions.

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Keywords Neuroendocrine tumor · Islet cell tumor · Pancreas neoplasm · Ampulla of Vater · Duodenum

Introduction

Pancreatic islet cell tumors were first described in 1902 by Nicholls et al. and are rare, indolent neoplasms that can be either "benign" or malignant.[1] In the last 10 years, the nomenclature of these lesions has evolved to pancreatic neuroendocrine tumor (NET) with a stress on the degree of tumor differentiation.[2–5] These NETs of the pancreas, ampulla, and duodenum are usually sporadic and classified according to their ability to secrete hormones—functioning or non-functioning. Functioning tumors are frequently diagnosed earlier than their non-functioning counterparts because of the development of hormonal symptoms. As a result, non-functioning NETs present later in the disease course and are adversely associated with survival.[6–8] Indications for surgery in patients with pancreatic and peri-

pancreatic NETs include systemic symptoms due to hormone release, local compressive symptoms, and prevention of malignant transformation and/or dissemination.[9] However, the optimal surgical management for pancreatic, ampullary, and duodenal NETs is controversial.

The first successful operation on a "benign" NET was an enucleation of a functioning pancreatic insulinoma in 1929.[10] Subsequently, surgeons were classically taught to enucleate such lesions. Over the last 40 years, however, the morbidity and mortality of pancreatic resection has diminished from nearly 25% to less than 5% in certain "centers of excellence".[11–13] As a result, the proportion of patients undergoing pancreatic resection has increased (5% in the last 15 years), and pancreatectomy has become the standard therapy in many institutions, even for small lesions.[13] However, data comparing these two surgical approaches for small pancreatic and peri-pancreatic NETs are lacking. Therefore, the purpose of this study was to document the morbidity, mortality, and outcomes of enucleation versus resection for small pancreatic, ampullary, and duodenal NETs at low risk for malignant transformation.

Methods

Multi-institutional retrospective review identified 271 patients with pancreatic, ampullary, and duodenal NETs who were operated on at four institutions or partner hospitals between January 1990 and October 2008. The participating institutions were Indiana University (IU), University of Wisconsin (UW), Northwestern University (NU), and the Medical College of Wisconsin (MCW). The IU, UW, NU, and MCW Institutional Review Boards each granted approval for the study. Electronic medical records, clinic charts, pathology reports, and tumor registries were used to determine patient demographics, pathology, treatment, and outcome data. The enucleation group included patients who underwent enucleation (Fig. 1), duodenal wall excision, or transduodenal ampullary tumor excision, while the resection group was comprised of patients treated by pancreaticoduodenectomy; distal, central, or total pancreatectomy; or partial pancreatectomy not otherwise specified (NOS). The transduodenal ampullary and local duodenal wall excisions were included in the enucleation group because formal pancreatic resection was not performed. The decision to perform an enucleation or resection was at the discretion of the attending surgeon. Prior to enucleation, the absence of liver metastases and peri-pancreatic lymphadenopathy was confirmed.

All specimens were reviewed by the pathologists at each institution and determined to be pancreatic or peri-pancreatic (ampullary or duodenal) NETs. Those tumors that came to surgery and were less than or equal to 3 cm by final pathology were included in this study. The 3-cm

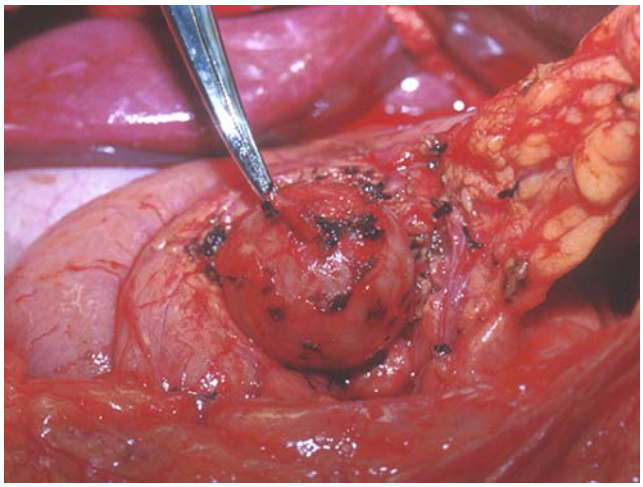

Figure 1 Operative photograph depicting the enucleation of a pancreatic neuroendocrine tumor.

cutoff was chosen in order to create comparable groups since enucleation is not indicated for patients with large tumors and/or nodal or distant metastases. In addition, LaRosa and colleagues recently classified pancreatic NETs into stepwise groups of increasing malignant potential, and found that among well to moderately differentiated tumors the best overall discriminative power for size was at a cutoff of 3 cm.[8] For the present investigation, malignant tumors were defined as having positive locoregional lymph nodes or the presence of distant metastatic disease and were excluded from the analysis. All tumors were stained for a variety of hormones including gastrin, glucagon, insulin, somatostatin, and vasoactive intestinal peptide (VIP) as well as neuroendocrine markers such as chromogranin A and synaptophysin. An NET was considered functional if symptoms from hormone release were present and/or the surgical specimen stained strongly for a specific hormone.

Morbidity was defined as any complication that occurred as a direct result of the enucleation or resection. Only complications that increased the hospital stay, required readmission, or necessitated invasive intervention were included. Postoperative pancreatic fistula was graded (A–C) as defined by the International Study Group on Pancreatic Fistula (ISGPF).[14] Retrospective chart review was required in each case to grade the fistulas. Mortality was characterized as death within 30 days of surgery. Blood loss and operative time were obtained from operative notes and anesthesia records. Follow-up and survival data were obtained on all patients from hospital records, clinic notes, and the Social Security Death Index database (SSDI; http://ssdi.rootsweb.ancestry.com/cgi-bin/ssdi.cgi). Survival was calculated from the date of surgery to the date of death, last known follow-up, or last SSDI update (February 17, 2009; last accessed March 9, 2009).

Data are presented as mean±standard error of the mean (SEM) except where otherwise specified. Statistical analyses were performed by two-sided independent *t* test and chi-square analysis for continuous and categorical variables, respectively, with statistical significance achieved at $P<0.05$. For analysis of fistula severity, the proportion of grade A fistulas (less severe) was compared by chi-square to the proportion of grade B and C (more severe) fistulas. Survival rates were analyzed by the Kaplan–Meier actuarial method, with statistical significance determined by the log-rank statistic using SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL, USA).[15]

Results

One hundred twenty-two (45%) of 271 patients with pancreatic, ampullary, and duodenal NETs met all study criteria and were included in this investigation. One hundred nineteen patients were excluded on the basis of positive lymph nodes and/or metastatic disease, and 30 additional patients who had no evidence of nodal or metastatic disease were excluded for size >3 cm. All 30 of these patients underwent resection; thus, no enucleation patients were excluded based on size. A total of 124 operations were performed and divided into two groups: enucleation ($n=37$) and resection ($n=87$). Two patients underwent both an enucleation and a distal pancreatectomy (DP) during the same operation. The median age of the patients was 53 years (range 23–90 years). The two groups were similar with respect to mean age and gender (Table 1).

Several different surgical procedures were performed in these patients and are summarized in Table 2. In the enucleation group, two of the 32 (6%) procedures were completed laparoscopically; whereas in the resection group, eight of 56 (14%) patients had a laparoscopic distal pancreatectomy. No splenectomies (0%) were required in any of the enucleated patients who had pancreatic tail tumors ($n=9$). Additionally, 16 of the 50 (32%) patients in the resection group with pancreatic tail tumors had spleen-preserving distal pancreatectomies. Therefore, when applicable, patients with tail lesions underwent significantly more splenectomies compared to the enucleation patients ($P=0.0003$). However, seven of the eight patients who had laparoscopic distal pancreatectomies had splenic-preserving procedures.

A total of 128 NETs were enucleated ($n=39$) or resected ($n=89$) during the 124 procedures (Table 3). Overall, 39% of the tumors were located in the head of the pancreas, ampulla, or the duodenum (Table 3). Tumors that were enucleated were significantly more likely to be in the head of the pancreas when compared to tumors that were resected ($P=0.003$). The mean and median size of the lesions was similar between the enucleation and resection patients (Table 3). Functional status was able to be determined for 91 of 128 (71%) tumors (Table 3). Patients who underwent enucleation had a smaller proportion of non-functioning tumors compared to the patients who had resections ($P<0.0001$). The histologic subtypes seen on pathology are shown in Table 3.

Table 1 Patient Demographics

Variable	Enucleation	Resection	Total	*P* value
N, patients	36	86	122	
N, operations	37	87	124	
Age (years)	56±2	52±1	53±1	0.14
%, Female	54	56	55	0.83

Data are presented as mean±standard error of the mean

Table 2 Surgical Management

Operative details	Enucleation ($n=37$)	Resection ($n=87$)	Total ($n=124$)
Enucleation (%)	32 (87)		32 (26)
Distal pancreatectomy (%)		56 (64)	56 (45)
Pancreaticoduodenectomy (%)		26 (30)	26 (21)
Central pancreatectomy (%)		3 (4)	3 (2)
Transduodenal ampullary excision (%)	3 (8)		3 (2)
Duodenal wall excision (%)	2 (5)		2 (2)
Partial pancreatectomy, NOS (%)		1 (1)	1 (1)
Total pancreatectomy (%)		1 (1)	1 (1)
Splenectomy (%)	0 (0)*	34 (68)	34 (27)

NOS not otherwise specified

*$P=0.0003$ vs. resection (only for tumors located in the tail of the pancreas)

Table 3 Tumor Pathology

	Enucleation ($n=37$)	Resection ($n=87$)	Total ($n=124$)
Location			
Head/ampulla/ duodenum (%)	23 (59)*	27 (30)	50 (39)
Body/tail (%)	16 (41)	62 (70)	78 (61)
Mean size (cm)	1.8±0.1	1.7±0.1	1.7±0.1
Median size (cm)	1.7	1.6	1.7
Pathology			
Insulinoma (%)	22 (63)	11 (20)	33 (32)
Non-functioning (%)	8 (23)**	42 (75)	50 (55)
Gastrinoma (%)	3 (9)	3 (5)	6 (7)
Glucagonoma (%)	2 (6)	0	2 (2)

*$P=0.003$ vs. resection, **$P<0.0001$ vs. functioning tumors

Examination of patient intraoperative and hospital data revealed that the enucleated and resected patients had comparable blood loss (P=0.11, Table 4). The mean operative time and length of stay between the two groups also was similar (P=0.11 and P=0.50, respectively; Table 4). However, when patients with tumors in the head of the pancreas were analyzed separately, both blood loss and operative time were greater after pancreaticoduodenectomy when compared to enucleation (blood loss=874±264 vs. 286±81 ml, P=0.04; operative time=334±30 vs. 229±34 min, P=0.03, respectively). In addition, the patients who underwent pancreaticoduodenectomy had a longer length of stay than patients who had enucleation (9.3±0.6 vs. 6.9±0.9 days, P=0.03).

We also analyzed the overall morbidity experienced by the patients in this study which showed a similar rate of complications after enucleation and resection (P=0.69, Table 4). Patients who underwent enucleation experienced pancreatic fistula formation more frequently than resected patients (P<0.01, Table 4). However, when the fistulas were graded on an A, B, C scale according to the ISGPF classification, the majority of fistulas in enucleated patients was grade A, and the remainder was grade B (Table 4).[14] No grade C fistulas developed after an enucleation. Conversely, fistulas that formed after resection were mostly grade B, and 15% were grade C (Table 4). Comparison of the proportion of grade A (less severe) fistulas to the proportion of grade B and C (more severe) fistulas revealed that the fistulas tended to be worse in patients who underwent resections, though this difference did not reach statistical significance (P=0.07). On the other hand, the percentage of infectious complications in the two groups was similar (P=0.18, Table 4). Small bowel obstruction, ileus, or delayed gastric emptying occurred after one (2.7%) enucleation as opposed to ten (11.5%) resections (P=0.17). The only operative death in the series occurred after a distal pancreatectomy, and the 30-day mortality rates were similar between enucleated and resected groups (P=1.00, Table 4).

In addition to examining complications, we measured survival and recurrence. Follow-up ranged from 1 to 161 months (Table 4). The 5-year survival of the patients in this study was 91.9%, which is consistent with the low malignant potential of small, node-negative tumors without evidence of metastatic disease. No difference in 5-year survival was detected between enucleated and resected patients (Fig. 2, Table 4). While nodal and distant metastases were absent in all patients at initial surgery, five patients who underwent resections experienced systemic recurrence of their disease. The incidence of systemic disease recurrence was comparable between patients who had enucleations versus resections (0% vs. 5.7%, P=0.32). No local recurrences were observed during the follow-up period.

Table 4 Outcome Data

	Enucleation (n=37)	Resection (n=87)	Total (n=124)
Estimated blood loss (ml)	365±70	690±135	596±99
Operative time (min)	216±22	250±13	240±11
Length of stay (days)	8.7±1.2	10.2±1.3	9.7±1.0
Complications (%)	18 (49)	38 (44)	56 (45)
Complication type			
Infectious (%)	3 (8)	17 (20)	20 (16)
Fistula (%)	14 (38)*	13 (15)	27 (20)
A	8 (57)	3 (23)	11 (41)
B	6 (43)	8 (62)	14 (52)
C	0	2 (15)	2 (7)
30-day mortality (%)	0 (0)	1 (1.1)	1 (0.8)
5-year survival	35 (94)	78 (91)	113 (92)
Mean follow-up (months)	49.7±6.6	50.3±4.7	50.1±3.8
Median follow-up (months)	42	41	41

*P<0.01 vs. resection

Discussion

In this series, we analyzed 122 patients with small (≤3 cm) pancreatic, ampullary, and duodenal NETs based upon the type of surgical treatment (enucleation vs. resection) received over an 18-year period at four institutions. Patients undergoing enucleation were more likely to have functional tumors in the head of the pancreas and less likely to have a splenectomy. The estimated blood loss, operative time, length of stay, overall morbidity, and all-cause mortality were similar between the enucleations and resections.

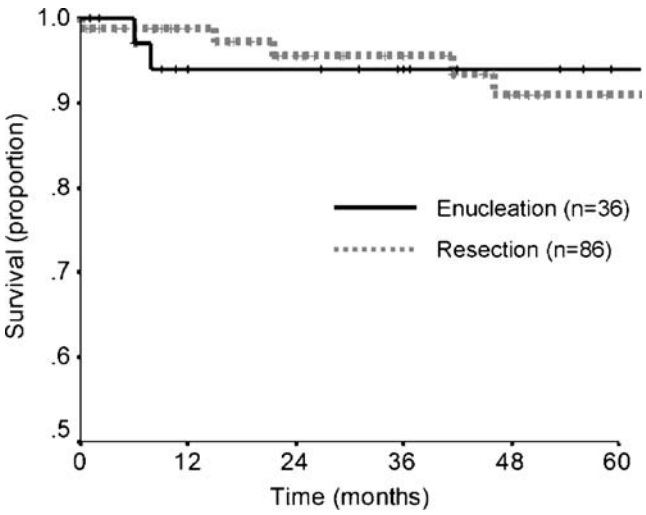

Figure 2 Kaplan–Meier actuarial survival curve comparing patients who underwent enucleation (n=36) versus those who underwent resection (n=86) (P=0.50 by log-rank test).

While the pancreatic fistula rate was higher after enucleation, the fistulas tended to be less severe compared to those that occurred following resection. For patients with NETs in the head of the pancreas, enucleation was associated with decreased blood loss, operative time, and length of stay compared to pancreaticoduodenectomy.

The type of procedure performed for NETs of the pancreas, ampulla, and duodenum is important because surgical resection is considered to be the only curative modality.[16] Even for small tumors, the risk of malignant transformation is present. This risk is highlighted by the 4% overall recurrence rate in this study of patients with 3 cm or less tumors who were node negative and metastasis free. The operative strategy regarding these NETs has focused on the relative advantages and disadvantages of local, less invasive procedures versus a formal pancreatic resection. As the morbidity and mortality of pancreatic resection at high-volume centers has decreased, distal pancreatectomy of small pancreatic tail lesions has become the norm.[13] Similarly, pancreaticoduodenectomy, although more invasive than distal pancreatectomy, has grown to be an acceptable treatment option for small tumors of the pancreatic head, especially when in close proximity to the pancreatic duct.[13,17,18] Central or middle segment pancreatectomy is also being employed in patients with pancreatic neck lesions.[19,20] Reports of safe and effective laparoscopic resections have added to the types of surgical resections performed.[21–23] However, risks associated with formal pancreatic resection include loss of healthy pancreatic tissue (with possible endocrine or exocrine insufficiency), the potential for splenectomy with distal resections, and a variety of complications related to bowel anastomoses or dysfunction of the stomach. Our study confirms that the rate of splenectomy is higher in patients undergoing resection. In addition, small bowel obstruction, ileus, and delayed gastric emptying occurred more frequently after resection, though this difference was not statistically significant.

As an alternative to resection, enucleation has remained an important part of the surgical armamentarium for pancreatic, ampullary, and duodenal NETs. The guiding principles for enucleation are the size of the tumor, absence of evidence of malignancy, and proximity to the pancreatic duct.[18,24–26] Previous reported benefits of enucleation include reduced blood loss and operative time compared to resection, but not decreased length of stay.[22,25–28] Like resection, enucleations can be performed laparoscopically with reduced blood loss and operative time when compared to resection.[22,29,30] In this investigation, operative blood loss and time were statistically similar when all patients undergoing enucleation or resection were compared ($P=0.11$). However, when enucleation was evaluated against pancreaticoduodenectomy, the blood loss and operative time were greater after pancreaticoduodenectomy. Comparison of these same two procedures performed laparoscopically also supports this conclusion.[22] The length of hospital stay for our enucleated and resected patients was similar which confirms prior findings.[27] But our analysis indicated that hospital stay is significantly longer following pancreaticoduodenectomy than enucleation. In addition, enucleation has been shown to preserve pancreatic tissue.[18]

This investigation focused on small pancreatic and peripancreatic NETs with a relatively equal overall distribution of functional (45%) and non-functional (55%) lesions. A retrospective review of 125 patients with pancreatic NETs by Phan et al. revealed a similar proportion of functional hormone expression (52%).[31] The distribution of functional tumor types in their study showed that insulinomas were the most common followed by gastrinomas, VIPomas, and glucagonomas.[31] In the current series, the majority of functional tumors also were insulinomas, and the dispersion was similar, though no VIPomas were seen (Table 3). Thus, the functional classification of NETs in our study is comparable to previously published data.[9,31–33] We also found that enucleated tumors were more likely to be functioning and in the head of the pancreas. These findings may be the result of surgical preference. Non-functioning tumors were resected more often, likely because non-functional status is a known adverse prognostic factor for survival.[6–8] In addition, distal pancreatectomy is often the procedure of choice for pancreatic tail lesions.

In this study, we also examined the morbidity, mortality, and survival of enucleations compared to resections. The overall complication rate of 45% is comparable to rates observed in other studies that range from 14% to 50%.[18,27,28,30,31,34–37] Our data reveal that overall morbidity does not differ significantly between patients undergoing enucleation (49%) versus resection (44%). Enucleation has previously been shown to have similar morbidity to resection while preserving pancreatic tissue.[18] The 30-day mortality rate in this series (0.8%) also was comparable between the patients studied and was not different from previously reported rates for these operations.[11,12,36] While the overall morbidity and mortality were similar, pancreatic fistula development occurred more commonly following enucleation. After enucleation, 38% of patients developed a pancreatic fistula which is within the previously reported range for enucleated patients—16% to 38%.[22,27,30,31] In patients who were treated with resections, 15% formed fistulas which also is similar to other studies (range 9–26%).[22,27,30,31] Retrospective chart review in each case showed that the leaks following enucleation were ISGPF grade A or B pancreatic fistulas which, by definition, are not associated with other complications or prolonged hospitalizations. Comparison of grade A versus grade B and C pancreatic fistulas in the two groups

revealed that those fistulas diagnosed in the resected patients tended to be worse suggesting that the overall leak rate should be examined in the context of fistula grade. In terms of survival, when compared to tumors of other cell types, the prognosis of patients with pancreatic and peri-pancreatic NETs is very good and is excellent when only patients with "benign" or localized disease are evaluated.[7,8,33] With a mean follow-up of 50 months, the survival in our study was no different between the surgical groups. In addition, the overall mortality for the resection group is in line with other reports of formal pancreatic resections.[7,8,11,12]

The present study is limited by the non-randomized retrospective design and inherent selection bias. Thus, resection may have been performed more often in patients with more aggressive disease. The resection group did have more systemic recurrences and a larger proportion of non-functioning tumors. Because enucleation is not indicated for patients with large tumors, lesions in close proximity to the pancreatic duct, or in the known presence of nodal or metastatic disease, a size limitation was essential to creating comparable groups. In recent years, laparoscopic approaches to NETs have been reported with increasing frequency.[22,29,30] Therefore, in the future, open enucleation will need to be compared to laparoscopic enucleation. An analysis of the associated costs of these procedures also might enhance forthcoming studies. Due to the rarity of pancreatic and peri-pancreatic NETs, multi-institutional studies and larger population-based data sets also will be important to analyze in order to advance future practices.

In conclusion, this multi-institutional retrospective review of 122 patients compared enucleation to resection for small pancreatic, ampullary, and duodenal NETs. The overall effectiveness of enucleation and resection for these NETs is comparable, with similar morbidity, mortality, and survival.[9,31] The surgical procedures also were similar with respect to estimated blood loss, operative time, and length of hospital stay. However, enucleation resulted in decreased blood loss, operative time, and duration of stay compared to pancreaticoduodenectomy when just patients with NETs in the head of the pancreas were considered. Furthermore, enucleation was associated with a significantly lower rate of splenectomy compared to all distal pancreatectomies. While enucleated patients had a higher incidence of pancreatic fistula formation compared to the resection group, the fistulas that formed after resection were mostly grade B and C, clinically significant fistulas. Therefore, enucleation of small pancreatic and peri-pancreatic NETs is safe and does not compromise long-term survival. This analysis further confirms that enucleation of small NETs with low malignant potential remains a viable operative approach. The procedure of choice in these patients with smaller NETs may be enucleation for lesions in the pancreatic head and distal pancreatectomy with splenic preservation for lesions in the pancreatic tail.

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ORIGINAL ARTICLE

Prognostic Factors and Adjuvant Chemoradiation Therapy After Pancreaticoduodenectomy for Pancreatic Adenocarcinoma

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Abstract
Background The aim of this study was to determine prognostic factors for survival after resection of pancreatic adenocarcinoma (PC) and to compare outcomes after surgery alone versus surgery plus adjuvant therapy.
Methods We performed a retrospective review of 219 patients who underwent pancreaticoduodenectomy for PC with curative intent between 1995 and 2007. Data were collected prospectively. Postoperative adjuvant chemoradiation therapy (CRT) consisted of fluorouracil or gemcitabine-based chemotherapy; the median radiation dose was 45 Gy.
Results The 3- and 5-year overall survival (OS) rates were 24.3% and 14.2%, respectively. Median OS was 14.0 months [95% confidence interval (CI), 12–16 months]. Patients with metastatic lymph nodes experienced improved median survival (16 vs 10 months; $P<0.001$) and 3-year OS (3-year OS 28% vs 8%) after adjuvant CRT compared with those who had no CRT. Patients who underwent non-curative resection had the same effect (median OS, 13 vs 8 months; $P=0.037$). Lymph node metastasis and non-curative resection showed no significance on multivariate analysis. Poor differentiation [risk ratio (RR)=2.10; $P<0.001$] and tumor size >3 cm (RR=1.57; $P=0.018$) were found to be adverse prognostic factors; adjuvant CRT had borderline significance (RR=0.70; $P=0.087$).
Conclusions Adjuvant CRT benefited a subset of patients with resected PC, particularly those with lymph node metastasis and those undergoing non-curative resection. Multivariate analysis demonstrated that patients with tumors larger than 3 cm and poor differentiation had poor prognosis.

Keywords Pancreatic adenocarcinoma · Adjuvant chemoradiotherapy · Prognostic factor

Introduction

Pancreatic adenocarcinoma (PC) is one of the most lethal cancers, as indicated by its mortality incidence ratio of 98%.[1] Despite current multimodality therapy, treatment outcomes remain poor. Surgery is the only curative treatment option for this cancer entity, but only 10–15% of patients are candidates for potentially curative resection.[2–4] Some specialized centers have recently reported 5-year survival rates of over 20%.[5–7] It is not clear whether these improvements reflect positive patient selection or the effects of adjuvant treatment strategies.

Lymph node metastasis, tumor size, tumor differentiation, and resection margin status are known to be prognostic factors in PC.[7,8] Recently, some studies have shown that adjuvant chemoradiation therapy (CRT) improves survival after pancreaticoduodenectomy (PD) for PC and that a lack of adjuvant therapy is an adverse prognostic factor.[9–11] However, studies of the effects of adjuvant therapy following resection have produced mixed results. In the Gastrointestinal Tumor Study Group (GITSG) randomized controlled trial, there was a significant survival benefit in patients receiving CRT.[12,13] In contrast, trials in Europe have not confirmed a statistically significant survival benefit with adjuvant CRT, and some studies have even suggested a

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detrimental survival effect with CRT compared with chemotherapy or surgery alone.[14–16]

This study represents a single center experience with treating adenocarcinomas of the pancreatic head. We sought to identify prognostic factors and compare patient outcomes after surgery alone versus surgery plus adjuvant therapy.

Materials and Methods

We retrieved data from a prospectively collected database of all patients who underwent PD for periampullary neoplasms between January 1995 and December 2007 at Samsung Medical Center, Sungkyunkwan University. Our analysis was limited to patients who underwent PD for ductal adenocarcinoma of the pancreatic head. Those with adenocarcinoma arising from intraductal papillary mucinous neoplasms or mucinous cystic neoplasms were excluded. A total of 219 patients were enrolled. Diagnostic workup consisted of routine laboratory testing, chest radiography, and contrast-enhanced, multislice computed tomography. Magnetic resonance imaging or positron emission tomography was occasionally used for differential diagnosis of lesions in other organs. Diagnostic endoscopic retrograde cholangiopancreatography (with or without subsequent endoscopic drainage) and endoscopic ultrasonography were not used consistently. Surgical exploration was performed when there was evidence of resectable disease, which was defined as the absence of hematogenous metastases and absence of evidence for tumor extension to the superior mesenteric artery (SMA) or celiac axis by radiographic imaging. Limited invasion of the superior mesenteric or portal vein (SMPV) was not considered a contraindication to resection.

The standard surgical procedures for classical and pylorus-preserving PD and total pancreatectomy have been described previously.[17,18] Lymph node dissection was systematically performed in the hepatoduodenal ligament, along the common hepatic artery from the right side of the celiac axis and the right side of the SMA. If the paraaortic nodes were positive on frozen section examination, we sometimes performed paraaortic lymph node dissection depending on the surgeon's discretion. Otherwise, we did not routinely dissect them. Extended PD was performed in some patients. When arterial invasion was suspected, periarterial tissue, including the adventitia, was stripped off if possible and separated for permanent biopsy. Intraoperative blood loss and transfusion necessity were recorded from the anesthesia record.

Pathological findings were recorded in a standard format: histopathological diagnosis with grade of differentiation; tumor site and size; pathologic tumor node metastasis (TNM) stage[19]; extension to the duodenum, peripancreatic soft tissue, or bile duct; neural or lymphovascular ingrowth; total number of resected lymph nodes and positive lymph nodes, including location; and resection margin status (pancreatic, bile duct, and retropancreatic resection margin). Curative resection (R0) was defined as no tumor cells at the resection margin and no gross tumor remaining at the operative site or in other organs, R1 resection was defined as microscopic involvement of the resection margin, and R2 resection was defined as macroscopic remnant tumor at the operative site.

Postoperative pancreatic fistula formation, delayed gastric emptying, and post-pancreatectomy hemorrhage were defined as per the International Study Group of Pancreatic Surgery.[20–22] Other complications included intraabdominal abscess formation, respiratory problems (pneumonia, atelectasis, pleural effusion), wound problems (wound infection or dehiscence), and cardiac problems. Mortality was defined as the total number of in-hospital deaths or after-discharge deaths occurring within 90 days of the index operation. Concurrent, postoperative adjuvant CRT was usually recommended by a medical and/or radiation oncologist. Chemotherapeutic agents included fluorouracil (FU) or gemcitabine. FU-based therapy consisted of continuous infusion FU with radiation therapy or oral FU with radiation therapy and additional gemcitabine chemotherapy after CRT. Gemcitabine-based therapy consisted of a 30-min infusion of gemcitabine once a week, along with radiation therapy. The median daily radiation fraction size was 1.8 Gy and the total radiation dose was 45 Gy (range, 23–61 Gy). Patients who elected to receive no therapy did so after being fully informed about the potential risks and benefits of such therapy. Follow-up data were obtained through review of medical records or through direct patient contact.

Clinicopathologic variables were presented as medians with a range or frequency. Test of differences were done using the Mann–Whitney U test or t tests for continuous data and the chi-square test or the Fisher exact test where appropriate for categorical data. The primary endpoint was overall survival (OS). Survival was calculated using the Kaplan–Meier method. The long-rank test was used to analyze differences. Only variables with p values <0.1 on univariate analysis were included in the multivariate analysis, which was performed using Cox proportional hazards regression. Values of $p<0.05$ were considered statistically significant.

Results

Clinical Characteristics

The median age of these 219 patients was 60 years (range, 32–80 years). There were 128 men (58%) and 91 women (42%). Clinicopathologic data for patients who underwent PD according to R status are given in Table 1. Jaundice was the most frequent symptom (47%), followed by abdominal pain (38%), weight loss, and dyspepsia. Fifteen patients had

no symptoms. The 15 patients with incidentally detected tumors were compared to their symptomatic counterparts for clinicopathologic variables. No difference was noted between the groups, except with regard to increased bilirubin levels, intraoperative blood loss, and bile duct invasion (data not shown). There were 35 R1 resections (18%) and nine R2 resections (2%) recorded in the medical records or pathologic reports. Regarding the site of the positive resection margin, the retropancreatic area was the most common (21/35), followed by the vascular margin (five arterial, nine venous), pancreatic margin (3/35), and peripancreatic soft tissue margin (1/35). One patient was proven to have tumor cells in the wall of the inferior vena cava. Four patients had dual positive margins. R2 resection was unavoidable because of the extensive involvement of the SMA (n=5), branches of the superior mesenteric vein (n=3), and retropancreatic area (n=1). Patients who underwent non-curative resection had a greater median intraoperative blood loss, larger median tumor size, a greater median number of metastatic lymph nodes, a greater tendency for lymph node metastasis, and a greater need for SMPV resection compared to those patients who underwent R0 resection. Peripancreatic soft tissue invasion and adjuvant CRT showed borderline differences.

Outcomes

Postoperative complications developed in 73 (33%) patients (Table 4). Delayed gastric emptying and postoperative pancreatic fistula were most frequent (16% and 15%, respectively). Perioperative death occurred in three (1%) patients. The first sites of recurrence were as follows: locoregional in 90 patients (41%), distant organs (liver 65, lung 7) in 72 (33%), peritoneal carcinomatosis in 26 (12%), and paraaortic lymph nodes in nine (4%). Some patients developed their initial recurrence at more than one site. Recurrent disease was detected in 106 (61%) of 175 patients who underwent R0 resection and in 31 (71%) of 44 patients who underwent non-curative resection. Curative resection and non-curative resection were no different with respect to the pattern of first recurrence or recurrence rate. At last follow-up, 168 (77%) patients had died and 51 (23%) patients remained alive (30 without evidence of disease and 21 with disease). Of the 111 patients who underwent PD before 2004 (i.e., follow-up of at least 5 years or until death), 12 patients survived more than 5 years. Characteristics of long-term survivors are listed in Table 2. All long-term survivors underwent curative resection, had tumor sizes less than 3 cm, or were in AJCC stage I or II. Five of six patients with metastatic lymph nodes received adjuvant CRT.

Most tumors were proven pathologically to be stage T3 (89%, 194 of 219 cases); there were 18 (8%) T4, five T2, one T1, and one T0 tumors. Lymph node metastasis was identified in 139 (64%) patients. According to the AJCC classification system, stage 0 was present in one patient, stage I in five (2%), stage II in 194 (89%), stage III in 18 (8%), and stage IV in one. Among the 15 asymptomatic patients, 13 were T3 and two were T4; six were N0 and nine were N1; 12 were stage II, two were stage III, and one was stage IV. The patient with carcinoma in situ died of toxic hepatitis 50 months later without evidence of recurrence after PD. The 3- and 5-year OS rates were 24.3% and 14.2%, respectively. The overall median survival time was 14.0 months [95% confidence interval (CI), 12–16 months). For the whole group of 44 patients who underwent non-curative resection, the 5-year OS rate was 0% and the median survival time was 12 months (95% CI, 10–14 months). For the patients who underwent curative resection, the 5-year OS rate was 16.3% and the median survival time was 16 months (95% CI, 13–19 months, p=0.011; Fig. 1). In patients without metastatic lymph nodes, the 5-year OS rate was 16.5% and the median survival time was 16 months (95% CI, 13–19 months). For patients with lymph node involvement, the 5-year OS rate was 13.0% and the median survival time was 13 months (95% CI, 10–16 months; p=0.097). Survival correlated with tumor stage according to the AJCC staging system. For patients with stage II disease, the median OS was 15 months and the 5-year OS rate was 15.3%. For those with stage III disease, these figures were 9 months and 0%, respectively. One stage I patient has survived for 34 months and one has survived for 91 months.

Factors that affected OS at the p<0.10 level of significance in the univariate analysis were included in a multivariate Cox proportional hazards model (Table 3). After adjusting for these variables in an entering fashion, only tumor size >3 cm, poor differentiation, and high AJCC stage adversely affected OS. Although R status influenced OS on univariate analysis, non-curative resection did not adversely affect OS after controlling for all other factors. Lymph node metastasis showed borderline significance on univariate analysis and showed no significance on multivariate analysis. Because few patients were AJCC stages 0, I, or IV, exclusion of these patients revealed a loss of AJCC tumor staging significance on multivariate analysis. However, postoperative adjuvant CRT proved to have borderline significance on univariate and multivariate analysis regardless of the exclusion of AJCC stage 0, I, and IV patients. Therefore, we did further analysis of adjuvant therapy.

Adjuvant Treatment

We compared the characteristics in patients treated with surgery and adjuvant CRT and in those treated with

Table 1 Clinicopathologic Characteristics

	R0 resection (n=175)	R1/R2 resection (n=44)	p
Male patients	100 (57)	28 (64)	0.496
Age (years)[a]	60 (33–79)	60 (32–80)	0.364
Comorbid disease	71 (41)	15 (34)	0.492
On admission			
Asymptomatic	13 (7)	2 (5)	0.741
Hemoglobin (g/dl)[a]	13 (7–16)	12 (9–16)	0.696
Increased CA 19-9	122 (72)	37 (86)	0.076
Increased bilirubin	109 (63)	31 (71)	0.382
Preoperative biliary drainage	108 (62)	31 (71)	0.381
OP name			0.220
PPPD	78 (45)	14 (32)	
Whipple's OP	74 (42)	21 (48)	
Total pancreatectomy	23 (13)	9 (20)	
Intraoperative transfusion	63 (36)	19 (43)	0.389
Intraoperative blood loss (Ml)[a,b]	600 (100–8,000)	800 (100–3,500)	0.004
SMPV resection	26 (15)	14 (31)	0.015
Tumor size (cm)[a,c]	3.0 (1.3–7.0)	3.25 (1.5–6.0)	0.016
Tumor size >3 cm	51 (29)	22 (50)	0.012
Lymph node metastasis	105 (60)	34 (77)	0.036
No. of metastatic lymph nodes[a]	1 (0–20)	2 (0–20)	0.009
Perineural invasion	64 (37)	21 (48)	0.227
Peripancreatic soft tissue invasion	135 (77)	40 (91)	0.056
CBD invasion	124 (71)	33 (75)	0.709
Duodenal invasion	107 (61)	30 (68)	0.486
Postop. chemoradiation	97 (57)	32 (74)	0.054

Values in parentheses are percentages unless otherwise indicated

[a] Mann–Whitney U test used

[b] Estimated blood loss was not recorded in the anesthesia records of two patients

[c] Tumor size could not be evaluated in one patient

surgery alone (Table 4). The two groups were statistically comparable with respect to multiple factors, including gender, comorbid disease, bilirubin level, SMPV resection, tumor size, perineural invasion, common bile duct (CBD) invasion, duodenal invasion, and overall complications. However, there were significant differences between the groups with regard to the following factors: age, intraoperative transfusion, lymph node metastasis, number of metastatic lymph nodes, peripancreatic soft tissue invasion, postoperative length of stay, and postpancreatic hemorrhage. Patients who elected to receive no adjuvant therapy had a higher incidence of postoperative complications, but it did not reached statistical significance. We stratified the CRT groups and no CRT groups by R status, nodal status, or grade. Regarding lymph-node-negative patients (n=79), the 3-year OS rate was 31% in 40 patients without adjuvant therapy and 26% in 39 patients with adjuvant therapy (p=0.436). Regarding lymph-node-positive patients (n=139), there was improved OS in patients who underwent adjuvant therapy [n=92, 3-year OS 28%, median OS 16 months (95% CI, 11–21)] compared with those who did not undergo adjuvant therapy [n=42, 3-year OS 8%, median OS 10 months (95% CI, 7–13)] (p<0.001). Compared with surgery alone, adjuvant CRT also resulted in improved survival among patients who underwent non-curative resection (median OS, 13 vs 8 months) or who had well- or moderately differentiated tumors (median OS, 19

Table 2 Characteristics of an Actual 5-Year Survivor

Factor	Total (n=12)
Male	9 (75)
Age (years)	53.5 (42–68)
R0 resection	12 (100)
T1/T2/T3	1/2/9
N0/N1	6/6
AJCC (6th edition) I/II/III	2/10/0
Tumor size >3 cm	0 (0)
WD/MD/PD	2/8/1
SMPV resection	2 (17)
Adjuvant therapy +/–	8/4
Alive	8 (67)

Values in parentheses are percentages unless otherwise indicated

WD well-differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *SMPV* superior mesenteric or portal vein

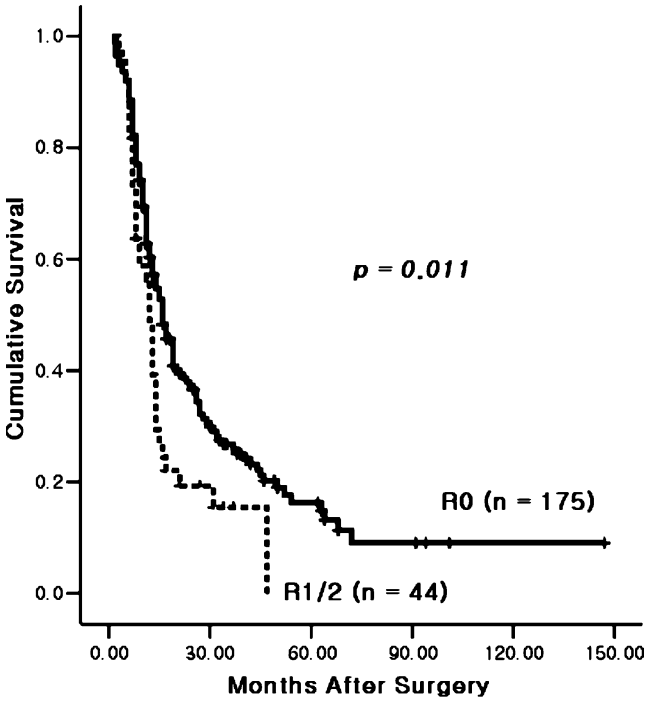

Figure 1 The 5-year overall survival (*OS*) rate in patients who underwent non-curative resection was 0% compared with 16.3% in those who underwent curative resection (log-rank test).

vs 13 months; Fig. 2). Patients who underwent curative resection or who had poorly differentiated tumors did not show the same effect. On the other hand, chemotherapeutic agents themselves did not affect OS.

Discussion

Ductal adenocarcinoma of the pancreas occurs most commonly in the head of pancreas. It remains a major cause of cancer death in western and Asian countries. Since the introduction of PD, there have been many efforts to improve resectability and the safety associated with this operation. In recent times, the perioperative mortality rate has been less than 5% for periampullary neoplasms, with an acceptably low morbidity rate.[5,7,23–27]

Generally, a positive surgical margin after resection of a solid tumor is a poor prognostic factor. Raut et al.[28] reported that R1 resection was associated with larger tumors, greater mean operative blood loss, longer hospital stays, and the need for vascular resection. They used multivariate analysis to demonstrate that tumor size and mean operative blood loss were the only covariates affecting margin status. In the present study, R1 and R2 resection are associated with larger tumors, greater intraoperative blood loss, a greater number of metastatic lymph nodes, lymph node involvement, peripancreatic soft tissue invasion, and the need for vascular resection and reconstruction. Greater tumor size, lymph node metastasis, number of positive nodes, and peripancreatic soft tissue invasion seem to be associated with more advanced disease. Furthermore, these factors may result in more vascular resection and a technically more difficult operation, potentially leading to more intraoperative blood loss.

Riall et al.[29] demonstrated that negative nodal status, negative resection margins, smaller tumor diameter, and well-

Table 3 Predictors of Survival in 219 Patients Who Underwent Pancreaticoduodenectomy for Pancreatic Adenocarcinoma

	Univariate analysis (*p*)	Multivariate analysis (Cox regression) (*p*)	Risk ratio	95% CI
Total bilirubin	0.042	0.957	1.000	0.976–1.026
CA 19-9 (U/dl)	0.001	0.122	1.000	1.000–1.000
Intraoperative transfusion (U)	0.008	0.120	1.134	0.97–1.33
Intraoperative blood loss (mL)	0.001	0.811	1.000	1.000–1.000
Tumor size >3 cm	<0.001	0.018	1.569	1.080–2.282
No. of positive LNs	0.003	0.176	1.034	0.985–1.085
Duodenal invasion (+)	0.006	0.114	1.373	0.927–2.033
Perineural invasion (+)	0.085	0.788	1.050	0.737–1.494
Poorly differentiated	<0.001	<0.001	2.104	1.401–3.161
Lymph node (+)	0.097	0.939	1.213	1.028–1.441
R1/2 resection	0.011	0.346	1.259	0.780–2.032
AJCC staging	<0.001	0.001		
Stage II		0.788	1.223	0.283–5.275
Stage III		0.480	1.773	0.362–8.677
Stage IV		<0.001	354.563	14.369–8,695.620
Adjuvant therapy (+)	0.092	0.087	0.701	0.467–1.053

CI confidence interval, *LN* lymph node

Table 4 Characteristics of Patients with Surgery and CRT or Those with Surgery Alone

	Surgery alone (n=84)	Surgery + CRT (n=129)	p
Male patients	46 (55)	78 (61)	0.478
Age >65	36 (43)	22 (17)	<0.001
Comorbid disease	35 (42)	49 (38)	0.667
Increased bilirubin	59 (70)	78 (61)	0.188
Total pancreatectomy	16 (19)	16 (12)	0.163
Intraoperative transfusion	43 (51)	37 (29)	0.001
Intraoperative blood loss (mL)[a]	700 (100–8,000)	600 (100–3,500)	0.057
SMPV resection	19 (23)	21 (16)	0.283
Poorly differentiation	12 (15)	34 (27)	0.058
Tumor size >3 cm	27 (33)	44 (34)	0.882
Lymph node metastasis	43 (52)	92 (71)	0.005
No. of metastatic lymph nodes[a]	1 (0–9)	1 (0–20)	0.002
Perineural invasion	37 (45)	45 (35)	0.194
Peripancreatic soft tissue invasion	59 (70)	111 (86)	0.008
CBD invasion	54 (64)	97 (75)	0.092
Duodenal invasion	48 (87)	86 (67)	0.192
Length of stay[a]	21 (9–87)	16 (9–55)	<0.001
Complications (1 or more of below)	34 (41)	39 (30)	0.141
POPF	17 (20)	15 (12)	0.116
DGE	19 (23)	17 (13)	0.092
PPH	9 (11)	2 (2)	0.008
Intraabdominal abscess	8 (10)	12 (9)	1.000
Wound problem	8 (10)	4 (3)	0.067
Respiratory problem	9 (11)	7 (5)	0.186
Others	6 (7)	1 (1)	0.016

Three patients were unavailable whether underwent CRT or not and three patients died of postoperative complication. Values in parentheses are percentages unless otherwise indicated

CRT chemoradiation therapy, *SMPV* superior mesenteric or portal vein, *CBD* common bile duct, *POPF* postoperative pancreatic fistula, *DGE* delayed gastric emptying, *PPH* postpancreatectomy hemorrhage

[a] Mann–Whitney *U* test used

differentiated carcinoma were predictors of long-term survival in 564 patients with pancreatic malignancies. In the same patients, 5- and 10-year OS rates were 17% and 9%, respectively. Other studies have noted similar results, identifying tumor size, lymph node metastasis, resection margin, tumor differentiation, postoperative complications, and adjuvant therapy as independent factors affecting long-term survival.[3,8,11,28,30–32] We also confirmed that tumor size and

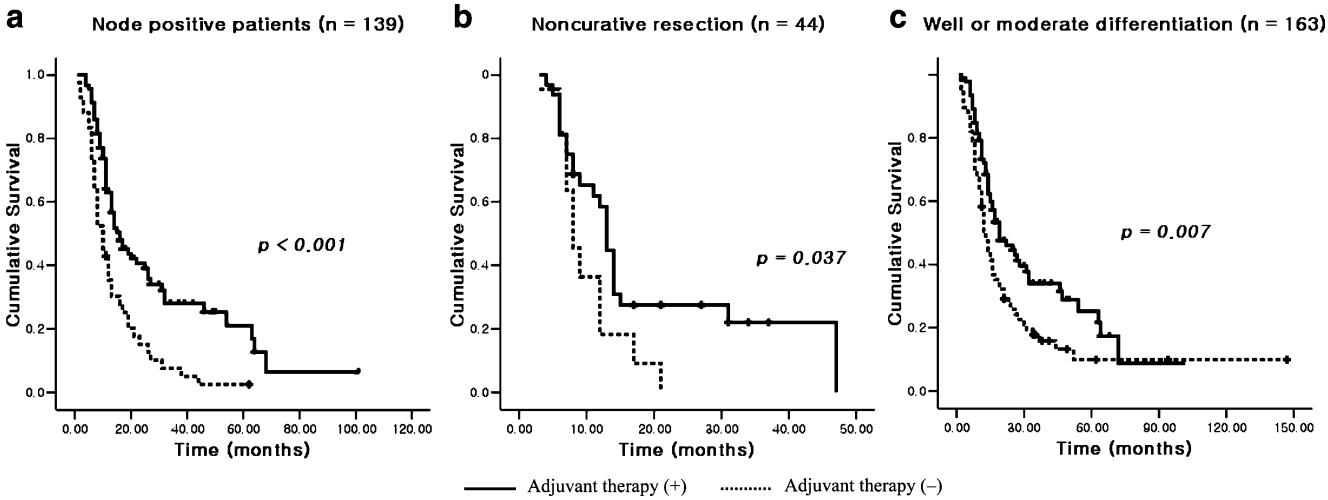

Figure 2 OS according to postoperative adjuvant therapy, stratified by nodal status, R-status, and grade (log-rank test).

tumor differentiation were important prognostic factors affecting OS in patients undergoing pancreatic resection with curative intent. In contrast, we found that lymph node metastasis and resection margin did not affect OS and that postoperative CRT affected OS with borderline significance.

The GITSG reported a significant survival benefit following treatment with 40 Gy of radiation combined with 5-FU therapy after resection.[12] A recent reanalysis of the European Organization for Research and Treatment of Cancer phase III trial found a 2-year OS benefit in patients who received postoperative CRT, which supports the earlier findings of the GITSG trial.[33] The large randomized trial from the European Study Group for Pancreatic Cancer suggests that adjuvant RT is not beneficial and is possibly even deleterious in the setting of PC resection. Despite the contradictory results of the previously reported phase III trials, several retrospective studies have demonstrated an OS benefit with the addition of adjuvant CRT in the setting of PC resection.[3,9,10,34] In the present study, patients with node positivity and those undergoing non-curative resection clearly benefited from adjuvant CRT. Furthermore, five patients with metastatic lymph nodes underwent adjuvant CRT and survived for more than 5 years. There is potential bias in patient selection in any retrospective analysis because the argument can be made that patients who receive adjuvant CRT are inherently healthier. However, this bias may be offset by a competing bias to refer patients for adjuvant CRT when they have negative prognostic factors. In the present study, patients who had complications had a tendency of receiving no CRT, but it failed to reach statistical significance. It might be because of the severity of postoperative complications and medical culture. We found a significant difference in adverse prognostic factors between patients who received CRT and those who did not receive CRT.

There are several limitations to the current study. First, it was a retrospective study even though the data were collected prospectively. There were also relatively few patients in the CRT and non-CRT subgroups stratified by tumor grade or R status.

This large, single-institution analysis supports the idea that adjuvant CRT benefits patients with resected pancreatic adenocarcinomas, especially those with adverse prognostic factors such as lymph node metastasis and non-curative resection. Multivariate analysis demonstrated that patients with tumors larger than 3 cm and poor differentiation had poor prognosis.

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ORIGINAL ARTICLE

Simvastatin Improves Wound Strength after Intestinal Anastomosis in the Rat

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Abstract
Background Simvastatin is a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor commonly known as a cholesterol-lowering drug with additional pleiotropic effects. Also, it is demonstrated that it prevents postoperative peritoneal adhesions in rat. This study was designed to assess its effects on the healing process of colonic anastomosis.
Methods Thirty-two male Wistar albino rats were randomized into two groups and subjected to colonic anastomosis. The study group was treated with simvastatin and the control group received only tap water instead. The rats were killed 3 and 7 days postoperatively. Wound complications, intra-abdominal abscesses, and anastomotic leaks and stenosis were recorded. Four types of assessment were performed: bursting pressure, hydroxyproline content, histopathology, and biochemical analysis.
Results Compared to the control group, simvastatin-treated rats displayed a higher bursting pressure ($p<0.001$) and anastomotic hydroxyproline content ($p<0.05$). Simvastatin treatment leads to a significant decrease in malondealdehyde levels ($p<0.05$) and increase in paraoxonase activity ($p<0.001$) at both time points. Histopathological analysis revealed that simvastatin administration leads to a better anastomotic healing in terms of reepithelialization, decreased granuloma formation, reduced ischemic necrosis, and inflammatory infiltration to muscle layer.
Conclusion Clinically relevant doses of simvastatin do not have a negative impact on colonic anastomosis but improve intestinal wound healing in rats.

Keywords Simvastatin · Wound healing · Anatomosis · Dehiscence · Bursting pressure · Hydroxyproline

Introduction

Colorectal cancer (CRC) is one of the most common neoplasms of the digestive system and one of the most lethal causes of cancer death worldwide. The most studied

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risk factors causing CRC development are heredity, age, low-fiber and high-fat diet, alcohol, tobacco use, obesity, low physical activity, and environmental pollution. All of these factors could lead to hypercholesterolemia, which in turn increases the risk of CRC development.[1]

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, commonly known as statins, were first introduced as cholesterol-lowering drugs. The clinical and experimental research over 20 years revealed additional pleiotropic effects of statins, independent of lipid lowering. In fact, these so-called pleiotropic effects are now considered to contribute significantly to the morbidity and mortality benefit observed in patients with coronary heart disease who are treated with statins. Pleiotropic effects have been demonstrated to comprise immunomodulation, improvement of endothelial and microvascular function, anti-inflammatory action, survival benefit in sepsis, antimitogenic and antioxidant properties and anti-thrombogenic and profibrinolytic activities.[2–7] Recent experimental and epidemiologic evidence suggests that statins might also exert provocative and unexpected benefits including chemopreventive and/or chemotherapeutic effects on CRC.[8,9]

Since CRC is a disease mainly affecting the elder population and suffering from hypercholesterolemia as a risk factor, most of the cases are under statin therapy at the time of diagnosis. The current method of curative treatment for CRC is surgical resection with an anastomotic reconstruction. Currently, anastomotic complications constitute worrisome problems, both for surgeons and patients. Anastomotic leakage or dehiscence is not only a significant cause of morbidity and mortality in the early postoperative course but also is associated with worse long-term survival and increased local recurrence.[10] Accordingly, agents with the potential of beneficial effect on anastomotic wound healing attract great enthusiasm over researchers. In the present study, we approached the question of whether treatment with clinically relevant doses of simvastatin (SIM), with known pleiotropic effects, might improve or alter wound healing parameters in an experimental model of left colonic anastomosis. The results of the present study might shed some valuable light on the safety of statin use during perioperative course in terms of anastomotic complications.

Materials and Methods

Animals

The surgical procedure, use of anesthesia, and animal care methods in the experiments were consistent with the guidelines in the National Institute of Health's Guide for the Care and Use of Laboratory Animals (National Institutes of Health publication no. 86-23, revised 1985, Bethesda, MD, USA) and approved by the Zonguldak Karaelmas University, The School of Medicine Ethics Committee. Thirty-two male Wistar albino rats weighing 300–340 g were included in the study. The animals were housed in wire bottom cages at room temperature with a 12-h light/dark cycle. All animals had free access to a standard laboratory diet and allowed water ad libitum. All animals were weighed before the administration of the drug, before the operation, and before the killing. The rats were randomly assigned into two groups of 16 each, the study (S) or untreated control (C) group. To investigate early and late healing at the anastomosis site, half of the subjects in each group was killed on postoperative day (POD) 3 (S3 group and C3 group, $n=8$), and the other half was killed on POD 7 (S7 group and C7 group, $n=8$).

Surgical Procedures

Neither mechanical nor antibacterial bowel preparation was performed. After an overnight fast, all rats were anesthetized by an intramuscular injection of ketamine hydrochloride 50 mg/kg (Ketalar; Parke Davis, Eczacibasi, Istanbul, Turkey) and xylazine 5 mg/kg (Rompun; Bayer AG, Leverkusen, Germany). Animals were allowed to breathe spontaneously during the surgery. A heating lamp was used to preserve the body temperature at approximately 37°C. To prevent postoperative dehydration, 5 ml Ringer's lactate solution was injected subcutaneously. The abdomen was shaved and prepared with povidone–iodine, then sterile covers. A midline laparotomy was performed and 1 cm of the left colon was resected at the colorectal junction, 2 cm proximal to the peritoneal reflection, in all rats. The fecal content of the anastomotic ends were milked out. A standardized end-to-end anastomosis was performed with a single layer interrupted inverting sutures of 6/0 polypropylene (6–0 monofilament polypropylene; Prolene, Ethicon, UK). All anastomosis included eight equidistant stitches. The laparotomy was closed with continuous 3/0 silk sutures (3–0 silk, Dogsan, TR). All anastomosis were created by the same surgeon who was experienced with the technique.

Drug Administration

Rats in all four groups were allowed to feed since the first 24 h. SIM (Zocor, Merck Sharp&Dohme, Istanbul, Turkey) was administered in a dose of 10 mg/kg by mouth with the use of a 4-F fine gavage catheter once per day. In the study groups, drug administration started 1 week before anastomosis and was maintained throughout the study. In the control groups, only the same volume of normal saline was administered during the entire period of this study.

Assessment of Anastomosis

On postoperative days 3 and 7, all animals were weighed and anesthetized again and subjected to relaparotomy. Four types of evaluation were performed as follows:

Macroscopic Healing

Any abscess of anastomotic leakage was recorded and rats were killed by means of a cardiac puncture. The peritoneal cavity was carefully inspected for adhesions. Intra-abdominal adhesions were assessed and graded by two surgeons blind to the groups of the rats using a standard scale according to the following criteria:[11] 0 point: No adhesion; 1 point: Single, easily dissectible adhesion; 2 points: Multiple, easily dissectible adhesion; 3 points: Single, dense adhesion; 4 points: Multiple, dense adhesions.

Measurement of Colonic BP

Anastomotic strength was measured in vivo by determining the bursting pressure. A catheter was inserted through the anastomosis per rectum. The lumen of the colon was cleaned of fecal content by gentle washout with saline. Without disturbing the adhesions, the wound was isolated by ligation of each anastomotic end with a 0 silk, 2 cm proximal and distal to the anastomosis line. The distal catheter was connected via a pressure transducer (Abbott Single Transpact, USA) to monitor (Petas, KMA 800 S/N 1894, Turkey). The colon was filled with a continuous flow of physiological saline at a rate of 4 ml/min using an infusion pump (Abbott LC 5000 infuser, USA). The pressure in the bowel was monitored during injection and the bursting pressure (mmHg) was recorded as the maximum pressure achieved during the injection phase. The site of rupture (within or outside the anastomotic line) was noted.

Obtaining the Samples

After bursting, a 2-cm segment of the colon including the anastomosis was resected, transected longitudinally, and rinsed with saline to remove intestinal contents. One third of this sample was fixed in 10% formalin for histopathological examination. The remaining two thirds, wrapped in aluminum foil, was kept in a biochemistry laboratory for tissue hydroxyproline (OHP) measuring.

Determination of OHP Level

After weighing, tissue samples were frozen (by bedside liquid nitrogen), lyophilized, and pulverized. Twenty-five-microliter samples taken from hydrolyzation were lyophilized and soluted in the 1 ml 50% (*v*/*v*) isopropyl alcohol. Chloramine-T was added to these samples 10 min later. Then, they were incubated for 90 min at 50°C after adding 1 ml Erlich's reagent. A color change after the reaction was evaluated under 560-nm wavelength spectrophotometer. Under the same conditions, OHP standards with 0.2, 0.4, 0.6, 0.8, 1.2, and 1.6 mg were also studied. Sample concentrations were calculated with the help of standard curve. Results were calculated as micrograms per milligram of wet tissue.[12]

Biochemical Analysis

Blood samples were centrifuged at 3,000 rpm for 10 min and serum aliquots were stored at −60°C for further examination. Oxidative stress and lipid peroxidation was determined by measuring serum malondealdehyde (MDA) and paraoxonase (PON) activity. Since PON is a high-density lipoprotein (HDL)-associated factor, serum HDL levels were also assessed. Serum MDA levels were measured with Hunter's method and PON activity was assessed with Eckerson's method on UV-1601 Shimadzu spectrophotometer.[13,14] HDL lipoprotein levels in the serum were measured with Roche Diagnostics (Mannheim, Germany) kit on Roche/Hıtachi Moduler P800 analyzer.

Histopathological Analysis

A segment of each anastomotic ring was removed for histological examination and fixed in 10% formaldehyde. The samples for histology were dehydrated and embedded in paraffin. From all paraffin blocks, 5-lm sections were cut, and staining was performed with hematoxylin and eosin. Peri-anastomotic colonic segments were sampled for examination by an expert pathologist blinded to experimental groups. Ten specimens were analyzed per group. Five high power fields were evaluated in per anastomotic region. Mucosal ischemia was graded following the scale proposed by Chiu et al.[15] (Table 1). Histological changes of anastomotic wound healing, granulation tissue development, local inflammatory response, and neovascularization were determined according to Houdart et al. and Hutschenreiter et al. parameters as modified by Garcıa et al.[16–18] (Table 2).

Statistical Analysis

Statistical analysis was performed using the SPSS version 11.5 software package (SPSS, Chicago, USA). Quantitative results are given as means (±SD) for bursting pressure, tissue HP content, MDA level, PON activity, and HDL concentration and as medians (±interquartile ranges) for histopathological parameters and adhesion scores. Statistical comparisons of the data expressed as means (±SD) were analyzed by

Table 1 Chiu Scale of Mucosal Ischemia[15]

Grade	Definition
0	Normal mucosal villi
1	Development of subepithelial Gruenhagen's space, usually at the apex of the villus, often with capillary congestion
2	Extension of the subepithelial space with moderate lifting of epithelial layer from the lamina propria
3	Massive epithelial lifting down the sides of villi, a few tips may be denuded
4	Denuded villi with lamina propria and dilated capillaries exposed
5	Digestion and disintegration of lamina propria; hemorrhage and ulceration

factorial variance analysis model with two factors. Differences among the groups in terms of histopathological parameters were evaluated using Kruskal–Wallis variance analysis test, and multiple comparisons between the groups were performed with nonparametric Tukey's test. A value of $p<0.05$ was assumed to be statistically significant.

Results

Surgical Morbidity and Mortality

All animals from both the study and control groups survived throughout the experimental procedure. Neither anastomotic leakage nor septic complications were observed.

Macroscopic Healing

Neither anastomotic leakage nor septic complications were observed. Similarly, none of the rats in the four surgery groups developed intestinal obstruction. The adhesion scores for C3 and S3 groups were similar ($p>0.05$). The same was valid for the adhesion scores in the groups killed at 7 days ($p>0.05$). The comparison in terms of sacrification day revealed that adhesion scores was highest on POD 7 in both groups ($p=0.006$).

Table 2 Parameters of Histologic Changes of Anastomotic Wound Healing, Granulation Tissue Development, and Local Inflammatory Response[16–18]

1. Mucosal anastomotic reepithelialization				
Grade 0	Absence of epithelialization on the anastomotic line			
Grade 1	Incomplete coating of the anastomotic wound with a single layer of cells			
Grade 2	Complete coating of the anastomotic wound with a single layer of cells			
Grade 3	Complete reepithelialization with glandular epithelium			
2. Inflammatory granuloma and granulation tissue formation				
	Inflammatory cell presence	Neovascularization	Fibroblasts	Fibrosis formation
Grade 1	Absence	Absence	Absence	Absence
Grade 2	Slight	Slight	Slight	Slight
Grade 3	Mild	Mild	Mild	Mild
Grade 4	Intense	Intense	Intense	Intense
3. Muscle layer destruction				
	Ischemic necrosis	Muscle layer continuity	Inflammatory infiltration	
Grade 1	Absence	Complete interruption	Absence	
Grade 2	Slight	Muscle synechia	Slight	
Grade 3	Mild	Complete restitution	Mild	
Grade 4	–	–	Intense	
4. Anastomotic wound inflammatory infiltration				
	Neutrophils	Lymphocytes	Histiocytes	Giant cells
Grade 1	Absence	Absence	Absence	Absence
Grade 2	Slight	Slight	Slight	Slight
Grade 3	Mild	Mild	Mild	Mild
Grade 4	Intense	Intense	Intense	Intense

Bursting Pressure

The mean±SD bursting pressure (BP) was found to be significantly higher in the S3 group than the C3 group (139.9±19.3 vs 94.1±24 mmHg, $p<0.001$). For all 3-day-old anastomosis, bursting occurred at the suture line in both groups. The mean±SD bursting pressure was also found to be significantly different in animals killed on POD 7. The measured values were 211.1±30.9 mmHg for the C7 group and 232.6±31.1 mmHg for the S7 group ($p<0.001$; Fig. 1). Four ruptures at POD 7 were observed at the anastomosis site for the control group; the others were noted to burst in the distal segment. All of the 7-day-old colonic segment ruptures were determined to be outside the anastomosis, generally in the proximal segment in the study group. Table 3 demonstrates the group results of bursting pressure and anastomotic OHP content.

OHP Levels

Anastomotic OHP content was found to be significantly increased in the S3 group compared to the C3 group (0.47±0.04 vs 0.38±0.04 μg/mg wet tissue weight, $p<0.05$). Similarly, there was significantly greater anastomotic OHP content in the S7 group than C7 (0.48±0.04 vs 0.41±0.05 μg/mg wet tissue weight, $p<0.05$; Fig. 2).

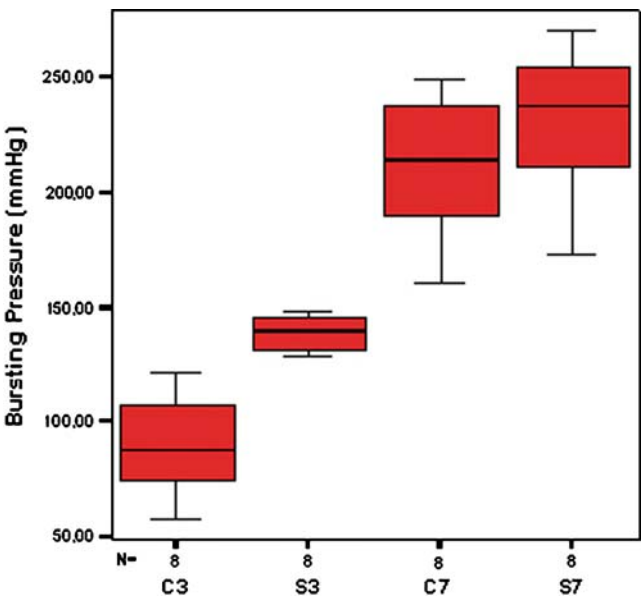

Figure 1 Values of measured mean±SD bursting pressures of study and control group subdivisions during experimental period. On PODs 3 and 7, anastomotic bursting pressure values were significantly higher in the SIM group than in the control group ($p<0.001$; factorial variance analysis model with two factors).

Biochemical Analysis

Table 4 shows the group results for serum MDA levels, PON, activity and HDL concentrations. The control group animals killed on POD 3 were found to have significantly higher serum MDA levels compared with the S3 group (19.1±3.75 vs 14.3±1.01, $p<0.001$). Similarly, the MDA values for the groups evaluated on POD 7 were also different (16.85±2.21 vs 13.6±0.66 for C7 and S7, respectively, $p<0.05$). Serum HDL concentration was found to be significantly higher in the S3 group (44.5±11.8 vs 53.6±5.8, $p<0.05$). However, the results were similar for the groups evaluated 7 days after surgery ($p>0.05$). Furthermore, the comparison in terms of serum PON activity demonstrated that SIM treatment leads to a statistically significant increase at both time points (24.53±12.67 vs 8.15±2.24 on POD 3, 25.68±6.75 vs 11.59±7.32 on POD 7, $p<0.001$).

Histological Analysis

The results of mucosal ischemia grading according to the Chiu scale are listed in Table 5. Differences between the S3 and C3 groups were not statistically significant, but only grade 1 ischemic changes were seen in 87.5% of the rats in S3 group; on the contrary, severe ischemic changes (grades 4–5) were detected in 25% of the controls ($p>0.05$). Additionally, the degree of mucosal ischemia was noted to be decreased in S7; however, it reached no significance ($p>0.05$).

Anastomotic healing examination according to the modified Houdart and Hutschenreiter scale revealed no differences in neovascularization, fibroblast, and perianastomotic fibrosis scores among the S and C groups on both PODs 3 and 7 ($p>0.05$). The ischemic necrosis and inflammatory infiltration to muscle layer were higher in the C group than in the S group either on the third or seventh day after surgery ($p<0.05$). Inflammatory cell presence in the granulation tissue was found to be higher in the C3 group ($p=0.048$); however, it reached no significance on POD 7. A significantly higher mucosal anastomotic reepithelialization score was detected in the S3 group compared with the C3 group ($p=0.001$), but results were similar among groups on POD 7. There was also evidence of significantly higher neutrophil presence in the anastomotic wound of the C group compared with the S group both at PODs 3 and 7 ($p=0.001$). Histological changes after SIM administration showed a significantly lower lymphocyte infiltration ($p=0.002$) and decreased histiocyte infiltration ($p=0.037$), and reduced presence of giant cells in the treatment group ($p=0.012$), revealing reduced granuloma formation, was also detected on POD 3. Finally, SIM treatment revealed a remarkable, but not

Table 3 BP and OHP Results on POD 3 and POD 7

	POD3			POD7		
	Untreated control	SIM	*p* value	Untreated control	SIM	*p* value
BP (mmHg)	94.1±24	139.9±19.3	<0.001	211.1±30.9	232.6±31.1	<0.001
OHP (OHP/mg tissue)	0.38±0.04	0.47±0.04	<0.05	0.41±0.05	0.48±0.04	<0.05

significant, tendency toward enhanced neovascularization and decreased inflammatory infiltration in muscle layer on POD 7 (Figs. 3, 4, 5, and 6).

Discussion

Anastomotic complications, mainly leakages, have long been one of the most disastrous consequences leading to either high local recurrence risk or death.[10,19] Various objective and subjective factors have been accused of anastomotic failure. Mounting evidence suggests that disruption of normal wound healing independent of the nature of insult causes anastomotic problems. For instance, older age, associated chronic diseases (diabetes mellitus, chronic renal failure), ischemia, emergency or distal colonic surgery, and many other factors influence healing by means of cellular and humoral pathways. The relationship and the similarity between the risk factors of CRC and hypercholesterolemia raised the concern that there might be an association between these two entities.[1] Moreover, Poynter and Hoffmeister et al. reported a considerable risk reduction of CRC in patients under statin theraphy.[8] Nevertheless, analysis of large cohort studies and editorials did not support this hypothesis and conflicting results have been published, so controversies still remain.[20,21] As a matter of fact, in terms of risk factors, it is obvious that both of the diseases possess similarities. However, to make a generalization is something out of the scope of the present study. We aimed to evaluate the effect of statin therapy on left colonic anastomosis under normal circumstances. Since some of the CRC patients are on statin therapy at the time of diagnosis, we hypothesized that this agent might alter anastomotic healing with or without apparent interference with other vital components of the repair process. We believe that the aforementioned pleiotropic effects of statins, most of which are relevant to wound healing, deserve consideration. Additionally, Adah et al.[22] and Serin-Kılıçlıoglu and Erdemli[23] demonstrated that SIM exerts a significant positive effect on fracture healing.

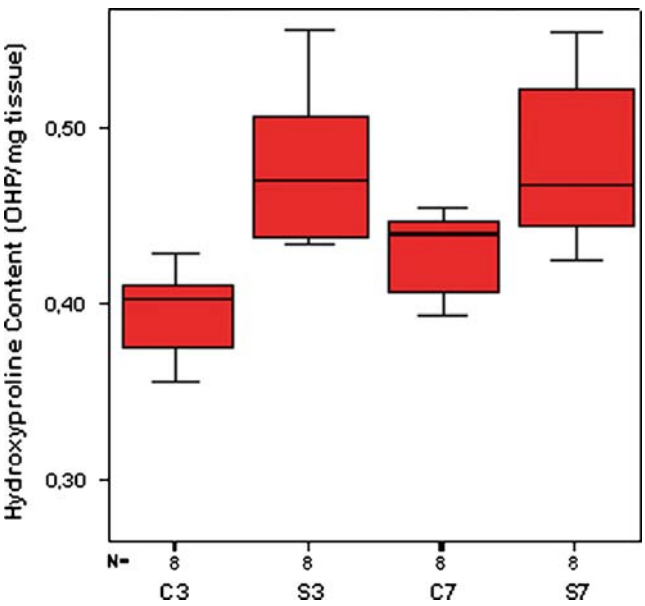

Figure 2 Colonic anastomotic hydroxyproline contents (mean±SD) in the same groups as in Fig. 1. On PODs 3 and 7, colonic anastomotic tissue OHP contents were significantly higher in the SIM group than in the control group ($p<0.05$; factorial variance analysis model with two factors).

Statins are a class of agents designed to treat hypercholesterolemia; however, recent in vivo and in vitro studies have demonstrated that the drugs have additional vasculoprotective effects independent of cholesterol lowering: statins improve endothelial function, reduce vascular inflammation, decrease platelet aggregation, enhance endothelial processes involved in angiogenesis, and promote angiogenic processes, including endothelial cell proliferation and migration.[24,25] Statins seem to be broad-spectrum agents with more than one pleiotropic effect by a dose-dependent manner. Certain preclinical studies have led to the speculation that statins are pro-angiogenic at low (clinically relevant) doses but anti-angiogenic at high doses, raising concern that clinically relevant doses might enhance tumor-associated angiogenesis.[26] SIM enhances endothelial differentiation of peripheral blood mononuclear cells and induces pro-angiogenic cytokine IL-8 secretion from monocytes.[27] Moreover, SIM stimulates vascular endothelial growth factor released in vascular smooth muscle cells which might account for the pro-angiogenic effect of the agent.[28] Neovascularization was determined to be superior after statin administration particularly at POD 7, but it reached no significance in our study.

Table 4 Serum MDA, PON, and HDL Results on POD 3 and POD 7

	POD3			POD7		
	Untreated control	SIM	*p* value	Untreated control	SIM	*p* value
MDA (ng/ml)	19.1±3.75	14.3±1.01	<0.001	16.85±2.21	13.6±0.66	<0.05
PON (μ/L)	8.15±2.24	25.87±9.29	<0.0001	11.59±7.32	25.68±6.75	<0.001
HDL (mg/dl)	44.5±11.8	53.6±5.8	<0.05	49.87±8.7	45.5±7.4	>0.05

MDA malondialdehyde, *PON* paraoxonase, *HDL* high-density lipoprotein

Inflammation is an imperative phenomenon for successful wound healing. Nevertheless, over-inflammation leads to impaired wound healing due to increased collagenolysis and delayed reepithelization, resulting in anastomotic complications.[29] Statins inhibit neutrophil infiltration in skeletal muscle reperfusion injury.[30] Shao et al.[31] suggested that SIM suppresses lung inflammatory response in a rat model of cardiopulmonary bypass. The ischemic necrosis and inflammatory infiltration to muscle layer were found to be decreased in SIM-treated rats in the present study, which is consistent with previous reports by Pruefer et al.[3] focusing on anti-inflammatory effects of the agent. The hypothesis of partial inhibition of the undesirable effects of the inflammatory phase on wound healing might provide an explanation for this significance in SIM-treated rats, particularly at POD 3.

Collagen is the major structural protein providing biomechanical strength to the colonic wall and determining early anastomotic resistance by rendering anchorage to the submucosal sutures. Collagen degradation is another important step of wound healing in which matrix metalloproteinases (MMP) play crucial roles. During the first 3–5 days after anastomosis, collagenolysis exceeds collagen synthesis and the balance shifts, favoring the former, resulting in loss of anastomotic strength with minimal values after approximately 3 days.[32,33] During this early phase of the healing process, known as inflammatory stage, anastomotic strength and integrity depend on the suture-holding capacity of the submucosa and anastomosis is theoretically under the greatest risk for leakage. Thereafter, wound strength increases rapidly, between the fifth and seventh days after surgery, collagen synthesis peaks during proliferative phase, and the healing process is dominated by the formation of a new matrix.[29] This postoperative pattern has been attributed to physiologic changes in matrix metabolism during this period and occurs even in a case in which the anastomosis is created under ideal circumstances. Therefore, the third and the seventh postoperative days were used to evaluate the early and late anastomotic wound healing process in our study. Although many techniques have been developed to assess anastomotic healing, bursting pressure demonstrating mechanical healing and tissue OHP content showing biochemical healing are the most commonly used parameters. Therefore, we evaluated bursting pressure and tissue OHP content as indicators of anastomotic strength and collagen deposition both on the early (POD 3) and late (POD 7) phases of the healing process. HMG-CoA reductase inhibitors reduce MMP-1 and MMP-9 activity in human smooth muscle

Table 5 The Results of Mucosal Ischemia According to Chiu et al.

	POD3[a]				POD7[b]			
	Untreated control		SIM		Untreated control		SIM	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
Grade 0	0	0	0	0	0	0	0	0
Grade 1	0	0	6	87.5	5	62.5	6	75
Grade 2	6	75	1	12.5	0	0	0	0
Grade 3	0	0	1	12.5	1	12.5	0	0
Grade 4	1	12.5	0	0	1	12.5	2	25
Grade 5	1	12.5	0	0	1	12.5	0	0

[a] Difference between untreated control group and SIM treatment group on POD 3 is not significant, $p>0.05$, Kruskal–Wallis variance analysis test

[b] Difference between untreated control group and SIM treatment group on POD 7 is not significant, $p>0.05$, Kruskal–Wallis variance analysis test

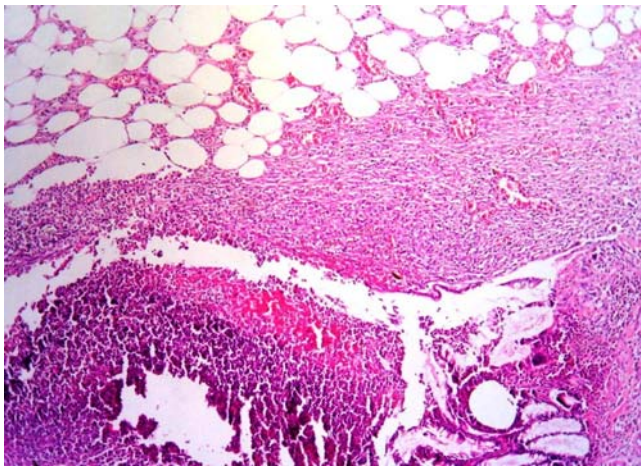

Figure 3 Full thickness ulceration extending to subserosal fat with dense exudation and granulation tissue in control group on POD 3.

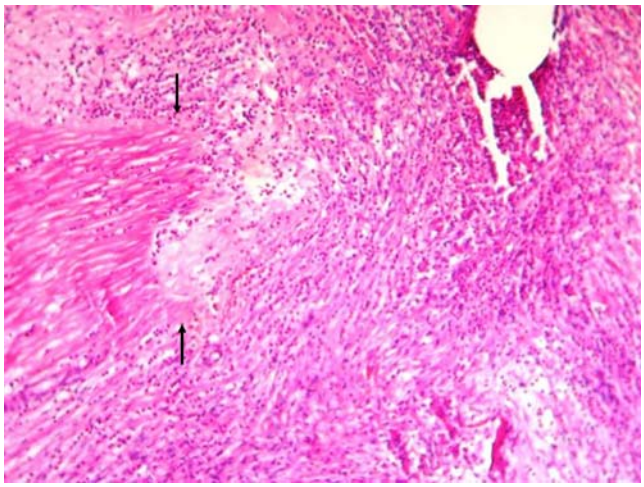

Figure 5 Interruption of muscle layer in control group on POD 7.

cells and varicose veins.[34–36] Similarly, in the present study, OHP levels predicting collagen content and bursting pressure were determined to be superior at both time points for simvastatin-treated rats. The underlying mechanism responsible for this variation over MMPs will be the topic of a further study.

Oxidative damage has long been investigated as an adjunct in impaired wound healing, particularly under ischemic conditions, which is one of the most accused reasons of anastomotic leakage. Rugale et al.[6] and Sun et al.[37] demonstrated the antioxidant properties of SIM against ischemia–reperfusion injury and angiotensin II hypertension. In the present study, MDA and PON activities were used as oxidative stress markers. MDA levels predicting lipid peroxidation was found to be decreased, and PON activity, inhibiting the oxidative modification of low-density lipoprotein, was determined to be increased at both time points in SIM-treated rats, revealing further evidence of statin pleiotropism against oxidative damage.

Intraperitoneal administration of statins decreases postoperative adhesions by increasing peritoneal fibrinolytic activity.[38] However, we did not observe significant difference in terms of adhesions between groups. This result might be attributed to both route (oral) and the dose (clinically approved doses) of drug application in the present study. Consistently, the significantly higher bursting pressures determined in SIM-treated rats on POD 3 support the hypothesis that anastomotic strength is not determined by the perianastomotic adhesions but by the suture holding capacity of the preexisting matrix instead. At this point, the pleiotropic effects of statins on MMP inhibition again merit further investigation that decreased matrix degradation might be the responsible factor for improved anastomotic strength in the early healing process.

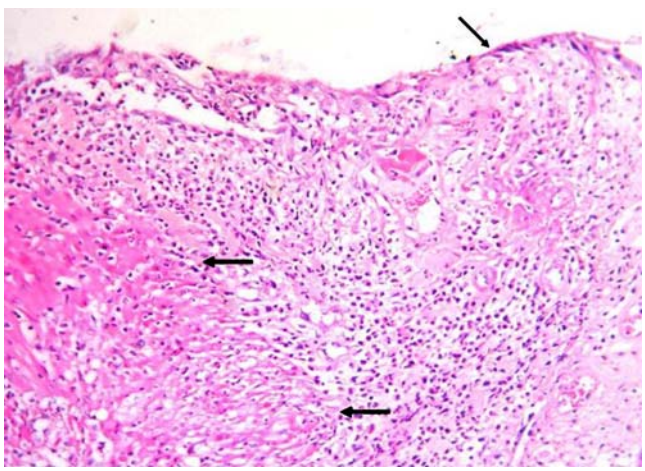

Figure 4 Surface epithelization (*thin arrow*) overlying inflammatory reaction and necrotic muscles (*thick arrows*) in SIM-treated rats on POD 3.

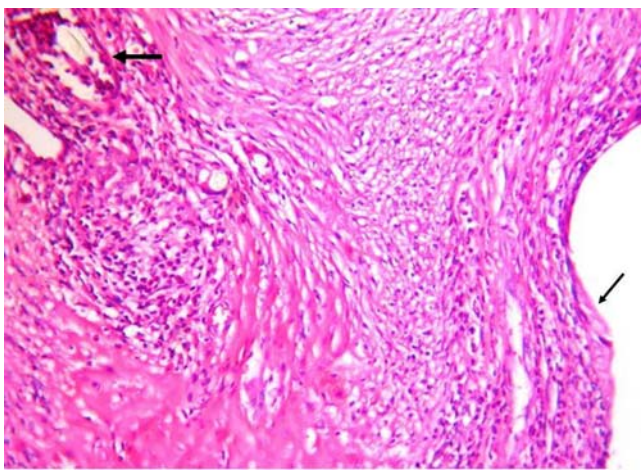

Figure 6 Single epithelial layer formation (*thin arrow*) and decreased inflammation with relatively preserved muscles and foreign body reaction (*thick arrow*) in SIM-treated rats on POD 7.

Another important issue is that statins exhibit immunomodulatory effects independent of lipid lowering which have been proven by means of sepsis models in terms of improving survival.[2,4] Nevertheless, the present study has no power to evaluate this effect, since septic complications have not been determined in any of the test objects.

Conclusion

The data from this study demonstrate that the administration of SIM to rats with colonic anastomosis significantly enhances the wound healing by means of increasing mechanical strength and the amount of OHP (reflecting collagen level) in the tissue at the anastomosis site. Hence, we propose that SIM might be safely used on patients with intestinal anastomosis at clinically relevant doses. The aforementioned pleiotropic effects of statins, most of which are relevant to wound healing, deserve attention. Nevertheless, further studies are required to elucidate the mechanisms by which statins offer these protective functions.

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CASE REPORT

Rapid Reversal of Parenteral-Nutrition-Associated Cirrhosis Following Isolated Intestinal Transplantation

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Abstract
Introduction Liver disease and the development of hepatic fibrosis are complications associated with total parenteral nutrition (TPN). Patients developing cirrhosis and portal hypertension in the setting of intestinal failure have a high mortality and may require combined liver and intestinal transplantation which carries much higher morbidity and mortality than isolated intestinal transplantation.
Discussion Recently, regression of hepatic fibrosis in patients with TPN liver disease has been described following intestinal transplantation. To date, there has been no demonstration of the reversal of established cirrhosis due to long-term TPN injury. Herein, we describe a patient with intestinal failure who developed cirrhosis from long-standing TPN injury and underwent isolated intestinal transplantation. He had no overt clinical stigmata of portal hypertension and had preserved liver function. Serial liver biopsies were reviewed and assessed with standard histology and quantitation of fibrosis using image analysis. Dramatic regression of fibrosis and reversal of cirrhosis were observed 17 months posttransplantation. Image analysis demonstrated a 14% total decrease in the percentage area of fibrosis.
Conclusions Cirrhosis related to TPN may be rapidly reversible after isolated intestinal transplantation. Such patients may be able to undergo isolated intestinal transplantation if they do not have hepatic synthetic compromise or clinical stigmata of portal hypertension.

Keywords TPN · Intestinal transplantation · Cirrhosis · Hepatic fibrosis

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Introduction

Liver disease and the development of advanced hepatic fibrosis are complications associated with total parenteral nutrition (TPN) especially in the setting of short bowel syndrome and intestinal failure.[1–5] Patients developing cirrhosis and portal hypertension in the setting of intestinal failure have a high mortality and may require combined liver and intestinal transplantation.[6] Survival after intestinal transplantation has improved significantly over the past decade but outcomes are not as good in patients requiring combined intestinal and liver transplantation. Overt clinical manifestations of portal hypertension rarely develop in such patients, possibly because of decreased portal inflow making the decision whether to perform a combined liver–intestine procedure versus isolated intestinal transplantation problematic.[2,6–10]

Hepatic fibrogenesis is a result of chronic liver damage and numerous studies have shown that treatment of the

inciting cause of liver injury can lead to regression of fibrosis and even cirrhosis over time. Reversal of cirrhosis has been demonstrated in patients suffering from autoimmune hepatitis, biliary obstruction, iron overload, nonalcoholic steatohepatitis, hepatitis B and C, and cardiac cirrhosis.[11–17] Recently, appreciable regression of hepatic fibrosis in patients suffering from TPN liver disease has been described following intestinal transplantation.[18] To date, there has been no demonstration of the reversal of established cirrhosis occurring due to long-term TPN injury. Herein we describe a patient with intestinal failure having histologically proven cirrhosis from long-term TPN use who demonstrated reversal of cirrhosis within 17 months of undergoing isolated intestinal transplantation. This reversal was demonstrated both histologically and by quantitative assessment of the total amount of hepatic fibrosis using image analysis.

Case History

A 38-year-old man with chronic intestinal pseudo-obstruction due to degenerative visceral neuropathy underwent isolated small intestinal transplantation in February 2007. He had suffered multiple episodes of catheter-related bacteremia and fungemia, a right upper extremity deep venous thrombosis, osteoporosis, and severe iron deficiency anemia. He had been TPN-dependent with limited oral intake for the last 8 years. The patient had a previous jejunal as well as ileocolic resection and had lost close to 40 lb over the previous year, in large part due to minimization of the calories provided by TPN because of abnormal liver chemistry tests. Six months prior to transplantation, a percutaneous liver biopsy showed cirrhosis and abdominal imaging demonstrated splenomegaly and portal hypertension. TPN composition in the months leading to transplantation consisted of 250 g dextrose, 50 g lipid, 80 g amino acids, in 2,200 cm^3 volume. Liver chemistry and liver function tests are shown in Table 1.

Small intestinal transplantation was undertaken using a 45-year-old male donor with the surgical and immunosuppressive protocol previously described.[19] The native explanted small bowel measured 231 cm and was distended up to 15 cm in diameter; the length of the grafted small intestine was 305 cm. Postoperative course was uneventful with TPN discontinued on postoperative day 3 and enteral feeding initiated on day 4. Seventeen months after transplantation, the patient continues to do well never having had an episode of rejection or evidence of hepatic decompensation. He is eating ad lib, is off all supplementary enteral feeding, and has had his ileostomy reversed and gastrostomy tube removed. His postoperative liver chemistry tests are shown in Table 1.

Methods

A total of three formalin-fixed paraffin-embedded liver biopsies, all of adequate length, were studied. Hematoxylin and eosin and Masson trichrome-stained slides were read by a liver pathologist (MIF). In order to objectively quantitate the amount of fibrosis, trichrome-stained slides were utilized for image analysis as has been previously described.[20,21] The entire length of the trichrome-stained biopsy specimen was photographed sequentially from end to end using a Nikon Digital Sight DS-L camera attached to a compatible microscope and photos were taken at ×40 magnification; longer biopsies thus required more images. A computerized algorithm for classifying red (liver parenchyma) and blue (collagen) areas on the trichrome slide was utilized as previously used by our group.[18,22] The total amount of collagen in each photographed image as measured by the blue area was quantitated via image analysis and was transformed into a green color. This was contrasted against the total of the nonfibrotic liver parenchyma as seen in the counterstained red area which appears as yellow in the image analysis profile. An additional algorithm was devised so as to include the hepatocytes containing steatotic vacuoles which would have otherwise been undiscernible to be nonfibrotic parenchyma (red area). Sums of the blue and red areas were then calculated; the percentage of total fibrosis was determined as $100 \times (\text{total blue area})/(\text{total blue area} + \text{total red area})$.

Table 1 Liver Chemistry and Function Testing Pretransplantation and Posttransplantation

	Platelet count (150–450)×10^3 per microliter	INR	Bilirubin (0.1–1.2) mg/dL	Albumin (3.5–4.9) g/dL	ALT (1–53) U/L	AST (1–50) U/L	Alkaline phosphatase (30–110) U/L
6 months pre-SBT	86	1.6	1.3	2.2	65	34	238
At SBT	73	1.6	2.1	2.5	79	53	364
3 months post-SBT	75	1.1	1.1	4.0	43	32	173
6 months post-SBT	107	1.1	1.1	4.0	32	31	176
17 months post-SBT	95	1.1	1.3	4.1	30	22	128

SBT small bowel transplantation

Table 2 Histologic Characteristics of Liver Biopsies

Bx #	Timing of Bx (months)	Length (cm)	Stage of fibrosis[a]	Grade of steatohepatitis[a]	Number of digital images	Percentage area of fibrosis[b]	Other findings
1	6 pre-SBT	4.1	4	3	16	18.7%	Arterialization of central venules; chicken-wire fibrosis
2	at SBT	2.6[c]	4	1	8	22.6%	Broad and dense fibrous septa; prominent Ito cells
3	17 post-SBT	1.7	2–3[d]	0	7	8.6%	Fragmented and very thin septa when present

Bx biopsy, *SBT* small bowel transplantation

[a] Kleiner et al.[23]

[b] Via image analysis

[c] All needle biopsies; biopsy 2 performed intraoperatively

[d] Incomplete septal cirrhosis

Results

The summary of the histologic assessment and image analysis results of the three biopsies is shown in Table 2. There was an increase in fibrosis between biopsies 1 and 2. Biopsy 3 was performed 17 months posttransplantation and demonstrated significant regression in the amount of fibrosis as well as a decrease in the percentage of fibrosis via image analysis (from 22.6% to 8.6%), representing an average fibrosis regression rate of 0.8% per month (see Fig. 1).

Figures 2, 3, and 4 illustrate the trichrome-stained slide and the corresponding image analysis for each liver biopsy specimen. Image analysis generated photographs showing corresponding fibrotic and nonfibrotic areas that were eventually used to calculate percentage area of fibrosis. In Fig. 2, which was obtained pretransplantation, note the steatohepatitis and cirrhosis with loose bridging fibrous septa that enclose nodules in Fig. 2a. This biopsy shows severe steatohepatitis[23] consistent with TPN-induced liver injury with nodules as well as prominent sinusoidal and perivenular fibrosis. Figure 2b is the corresponding image analysis. The image analysis program is extremely sensitive so that even minute amounts of fibrous tissue can be identified and correlated.

Figure 3a is the liver biopsy specimen at the time of transplantation showing denser and more organized fibroconnective septa that completely enclose the cirrhotic nodules. There is less fat present than in the previous biopsy. Figure 3b is the corresponding image analysis. The liver biopsy specimen post-small-bowel-transplant is shown in Fig. 4. Some fragments of liver tissue are incompletely bordered by thin fibrous septa whereas others have no fibrosis whatsoever, typical changes of incomplete septal cirrhosis; no fat is present. In some areas of the liver biopsy specimen, there is a dramatic change in that no discernible residual fibrosis is identifiable at all. A significant decrease in the amount of blue-stained areas in the trichrome stains is clearly shown between Figs. 2 and 4. On image analysis, there is a dramatic decrease in the darker area between Figs. 2 and 4 with almost no identifiable darker area present except for the normal amount of fibrosis in portal tracts.

Discussion

Regression of hepatic fibrosis and reversal of cirrhosis have been shown to occur in several liver diseases.[11–17] Recently, our group has demonstrated appreciable regression of hepatic fibrosis occurring in patients with short bowel syndrome and intestinal failure undergoing isolated intestinal transplantation upon restoration of normal bowel length and integrity.[18] None of the patients had biochemical or clinical stigmata of portal hypertension which prompted the performance of isolated intestinal transplantation versus a combined procedure that

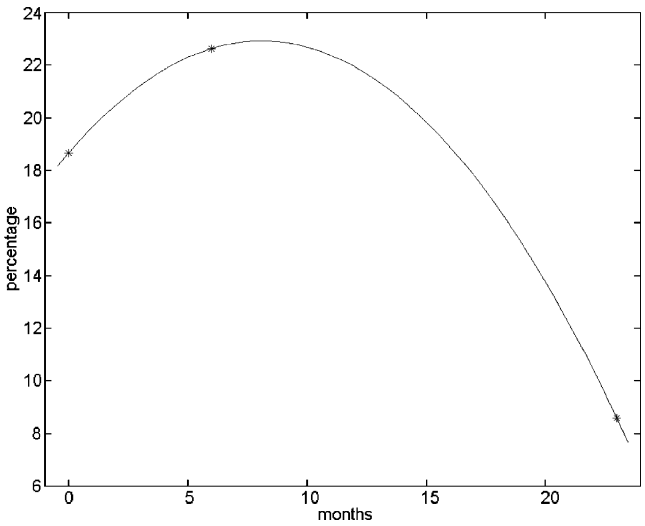

Figure 1 Rate plot depicting the percentage area of fibrosis as computed via image analysis (*y*-axis) versus time in months (*x*-axis). The three liver biopsies are shown as the time points. Note the increase in fibrosis between biopsies 1 and 2 and the dramatic decrease in fibrosis during the 17 months between biopsies 2 and 3.

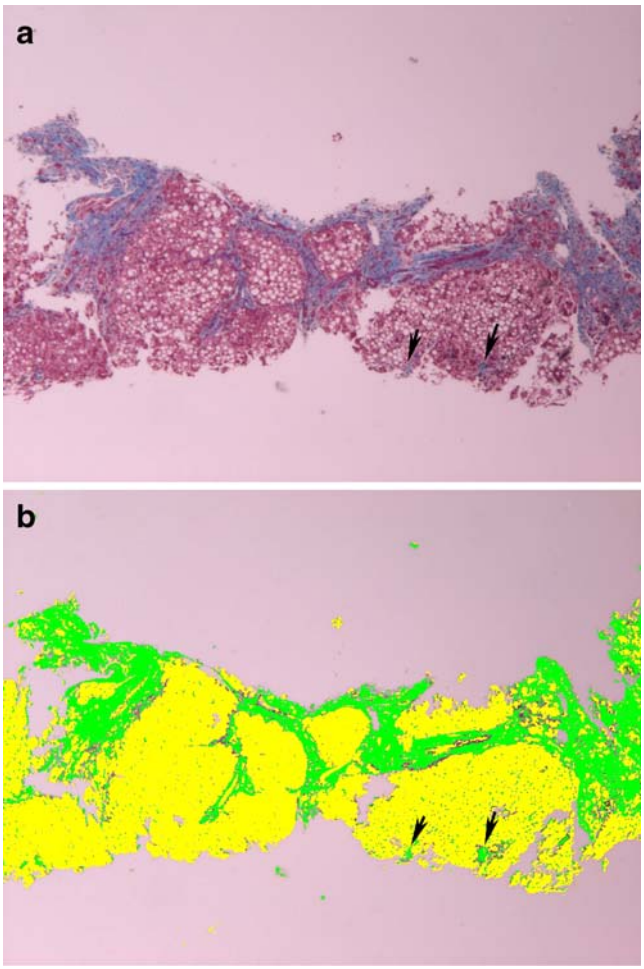

Figure 2 Liver biopsy 6 months pre-small-bowel-transplant. **a** shows a representative area seen on trichrome stain with the corresponding image analysis shown as **b**. The image analysis program is extremely sensitive so that even minute amounts of fibrous tissue can be identified and correlated (*arrows*). Note the steatohepatitis and cirrhosis with relatively loose fibrous septa that enclose nodules.

carries much greater morbidity and mortality. In the current report, the patient had histologic cirrhosis with portal hypertension as evidenced by thrombocytopenia and splenomegaly and subsequently had dramatic regression of cirrhosis within 17 months of the uncomplicated intestinal transplant.

The histologic findings in the above patient demonstrated an appreciable decrease in fibrosis and a remodeling of the liver's microarchitecture. Although the posttransplantation biopsy specimen was fragmented as one would see in the cirrhotic liver, nodules were in fact still present but incompletely surrounded by much thinner fibrous septa and in some areas of the biopsy there was no discernible fibrosis whatsoever. Fragmentation of liver biopsy specimens can be seen in incomplete septal cirrhosis. We believe that this regression was not only due to the discontinuation of TPN but also due to the return of adequate functional and anatomic bowel length. This regression might in part be owing to the improved portal blood flow that occurs with the new intestinal allograft or a decrease in portal endotoxemia that occurs in intestinal failure.[2,6] Quantitative image analysis showed advanced degrees of percentage total fibrosis in both biopsies 1 and 2 with appreciable decrease in the overall percent area of fibrosis 17 months posttransplantation. The percent total area of fibrosis in biopsies 1 and 2 is similar to what has been reported to be METAVIR F4 by Bedossa et al. whereas the last biopsy approximates F2.[24] Our patient currently has normal liver chemistry tests but continues to have thrombocytopenia that we feel is due to residual splenomegaly that has not regressed posttransplantation as can occur in some patients post-liver-transplantation.

Clinical manifestations of portal hypertension in the setting of TPN liver disease rarely develop in patients with short bowel syndrome, possibly because of decreased portal inflow.[2–4,7] The decision to perform a combined liver and

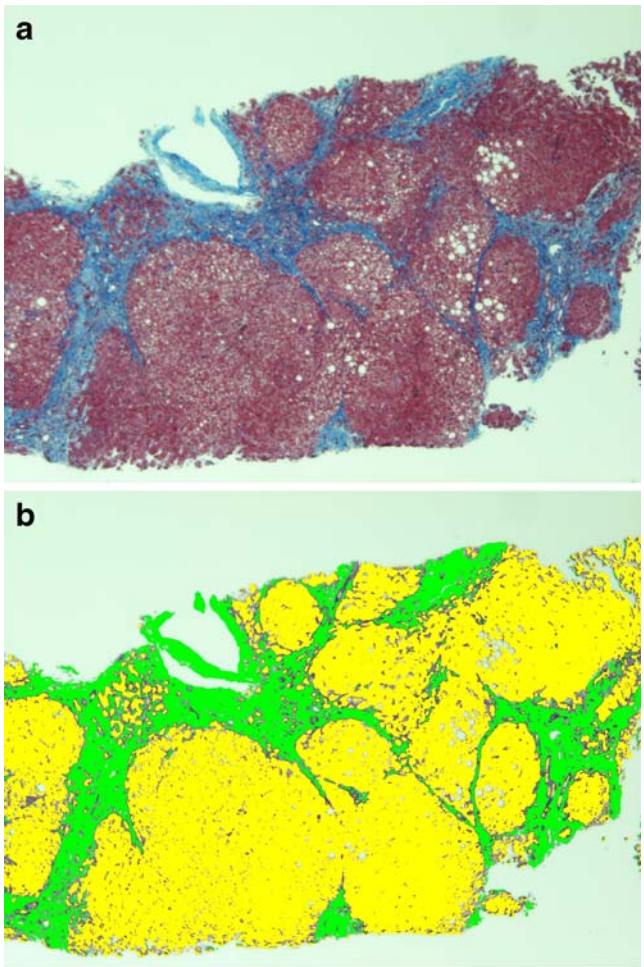

Figure 3 Liver biopsy at time of small bowel transplant. **a** shows a representative photo showing more organized and denser fibroconnective tissue that enclose the cirrhotic nodules and the corresponding image analysis in **b**. Although steatohepatitis is still present, there is considerably less fat than the previous biopsy.

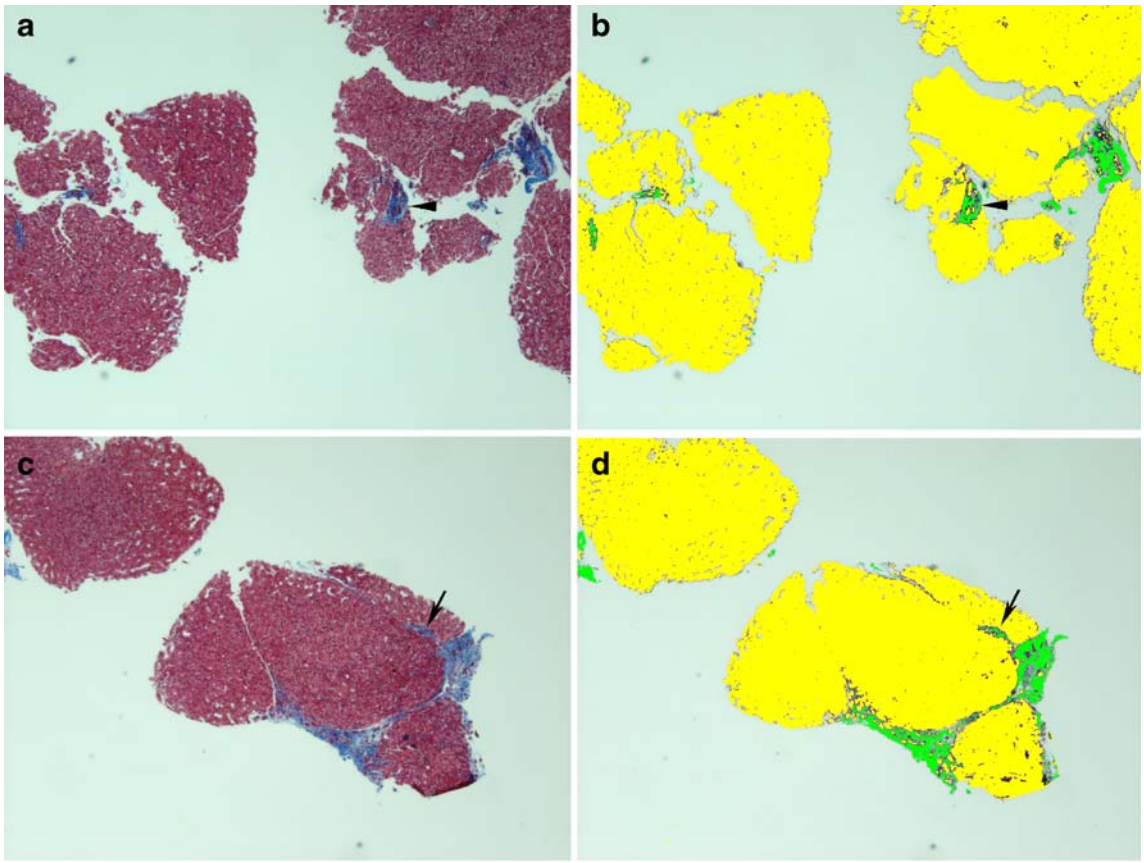

Figure 4 Liver biopsy 17 months after small bowel transplant. Two selected photomicrographs showing fragmented liver parenchyma, one devoid of fibrosis (**a**), and the other showing a thin fibrous septum partially bordering an incomplete nodule (**c**; *arrow*), typical changes of incomplete septal cirrhosis. The corresponding image analysis photos are shown in **b** and **d**. Note the dramatic decrease in the darker area between Fig. 2b and image Fig. 4b **b** with almost no identifiable darker area present except for the normal amount of fibrosis in portal tracts (*arrowhead*). Also note the absence of fat.

intestinal transplant is often based on the magnitude of hyperbilirubinemia and advanced fibrosis on liver biopsy.[1,2,8] The current report suggests that selected adult patients with cirrhosis due to TPN may be able to safely undergo isolated intestinal transplantation with the expectation of regression of hepatic fibrosis and cirrhosis over time. Caution has to be exercised in extending these findings to the pediatric population, as the mechanism for TPN-associated liver injury may be different in neonates and children, or to adult patients with appreciable hepatic synthetic compromise.[25] Patients having advanced hepatic fibrosis or cirrhosis from both TPN and another cause (e.g., primary sclerosing cholangitis in patients with Crohn disease suffering from short bowel syndrome) or patients not able to be weaned from TPN post-intestinal-transplantation) may not be expected to have such regression in their hepatic fibrosis. The patient described in our report had an uncomplicated postoperative course which we believe contributed to the regression process. There were no infections and TPN was rapidly weaned, thus eliminating several factors contributing to fibrosis progression pretransplantation. The results we report here may not be applicable to patients having early or late postoperative complications, the former possibly contributing to ongoing hepatic injury or ischemia and thus hepatic decompensation.

Sampling error is extremely unlikely to have accounted for the histologic findings demonstrated in this patient. All of the liver biopsies were more than of adequate length and had an adequate number of portal tracts. The performance of image analysis quantitatively demonstrated the decrease in fibrosis and objectively confirmed the histologic observations. In descriptions of the regression of cirrhosis in other disease entities, the decrease in fibrosis was defined by a lowering of fibrosis stage which may in itself be limited by sampling error and interobserver/intraobserver variability. Precedent does exist however for a similar type of regression of cirrhosis as shown in the current case. Wanless et al.[26] described a patient with chronic hepatitis B infection with cirrhosis and severe chronic hepatitis who after 30 months of treatment with lamivudine showed no

chronic active hepatitis or cirrhosis and only one incomplete fibrous septum. Incomplete septal cirrhosis was also seen in this patient as it was in our patient and is one of a continuum of several histologic findings described to occur in the regression of cirrhosis.

The reversal of cirrhosis demonstrated in the current report occurred within 17 months of intestinal transplantation. This is more rapid than in the majority of the other entities in which cirrhosis has been shown to regress. Cirrhosis has been reported to regress 10 years following heart transplantation,[17] 8–70 months post-bariatric-surgery,[14] 13–118 months with medical treatment for autoimmune hepatitis,[11] 4–10 years after treatment of thalassemia,[13] a mean of 21 months after interferon treatment for hepatitis C,[16] and 3 months to 9 years after treatment of common bile duct stenosis.[12] In many of the above, however, regression was denoted merely by a decrease of one to two stages of fibrosis without other accompanying histologic features described to occur in the regression of cirrhosis such as incomplete septal cirrhosis. The current case is the only study to date that has used image analysis to objectively quantitate the decrease in fibrosis seen with cirrhosis reversal.

In summary, the current report demonstrates the well-characterized reversal of cirrhosis and rapid regression of fibrosis post-intestinal-transplantation in a patient with TPN-associated liver injury. Of the many previously described cases of cirrhosis regression, reversal after TPN discontinuation with the reestablishment of normal bowel length and integrity appears to be one of the fastest to occur. These findings suggest that patients having cirrhosis from TPN-associated liver injury in the setting of short bowel syndrome may be able to undergo isolated intestinal transplantation if they do not have hepatic synthetic compromise or clinical stigmata of portal hypertension. This might allow these patients to avoid the extremely high mortality rates on the waiting list for patients awaiting combined liver and intestinal transplant and the accompanying lower posttransplant patient and graft survival rates as compared to isolated intestinal transplantation.

Conflicts of interest None

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CASE REPORT

Hepatic Resection for Metastatic Colon Cancer in Patients with Situs Inversus Totalis Complicated by Multiple Anomalies of the Hepatobiliary System: The First Case Report

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Abstract
Background Situs inversus totalis is a rare condition characterized by a mirror-image transposition of the abdominal and thoracic viscera. In order to develop safe techniques for hepatic resection, it is important to report surgical outcomes in cases complicated by situs inversus totalis and other anomalies.
Case The patient was a 64-year-old man with situs inversus totalis who had previously undergone sigmoidectomy with regional lymphadenectomy for sigmoid colon cancer at age 62. Despite postoperative adjuvant chemotherapy, tumor markers increased and multiple liver metastases were detected on abdominal ultrasonography. Enhanced computed tomography revealed not only liver metastases but also hepatobiliary anomalies associated with situs inversus totalis as follows: (1) portal vein located anterior to the common bile duct or hepatic artery, (2) proper hepatic artery arising from the superior mesenteric artery, (3) "left" (right in normal population)-sided umbilical portion of the portal vein and total ramification of intrahepatic portal branches from that point, (4) hepatic vein directly communicating to the "left" atrium. For the treatment of hepatic metastases from sigmoid colon cancer in a patient with situs inversus totalis, "left" hepatic lobectomy, partial hepatectomy, and radiofrequency ablation therapy were performed. The postoperative course was uneventful. Adjuvant chemotherapy has been continued for 2 years after the second operation and the patient is doing well without recurrence.
Conclusion Since situs inversus totalis is occasionally accompanied by multiple hepatobiliary anomalies, careful evaluation of the related anatomy using modern imaging modalities is crucial for safe hepatic resection.

Keywords Hepatectomy · Situs inversus totalis · Hepatic metastasis · Colon cancer

Introduction

Situs inversus totalis refers to a complete left-to-right side transposition of the asymmetrical thoracic and abdominal organs. Because it is a rare condition with an incidence of 1:5,000 to 1:20,000 adults,[1,2] most surgeons have little surgical experience with these patients. Although the surgical technique for situs inversus totalis does not differ from the usual method, it is difficult because of the mirror image reversal of the internal organs and the rarity of the condition. Moreover, the concurrent anomalies that often occur with situs inversus[2–5] make the surgical procedure more complex.

We document a patient with situs inversus totalis and concurrent multiple anatomical transposition in the hepatibiliary system. To the best of our knowledge, this is the first report of these anomalies being associated with situs inversus totalis. The patient underwent hepatic surgery for multiple hepatic metastases from colon cancer. The surgery and postoperative course were uneventful, mainly due to the scrupulous preoperative evaluation.

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Case

A 64-year-old Japanese man was referred to our institute for treatment of multiple hepatic metastases from colon cancer. His medical history included diabetes mellitus at the age of 40, when situs inversus totalis was first diagnosed, and sigmoid colon cancer treated with sigmoidectomy and regional lymphadenectomy at the age of 62. Although postoperative adjuvant chemotherapy was performed, recurrence with multiple hepatic metastases occurred.

On admission, blood tests showed normal transamylase levels but elevated levels of alkaline phosphatase at 345 U/l (normal range 130–280 U/l) and gamma-glutamy transpeptidase at 133 U/l (normal range 30–56 U/l). Tumor markers such as carcinoembryonic antigen and carbonic anhydrase 19–9 increased to 24.0 ng/ml (normal range <3.6 ng/ml) and 206 U/ml (normal range <40 U/ml), respectively. The indocyanine green retention rate at 15 min was 8.9%.

Positron emission tomography with [^{18}F] fluorodeoxyglucose (FDG-PET) and FDG-PET-CT showed multiple liver metastases without metastatic lesions in other organs. Enhanced abdominal CT showed not only situs inversus totalis but also anatomical vascular anomalies. The portal vein was located anterior to the common bile duct and the proper hepatic artery arose from the superior mesenteric artery instead of the celiac artery. In addition, the umbilical portion of the portal vein was "left" (right in normal population)-sided, with total ramification of the intrahepatic portal branches from that section (Fig. 1a, b). Furthermore, the three hepatic veins drained directly to the "left" atrium but not to the inferior vena cava (Fig. 1c).

To treat multiple hepatic metastases in this patient with situs inversus totalis, "left" hepatic lobectomy, partial hepatectomy, and radiofrequency ablation were performed (Fig. 2). Total operation time, intraoperative blood loss, and weight of resected specimen were 8 h and 50 min, 550 ml, and 680 g, respectively. The histopathological diagnosis was multiple hepatic metastases from sigmoid colon cancer.

The postoperative course was uneventful. Adjuvant chemotherapy has been continued for 2 years, and the patient is doing well without recurrence.

Discussion

Situs inversus totalis is a rare congenital condition with an incidence of 1 in 5,000 to 20,000 adults,[1,2] in which mirror-image transposition of internal organs occurs. With the emergence of sophisticated diagnostic radiological modalities, the diagnosis of situs inversus totalis has become relatively easy. However, since concurrent abnormalities often accompany this condition, careful attention should be

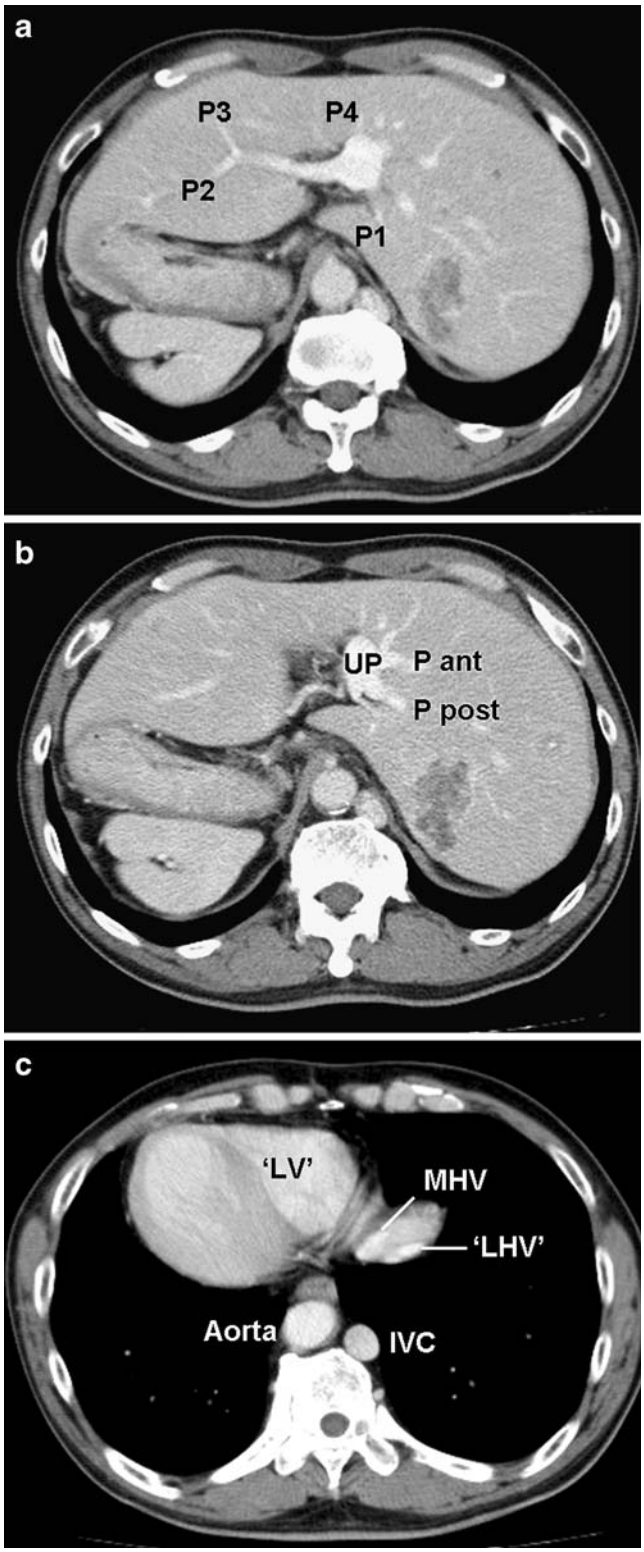

Figure 1 **a**, **b** Enhanced abdominal CT shows that the umbilical portion is "left"-sided with total ramification of the intrahepatic portal branches from that section. The umbilical portion is characterized by a *saccular shape*. *P ant* anterior branch of portal vein, *P post* posterior branch, *P1* Caudate lobe branch, *P2* "left" lateral posterior branch, *P3* "left" lateral anterior branch, *P4* left medial branch. **c** Hepatic veins drains directly to the "left" atrium but not to the inferior vena cava. "*LV*" "left" ventricle, *IVC* inferior vena cava.

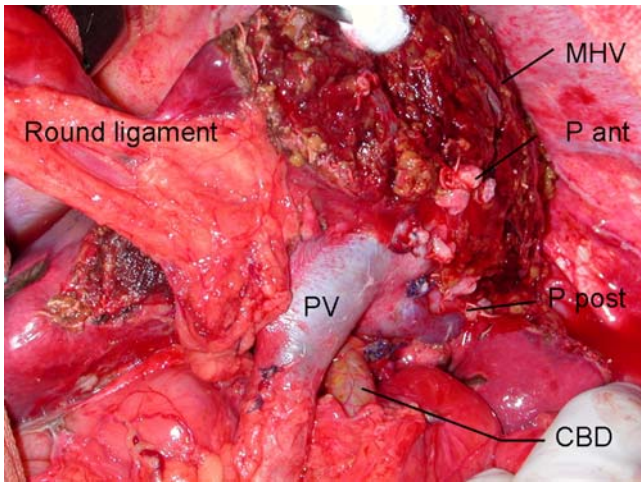

Figure 2 Postoperative photography shows that the portal vein (*PV*) is located in the anterior of the common bile duct (*CBD*) and the middle hepatic vein (*MHV*) is preserved.

given to their detection, especially in the hepatobiliary and cardiovascular systems.[2–5] The incidence of cardiovascular anomalies is approximately ten times higher in these patients than in individuals without situs inversus totalis.[5] For instance, the prevalence of associated congenital heart disease reportedly ranges from 3% to 5% among patients with situs inversus totalis,[3] and the reported incidence of hepatobiliary tract anomalies is also considerable.[1] Biliary atresia commonly accompanies situs inversus totalis in children, necessitating immediate medical treatment including liver transplantation. Variations in the hepatic artery have also been reported,[6–8] although an accurate incidence of such anomalies is unknown.

To the best of our knowledge, six cases of hepatectomy for hepatobiliary malignancies in patients with situs inversus totalis have been reported including our present case (Table 1).[6,7,9–11] Three of these cases showed hepatic artery variations. In one case, the left hepatic artery arose from the left gastric artery. In the second case, the right hepatic artery arose from the superior mesenteric artery, and in our case, the proper hepatic artery arose from the superior mesenteric artery. Preoperative detection of these aberrant blood supplies is helpful in performing a safe operation. Preoperative evaluation with angiography or enhanced multidetector CT is, therefore, essential. Considering that 50% of all cases showed hepatic artery variations; this particular anomaly might be related directly to the situs inversus condition. However, the number of reported cases is still low, and further studies are required.

The hepatic vein anomaly seen in the present case is also notable. In general, three main hepatic veins drain the liver into the inferior vena cava below the diaphragm,[12] and a single hepatic vein draining directly to the right atrium is occasionally reported.[13,14] However, it is rare to see the three main hepatic veins draining directly to the right atrium. A search of PubMed using the keywords, right atrium and hepatic vein, did not find any reports of this anomaly. This may be because the condition is rare, and this anomaly does not cause clinical symptoms. However, although this anomaly does not have clinical importance in the normal setting, preoperative detection is crucial in preventing unnecessary injury to the hepatic veins during their dissection.

The long straight "left" portal vein branching to the bilateral liver was another important and interesting finding. This anomaly was described as the total ramification of the intrahepatic portal venous branches from the umbilical portion[15,16] and was characterized by a saccular shape.[15] This anomaly has been found in one in 192 individuals without the association with situs inversus,[15] and only a few cases have been reported.[15–18] This variation may lead to serious complications during major hepatic resection if not detected.[16] Additionally in the present case, the round ligament was terminated in this portion and was diagnosed as the "left" umbilical portion. Normally, in situs solitus, the right umbilical vein disappears in early fetal life, while remnants of the left umbilical vein remain to form the umbilical portion of the portal system, round ligament of liver, and Arantius ligament.[19,20] However, if the left umbilical vein disappears early in life and the right umbilical

Table 1 Reported Cases of Hepatectomy for Malignancies with Situs Inversus Totalis

Year (reference no.)	Age	Gender	Cause of operation	Anomaly of hepatic artery	Treatment	Cholecystolithiasis/ Choledocolithiasis
Present	64	M	Metastasis	PHA from SMA	Right lobectomy	None
2003 ([9])	72	F	Metastasis	no	subsegmentectomy	Cholecystolithiasis
2003 ([10])	76	F	Cholangiocarcinoma	no	Right lobectomy	Choledocolithiasis
1996 ([6])	69	F	HCC	LHA from LGA	subsegmentectomy	Not described
1989 ([7])	66	F	HCC	RHA from SMA	Right lobectomy	Not described
1983 ([11])	37	M	HCC	no	Right lobectomy	Not described

HCC hepatocellular carcinoma, *LHA* left hepatic artery, *LGA* left gastric artery, *RHA* right hepatic artery, *SMA* superior mesenteric artery, *PHA* proper hepatic artery

vein remains, the latter develops into the umbilical portion and the round ligament deviates to the right.[19,20]

To our knowledge, this is the first report of the association of these combined multiple anomalies with situs inversus totalis. In addition to the left-to-right reversal of organs, these anomalies increased the surgical difficulty and operative risks in this case. Accurate preoperative evaluation with imaging modalities, including multidetector CT, is, therefore, important in developing appropriate surgical treatments in these complex cases.

In conclusion, since situs inversus totalis is often accompanied by multiple hepatobiliary anomalies, careful evaluation of the related anatomy using modern imaging modalities is crucial for safe hepatic resection.

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HOW I DO IT

Laparoscopic Paraesophageal Hernia Repair. How I do it

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Abstract
Introduction The approach to paraesophageal hernias has changed radically over the last 15 years, both in terms of indications for the repair and of surgical technique.
Discussion Today we operate mostly on patients who are symptomatic and the laparoscopic repair has replaced in most cases the open approach through either a laparotomy or a thoracotomy. The following describes a step by step approach to the laparoscopic repair of paraesophageal hernia.

Keywords Paraesophageal hernia · Hiatal hernia · Gastroesophageal reflux disease · Mesh repair · Laparoscopic fundoplication

The approach to paraesophageal hernias has changed radically over the last 15 years, both in terms of indications for the repair and of surgical technique.

During the 1970s surgeons advocated the elective repair of any paraesophageal hernia regardless of the presence of symptoms. The rationale for this approach was to avoid life-threatening complications such as obstruction and strangulation, and the risk of emergent surgery.[1,2] Today a more conservative approach has been taken by most surgeons, as they are reluctant to operate in the absence of symptoms.[3–5] Recently, in an elegant study using a Markow Monte Carlo decision analytic model, Stylopoulos and colleagues from the Massachusetts General Hospital showed that currently available data do not support any longer the routine elective repair of paraesophageal hernias.[6] They confirmed the recent belief that in patients who are asymptomatic and in whom the hernia has been an incidental finding, a "watchful waiting" approach is a reasonable alternative to the routine elective repair for the majority of patients. Therefore, today we operate only on symptomatic patients who experience symptoms due to gastroesophageal reflux disease (GERD; heartburn, regurgitation, cough), incarceration (pain, perforation), or obstruction (dysphagia, bleeding from venous stasis, dyspnea).

The advent of minimally invasive surgery has also brought a shift in the operative management of patients with a paraesophageal hernia, as the open approach through either a laparotomy or a thoracotomy has been almost universally replaced by a laparoscopic repair.[7–9] While the operation is more complex and has a longer learning curve than a fundoplication performed for GERD, it is still associated with a simpler and shorter postoperative course, a shorter recovery time, and a faster return to regular activity, even in elderly and high risk patients.[8]

The following describes a step by step approach to the laparoscopic repair of a paraesophageal hernia.

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Positioning and Trocar Placement

The patient is placed in a steep reverse Trendelenburg position with the legs extended on stirrups. The surgeon stands between the patient's legs. Five trocars are used for the operation, as for a regular fundoplication done for GERD (Fig. 1).[10]

The first port is placed in the midline, 14 cm distal to the xiphoid process. It is used for the camera (30° scope). The second port is placed in the left mid-clavicular line at the same level of port 1. It is used for inserting a Babcock clamp for traction on the gastroesophageal junction, and for inserting an instrument to take down the short gastric vessels. The third port is placed in the right mid-clavicular line at the same level of port 1 and 2. A fan retractor is used through this port to lift the left lateral segment of the liver to expose the gastroesophageal junction. This retractor is held in place by a self-retaining system fixed to the operating table. The last two ports are placed under the right and left costal margin, about 6 cm from the midline so that their axes form an angle of about 120°. This angle between the two ports located under the costal margins, allows easy dissecting and suturing. These ports are used for the insertion of graspers, electrocautery, and suturing instruments.

A common mistake is to place the trocars too low. If this happens, both the dissection and the suturing become very difficult, as the instruments might not reach. If the angle between ports 4 and 5 is <60°, suturing becomes almost impossible.

Dissection of the Hernia Sac and Mobilization of the Esophagus

We start by gently pulling the herniated stomach out of the posterior mediastinum down into the abdomen using a Babcock clamp. Rather than starting the dissection by opening the gastro-hepatic ligament, we prefer to divide initially the short gastric vessels and reach the left pillar of the crus as suggested by Horgan and colleagues.[4] Subsequently we open the hernia sac at the junction with the left crus and start the mobilization of the esophagus. This "left crus" approach reduces the risk of injuring a replaced or accessory left hepatic artery, with resultant bleeding which may be difficult to control if the proximal stump of the artery retract above the diaphragm. We position a Penrose drain early around the esophagus as it facilitates subsequent exposure and dissection. We try to resect the entire sac but when it extends high in the mediastinum we prefer to transect it at the level of the esophageal hiatus. In our experience, we have never encountered a postoperative mediastinal fluid collection. For this reason, we do not feel that a mediastinal drain is necessary. Over time we have learned to extend the dissection more proximally in order to have 3 to 4 cm of esophagus below the diaphragm. With this more extensive dissection in the posterior mediastinum, it is quite rare to see a "short esophagus". However, if the gastroesophageal junction goes back above the diaphragm as soon as traction is removed, a lengthening procedure (Collis gastroplasty) will be necessary. Even though we have not used this technique in our own experience, we recognized that some of the recurrences we had might have been due to a shortened esophagus.[11] Of the different techniques available, we feel that a wedge gastroplasty with a linear stapler is probably the easiest to perform.[12–14] A bougie must be placed inside the esophagus to avoid narrowing of the lumen. Even though a small gastric pouch is left above the wrap with some acid-producing parietal cells, this can be easily controlled by proton pump inhibitors.

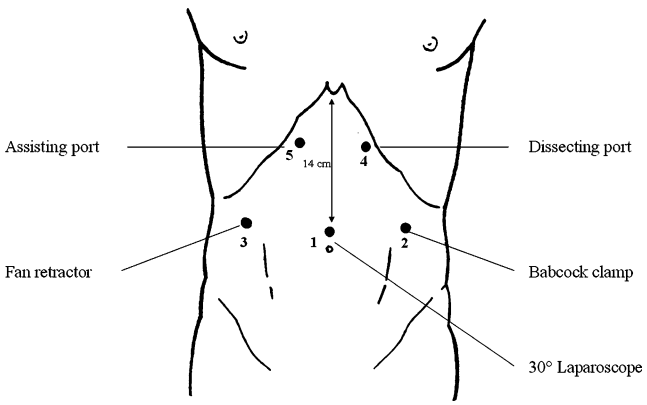

Figure 1 Position of trocars for laparoscopic paraesophageal hernia repair.

Closure of the Esophageal Hiatus

This is one of the critical steps of the operation. As many patients are elderly and the hiatus is quite enlarged, the pillars of the crus can be quite thin or the closure behind the esophagus can be under tension. Rather than starting at the bottom of the hiatus and moving upward, we prefer to place the first stitch just 1 cm posterior to the esophagus, securing it with an extracorporeal jamming knot (a capstan knot in nautical terminology, Fig. 2) to overcome the tension (Fig. 3).[11] This step makes the closure simpler. It is usually done under tension if it is started at the bottom of the left and right pillar of the crus. Subsequent intra-corporeal stitches are placed below the first one. Sometimes 1 or 2 additional stitches are placed anterior to the esophagus to further narrow the hiatus. We do not use pledgets or mesh.

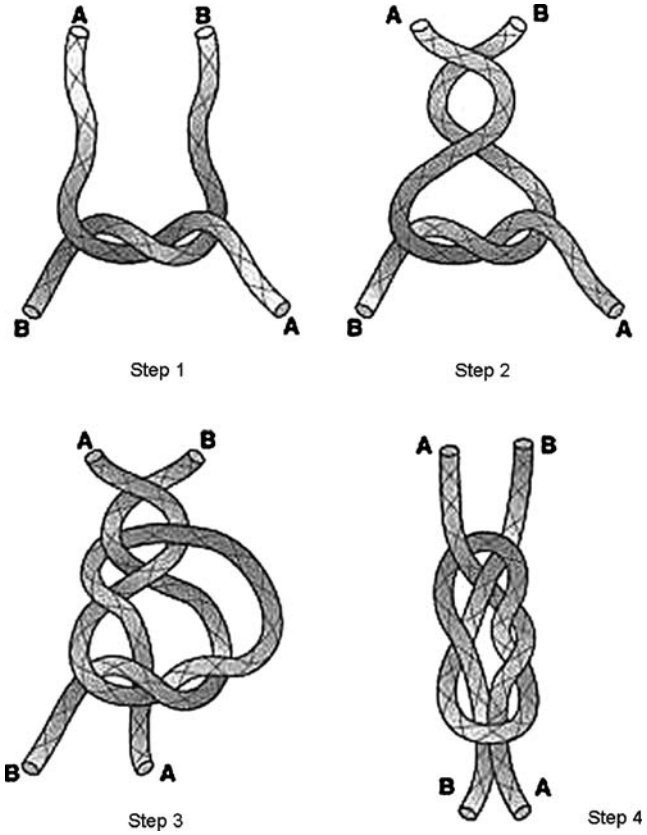

Figure 2 Capstan knot.

Fundoplication

This is the last step of the operation. The rationale for a fundoplication is the following: (1) it corrects reflux in most patients, if it was present preoperatively; (2) it prevents the development of reflux due to the extensive dissection; and (3) it is a very good form of gastropexy, which helps keeping the stomach below the diaphragm.[15] We do prefer a total fundoplication, adding extra stitches to secure the wrap to the pillars and to the crus (Fig. 4).[16]

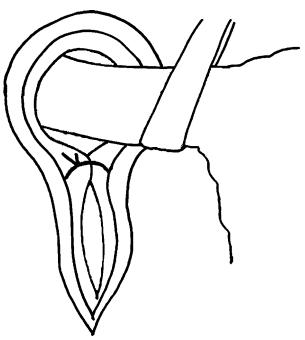

Figure 3 Technique for closure of the esophageal hiatus. The first stitch is placed just posterior to the esophagus.

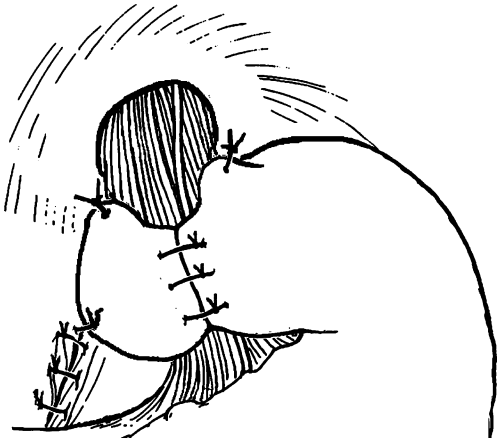

Figure 4 Total fundoplication.

Postoperative Course

Patients are fed the morning of the first postoperative day. They are instructed to avoid meat or bread for about 3 weeks. About 80% of patients are discharged within 48 h. The hospital stay of the remaining 20% is usually prolonged 1 or 2 days because of comorbid conditions often present in this patients. Most patients are able to resume their regular activity within 2 to 3 weeks.

Comments

After the initial enthusiasm with the laparoscopic repair, it became clear that this approach was associated with a higher than expected incidence of hiatal hernia recurrence.[17,18] For instance, Hashemi and colleagues compared the outcomes of laparoscopic and open repair of large type III hiatal hernia, using both symptomatic assessment and a barium study.[17] They found that re-herniation was present in 42% of the patients in the laparoscopic group but in 15% only in the open group. This problem was mostly blamed on the failure of the diaphragmatic closure, and even though some of these recurrent hernias were small and asymptomatic, it raised the question of reinforcing the hiatal closure by using mesh. The basic idea was to accomplish a tension-free repair, trying to reproduce the experience of mesh repair of inguinal and ventral hernias. In a prospective randomized trial comparing simple cruroplasty versus polytetrafluoroethylene patch (PTFE) repair, Frantzides et al. showed a recurrence rate of 22% in the former and 0% in the latter group.[19] These results were confirmed by others.[18,20] However, while it has become widely accepted that the use of mesh decreases recurrences, some concern has arisen about placing non-absorbable

material next to the esophagus, recreating the problems due to the use of the Angelchik prosthesis for treatment of GERD.[21] For instance, in a recent report, Tatum et al. reported two cases in which PTFE mesh had either eroded into the gastroesophageal junction requiring a total gastrectomy, or had caused an esophageal stricture requiring reoperation for removal of the mesh.[22] For this reasons, the use of a biological prosthesis has gained momentum, with the goal of reinforcing the hiatal closure by creating a scaffold containing extracellular collagen which serves as a temporary matrix, while avoiding the complications mentioned above. In a prospective, multicenter and randomized trial, Oelschlager et al. analyzed the outcome in 108 patients with paraesophageal hernia who were divided into two groups based on the type of hiatal closure: 57 patients underwent primary crural repair and 51 patients has the crural repair reinforced by the placement of a U-shaped mesh derived from porcine small intestinal sub-mucosa.[23] At 6-month follow-up, a barium swallow showed a recurrent hernia (>2 cm) in 24% of patients in the primary closure group but in 9% only when mesh was used. There were no cases of narrowing of the esophagus or erosion into the lumen. Very good results have also been obtained with onlay reinforcement of the crural closure by human acellular dermal matrix.[24] However, longer follow-up is needed to determine the efficacy and the safety of these synthetic prostheses.

Conclusions

Laparoscopic repair of paraesophageal hernia is a challenging operation with a long learning curve. Refinements in the technique have determined a better outcome, suggesting that the laparoscopic repair should be considered today the primary form of treatment of patients with symptomatic paraesophageal hernia.

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REVIEW ARTICLE

A Comprehensive Review of Single-Incision Laparoscopic Surgery (SILS) and Natural Orifice Transluminal Endoscopic Surgery (NOTES) Techniques for Cholecystectomy

Ronald Scott Chamberlain · Sujit Vijay Sakpal

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Abstract
Introduction Surgery of the gallbladder has evolved tremendously over the last century. Laparoscopic cholecystectomy is the gold standard for gallbladder removal and the most common laparoscopic procedure worldwide. In recent times, innovative techniques of natural orifice transluminal endoscopic surgery (NOTES) and single-incision laparoscopic surgery (SILS) have been applied in gallbladder removal as a step towards even more less-invasive procedures.
Discussion While NOTES and SILS represent the advent of essentially scarless surgery, limited applications of these technologies in human subjects exists. In this article, we present a comprehensive review of the potential benefits, limitations and risks of these novel techniques.
Conclusion While much remains unknown and unanswered surrounding these procedures, it is clear that extensive research and development with regards to the ethics and the technical aspects of these procedures as well as randomized studies to compare them with traditional laparoscopy are essential.

Keywords Cholecystectomy · Natural orifice transluminal endoscopic surgery · NOTES · Single-incision laparoscopic surgery · SILS

Introduction

Laparoscopy has blossomed over the last 20 years and is one of the most significant surgical advances of the twentieth century. However, the true birth of laparoscopy can be dated to over 100 years ago when George Kelling from Dresden, Germany introduced a cystoscope into the peritoneal cavity of a living dog and insufflated air to enhance the view.[1] Surgery of the gallbladder has similarly evolved over this same century. As cited by Bittner,[2] Langenbuch performed the first successful cholecystectomy on a 43-year-old man with symptomatic cholelithiasis in 1882. More than a century later (in 1985) German surgeon Eric Muhe applied the technique of laparoscopy to remove a gallbladder using a modified laparoscope, called the galloscope.[3] It was soon thereafter (1987) that the advent of the computer chip television camera allowed Phillipe Mouret to perform the first video-laparoscopic cholecystectomy.[4]

Today, laparoscopic cholecystectomy is the gold standard for gallbladder removal and the most common laparoscopic surgical procedure in the world.[5] Numerous reports have provided overwhelming evidence that laparoscopy provides better cosmetic results, less postoperative pain, and shorter recovery time when compared with open cholecystectomy.[2] However, the quest to develop even more minimally invasive surgical techniques in order to enhance the advantages of laparoscopy remains robust. This quest has led surgeons to seek to minimize the number and the size of incisions, or in the case of natural orifice transluminal endoscopic surgery (NOTES), to eliminate skin incision(s) altogether. The hope of these more minimally invasive procedures is that they will also lead

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to minimal or no post-procedural pain while improving cost-effectiveness and patient safety.

While totally incisionless surgery remains an impossible idea at present, NOTES, initially performed in animal models,[6] is now a clinically relevant idea with anecdotal procedures having been performed on human subjects worldwide. Reddy and Rao[7] are credited with performing the first transgastric appendectomy in a human without an external incision, and Marescaux et al.[8] performed the first cholecystectomy via a natural orifice. As a bridge between traditional laparoscopy and NOTES, recent focus has been on the development of single-incision laparoscopic surgery (SILS) to further minimize the invasiveness of laparoscopy by reducing the number of incisions, and hopefully the pain and complication(s) associated with them. SILS was described as early as 1992 by Pelosi and Pelosi[9] who performed a single-puncture laparoscopic appendectomy and in 1997 by Navarra et al.[10] who performed a laparoscopic cholecystectomy via two transumbilical trocars and three transabdominal gallbladder stay sutures. These innovations, either exclusively or in a hybridized fashion, have now been applied to a wide variety of surgical procedures.

A Review of Novel and Innovative Minimally Invasive Cholecystectomies

A large number of individualized techniques for NOTES or SILS for a variety of different operations have been described. The described procedures include appendectomies,[9,11–13] gastrostomies[14,15] and gastrectomies,[16,17] adrenalectomies,[18] colorectal[19–22] and bariatric[16] procedures, and urologic procedures[23,24] including donor nephrectomies.[25–27] To date, however, cholecystectomy appears to be the most common surgical procedure to which significant efforts have been applied toward the development of technique and equipment for both NOTES and SILS. We will spend the remainder of the article reviewing these novel and innovative techniques that have been described for more minimally invasive cholecystectomy, and provide a discussion of the positives and negatives associated with these innovations.

Natural Orifice Transluminal Endoscopic (NOTES) Cholecystectomy Techniques

Bessler et al.[28] have described a transvaginal laparoscopically assisted endoscopic cholecystectomy using a single 5-mm trocar and two 3-mm trocars through the anterior abdominal wall. The sole purpose of the 5-mm trocar was to introduce a clip applier while the 3-mm trocars were used to retract the gallbladder, induce and maintain pneumoperitoneum, and assist in the creation and dilation of an incision in the posterior fornix of the vagina for gallbladder removal. A double-channel endoscope was introduced transvaginally into the peritoneal cavity to permit dissection, and removal of the gallbladder was completed entirely with a hook knife and a grasper that was inserted through the endoscopic channels. Following removal of the gallbladder, the colpotomy was closed with absorbable sutures. The entire procedure took 3.5 h. A similar technique used by Marescaux et al.[8] required only a single 2-mm transumbilical needle port to create pneumoperitoneum and provide laparoscopic guidance for the colpotomy. Endoscopic scissors, grasper, and a unipolar round-tipped electrode were used to dissect and remove the gallbladder. The entire procedure took 3 h to complete.

Zornig et al.[29,30] have described a slightly different technique of transvaginal cholecystectomy in which the umbilical scope is replaced with a dissector, and the 10-mm 30° scope is introduced transvaginally. A total of 20 cholecystectomies were performed in this manner with an average operating time of 62 min. Reduction in operative time as compared with the prior techniques is likely attributable to insertion of instruments across two perpendicular planes which achieves better triangulation, and the fact that the majority of operated patients (14/20) had none-to-minimal signs of gallbladder inflammation. Note that one out of the three patients with chronic cholecystitis required an additional incision for insertion of a drain secondary to operative trauma to the liver tissue. Finally, Forgione et al.[31] have described a third transvaginal technique employing a single incision in the left upper quadrant which is used to create pneumoperitoneum, provide laparoscopic assistance to make the posterior colpotomy, while also permitting retraction of the gallbladder and insertion of a 5-mm laparoscopic clip applier. These authors also performed routine proctoscopy at the end of the procedure to exclude iatrogenic rectal injury. The mean operative time for the three cases reported was more than 136 min.

Single-incision Laparoscopic (SILS) Cholecystectomy Techniques

Navarra et al.[10] performed the first SILS cholecystectomy in 1997 using two 10-mm trocars and three transabdominal stay sutures to aid in gallbladder retraction. Piskun and Rajpal[32] described the use of two 5-mm trocars and two stay sutures in 1999. In both these methods, the two trocars were inserted through the umbilicus, with a bridge of fascia between them, and were used for a camera and a working instrument, respectively. The two umbilical fascial incisions were united by cutting the bridge between them to allow retrieval of the gallbladder following its removal. In place

of sutures, Cuesta et al.[33] have described a technique in which a percutaneous Kirschner wire is introduced subcostally and modified into a hook intra-peritoneally. This wire hook was used to provide exposure of Calot's triangle. The authors used this technique to successfully treat ten female patients with cholelithiasis, with an average operative time of 70 min.

Tacchino et al.[5] have reported a series of 12 single-incision laparoscopic cholecystectomies. In their technique, a single 12-mm umbilical incision was created to induce pneumoperitoneum with a Veress needle and expose the fascia for introduction of a 30° scope through a 5-mm trocar. Roticulator endoshear and endograsper inserted within two separate trocars, introduced to the left and right of the first, were used to perform dissection in a normal retrograde pattern. Two straight-needle sutures passed through the gallbladder fundus, near the infundibulum, and the right subcostal abdominal wall suspended the gallbladder and exposed the Calot's triangle. A thin percutaneous needle was used to empty the gallbladder. Following complete dissection and excision of the gallbladder, the suspension stitches were removed and the gallbladder retrieved through the umbilical incision in a standard fashion. Of the 12 patients that underwent this operation, two complications were observed (16.6%). In one case, the patient sustained trauma to the abdominal wall due to the multiple trocars inserted at the single umbilical incision and developed a subcutaneous hematoma that required evacuation. Another patient experienced persistent postoperative abdominal pain secondary to an intra-abdominal collection that most likely occurred due to bleeding from the liver which spontaneously resolved but extended the patient's hospital stay (length of stay, 7 days). Gumbs et al.[34] essentially imitated the procedures performed by Cuesta et al.[33] and Tacchino et al.,[5] except that they were able to operate with a deflecting laparoscope, an articulating grasper, a straight dissector, and without suspension sutures.

Rao et al.[35] described an innovative piece of instrumentation which they utilized to perform 20 SILS cholecystectomies. The equipment was termed an R-Port® (Advanced Surgical Concepts, Wicklow, Ireland), which consisted of a double-layered plastic cylinder that serves as a single port, and is introduced through a 15–25-mm incision in the umbilicus. The device has three valvular openings on the port which permit insertion of either three 5-mm or one 10-mm and one 5-mm instruments. The instrument shafts used were angulated to avoid clashing and provide triangulation during dissection. Using these tools, the authors successfully performed cholecystectomy in 85% of the patients upon whom it was attempted with an average operative time of 40 min. In seven of the 17 cases completed, a stay suture in the right subcostal area was required to expose the Calot's triangle. Two patients with choledocholithiasis required an additional R-Port® to insert the choledochoscope for CBD exploration. Importantly, the authors noted the complexity of the procedure, despite careful selection of patients which excluded those with severe acute cholecystitis or history of pancreatitis, but nevertheless achieved a successful outcome in the vast majority of patients. A similar technique, using a TriPort® system (Advanced Surgical Concepts, Wicklow, Ireland), has also been reported by Romanelli et al.[36] in the completion of their first case of SILS cholecystectomy. Merchant et al.[16] have reported the completion of 21 SILS cholecystectomies using a similar multi-channel port termed the Gelport® system (Applied Medical, Rancho Santa Margarita, CA, USA). The operative times ranged from 45–90 min; however, the average time per procedure was not reported. Their technique requires a wound retractor (part of the Gelport® system) to be inserted through a 1 cm umbilical incision to stretch the fascial diameter to 1.5 cm. The Gelport® is then latched on to the wound retractor ring allowing up to four instrument trocars including the videoscope to be inserted at any given time with "flexible fulcrums" that ease mutliplanar motions. All patients in the series by Merchant et al.[16] had symptomatic cholelithiasis, and one of the two who had acute cholecystitis required placement of an accessory port in the right upper quadrant to achieve safe dissection.

Zhu et al.[37] have performed a total of 40 different cases of transumbilical endoscopic surgery (TUES) using special instruments including a trichannel umbilical trocar (15 mm in diameter) which allows for insertion of a flexible endoscope or a laparoscope through the 5-mm channel and semirigid working instruments through each of the other two 2.8-mm channels. These authors have performed two cases of liver cyst fenestration and nine appendectomies using these instruments brought through a single abdominal incision. In addition, they have performed six cholecystectomies using a trichannel trocar and another 20 using a double-trocar technique through the umbilicus. In all cholecystectomies, a 2-mm grasper, inserted through an extra incision in the right upper abdomen, was used to retract the gallbladder. They were able to successfully remove the gallbladder using this technique in all but one case which required conversion to standard laparoscopic procedure for uncontrolled hemorrhage.

Palanivelu et al.[38] performed a study to assess the feasibility of a minimally invasive hybrid cholecystectomy technique. The procedure used a 2-mm Veress needle placed transumbilically to create pneumoperitoneum with the subsequent placement of a 15-mm double-channel endoscope through which working instruments were introduced. Another 3-mm trocar was inserted in the left hypochondrium to retract the gallbladder. Ten well-selected cholelithiasis patients (four males, six females;

average age 29.5 years), excluding those they thought may have complicated disease, underwent this hybrid procedure and 50% were completed successfully. Four of the ten cases were converted to conventional laparoscopic cholecystectomy due to uncontrollable hemorrhage from the cystic artery (two) and difficulty in dissection (two). One of the six patients who underwent the hybrid procedure was readmitted on the fourth postoperative day for a biliary leak (90 ml biloma) due to clip slippage from the cystic duct stump. This complication was treated with an endoscopic retrograde cholangiopancreatography (ERCP) and bile duct stenting. Table 1 provides an overview of comparative features of the above-described techniques of NOTES and SILS cholecystectomy, respectively.

Discussion

NOTES and SILS mark the beginning of a new era in the field of surgery. Endoscopic surgery via natural orifices is essentially surgery without a visible scar, and marks a prominent evolutionary leap in medicine. Single-incision laparoscopy purports to offer better cosmesis and avoidance of extra incisions, with an added benefit of the option to convert to multiport laparoscopy if necessary. It has further been suggested that both NOTES and SILS may be associated with reduced post-procedural pain when compared to traditional laparoscopy. While some of the aforementioned reports suggest a promising future for these innovative techniques, the promise currently remains unfulfilled as significant ethical, procedural, and technological questions remain (summarized in Table 2).

Natural orifice endoscopic procedures are performed with flexible endoscopy and at present most surgeons have little, or more commonly no experience with their use in the abdominal cavity (or elsewhere). In transgastric or transcolonic NOTES, the lack of sterilization and secure closure of the gastric or colonic wall remains the greatest challenge since the development of gastrointestinal leaks would represent a catastrophic complication which rarely follows routine laparoscopic cholecystectomies and appendectomies.[28,30,38] In our opinion, until improved technology and training is available and a robust discussion of the ethics of NOTES is held, the purported benefits of better cosmesis in no way outweigh the risks posed by potential intra-abdominal injuries. Though no meaningful data regarding complication of NOTES procedures are available in any form, it would appear that the paucity of infections or hernia following transvaginal pelvic surgery, even when the colpotomy is not routinely closed, makes the transvaginal route a preferred option over transgastric or transcolonic methods.[39] However, it is important to note that no information on the impact of the transvaginal approach on subsequent fertility and the potential for discomfort during sexual intercourse exists.

In our practice, an attending surgeon, a surgical resident and an assistant (usually a medical student) in addition to the nursing staff makes up the laparoscopic cholecystectomy operative team. We performed the last 100 laparoscopic cholecystectomies in an average time of 51 min. Most of the reported NOTES were carried out by a team of surgeons, gynecologists, and gastroenterologists in various combinations. This not only signifies the complexity of this technique, but also suggests that the reported operative times alone do not precisely reflect the cumulative man-hours invested by specialists in the performance of these procedures.

Varadarajulu et al.[40] surveyed 100 patients who were undergoing endoscopic ultrasound (EUS) or an ERCP for evaluation of abdominal pain, pancreatitis, or suspected choledocholithiasis. All patients were given information on the technique, complication rates, and benefits of laparoscopic cholecystectomy. In addition, the concept of NOTES, as an evolving less-minimally invasive technique, for gallbladder removal was described simultaneously. Patients were then queried regarding the cholecystectomy technique (laparoscopic versus NOTES) they preferred, reason(s) for their choice and the amount of risk that they were willing to assume if they selected NOTES. Seventy-eight percent of these patients expressed preference toward NOTES over laparoscopic cholecystectomy if the complication rates of the procedures in question were comparable. The most common reason given for preferring NOTES was to avoid incisional pain and scarring. This raises two important questions: what is the complication rate associated with NOTES and SILS cholecystectomy, and is the post-procedural pain following either NOTES or SILS cholecystectomy any different from that reported after traditional laparoscopy? We know that the incidence rate of major complications (common bile duct and major vessel injury) following three or four-trocar laparoscopic cholecystectomy is well documented at <1% with an overall complication rate of ≤3%.[40,41] Post-laparoscopic cholecystectomy pain and recovery time is also significantly lower when compared to the alternative open procedure.[2] Whether there is less postoperative pain associated with NOTES or SILS is so far a subjective conclusion and systematic objective assessments of post-procedural pain, as well as procedure-related complication rates, are lacking. Interestingly, among the patients surveyed by Varadarajulu et al.,[40] 82% (18/22) of those who preferred laparoscopic cholecystectomy over NOTES, irrespective of incisional pain and scarring, stated they considered the risk of complications and the proven safety and efficacy of the procedure as the most important variable. Even among those patients initially preferring NOTES to avoid pain and scarring, the

Table 1 All Published Reports of NOTES and SILS Cholecystectomies Through the Years 1997–2009

Authors	Approach to peritoneal cavity	Number of skin incision(s)	Number of skin trocar(s)	Number of attempted cases	Diagnosis	Success rate[a] (%)	Complication(s) Reasons for conversion to standard LC	Average operating time (min)
NOTES cholecystectomy								
Bessler et al.[28]	Transabdominal, transvaginal	1	3	1	Cholelithiasis	100	None	210
Marescaux et al.[8]	Transabdominal, transvaginal	1	1	1	Cholelithiasis	100	None	180
Zornig et al.[29,30]	Transabdominal, Transvaginal	1	1	14	Cholelithiasis	100	None	62
				3	Acute cholecystitis	100	None	
				3	Chronic cholecystitis	67	Hepatic injury	
Forgione et al.[31]	Transabdominal, transvaginal	1	1	3	Cholelithiasis	100	None	136
SILS cholecystectomy								
Tacchino et al.[5]	Transabdominal	1	3	10	Cholelithiasis	83[b]	None	55±7
				2	Cholecystitis		Subcutaneous hematomas (1) Hepatic injury (1)	
Cuesta et al.[33]	Transabdominal	1	2	10	Cholelithiasis	100	None	70
Rao et al.[35]	Transabdominal	1	1	18	Cholelithiasis	94	Difficult dissection	40
				2	Choledocholithiasis	0	Choledochoscope for CBD exploration (2)	
Merchant et al.[16]	Transabdominal	1	1	19	Cholelithiasis	100	None	45–90
				2	Acute cholecystitis	50	Difficult dissection	
Zhu et al.[37]	Transabdominal	2[c]	2	22	Cholelithiasis	100	None	30–150
				4	Gallbladder polyps	100	None	
Romanelli et al.[36]	Transabdominal	1	1	1	Cholelithiasis (history of pancreatitis)	100	None	68
Gumbs et al.[34]	Transabdominal	1	3	2	NR	100	None	<60
Palanivelu et al.[38]	Transabdominal	2[c]	2	10	Cholelithiasis	60	Hemorrhage from cystic artery (2) Difficult dissection (2) Bile leak (1)	148
Navarra et al.[10]	Transabdominal	1	2	30	NR	100	None	123
Piskun et al.[32]	Transabdominal	1	2	7	Cholelithiasis	100	None	NR
				3	Acute cholecystitis	100	None	

NR not reported, *CBD* common bile duct, *LC* laparoscopic cholecystectomy

[a] Success rate: percentage of patients that successfully underwent NOTES/SILS cholecystectomy without procedure-related complications

[b] The diagnosis of two patients that sustained procedure-related complications is not clarified

[c] Transumbilical endoscopic cholecystectomy aided with 2.8/3-mm graspers through separate abdominal incision

interest decreased to less than 15% when the complication rates of NOTES were stated as higher than that of traditional laparoscopic cholecystectomy.

One of the major challenges posed by both NOTES and SILS is the difficulty to attain similar critical views of tissue dissection with more limited instrumentation and field of view. SILS limits the number of ports that can be used through a single incision, and a single port with multiple instruments restricts their degrees of movement. Proximity of instruments when used through a single port often results in inadequate retracting abilities and loss of triangulation, which may lead to suboptimal exposure of Calot's triangle. The avoidance of clashing the operative instruments with each other and the scope, while maintaining pneumoperitoneum, may actually increase the complexity and technical challenges of the operation rather than decrease them. Most laparoscopic surgeons are familiar with rigid instruments and the suggestion made by Zhu et al.[37] to use semirigid instruments that may "bend", while potentially ingenious, requires education and training and may make tissue dissection and grasping initially more difficult. Dislodgement of single large tri-ports or multiple small ports through a single incision is another potential problem that may cause loss or leakage of pneumoperitoneum,

Table 2 Technical Challenges and Proposed or Implemented Solutions for Both NOTES and SILS Cholecystectomies, and the Problems that Remain

Challenge	Solution	Problem(s)
NOTES Cholecystectomy		
1. Visualization of the peritoneal cavity without skin incisions	Flexible endoscopy	Inexperience with its use in the abdominal cavity
2. Potential for gastrointestinal leaks due to unsecured closure	Transvaginal access	Concerns regarding its effects on fertility and sexual discomfort
SILS cholecystectomy		
1. Restricted number of working instruments	Single, large device with multiple ports or multiple ports through a single incision	Restricted movements and clashing of instruments
		Increased potential for development of fascial defects
		Difficulty maintaining pneumoperitoneum
		No escape for smoke created by tissue cauterization
2. Introduction of single, large or multiple ports	Development of circumferential skin flaps	Potential for subcutaneous hematoma or seroma formation
3. Loss of triangulation with straight instruments	Angulated instruments	Requires training and adjustment
	Semirigid instruments	"Bending" during retraction/dissection
4. Suboptimal exposure of the Calot's triangle	Retraction with hooks, stay sutures and/or percutaneous gallbladder drainage	Potential for bactobilia, and biliary leaks with bile peritonitis

thereby risking mishap. Also, smoke created by use of a monopolar electrocautery which would have no route for evacuation with a single port in place, is a further challenge to the operating surgeon's field of view.[36] Improved instrumentation and the use of crossed-over articulating graspers and dissectors may achieve triangulation, but their use requires adjustments which may translate into longer operative time to perform safe and precise dissection. The potential added costs for advanced instrumentation are unknown, but without significant demonstrable benefit to the procedure warrant investigation.

Purposeful percutaneous puncture of the gallbladder for drainage or introduction of suspension hooks which has been suggested by some authors for better visualization of the Calot's triangle may inadvertently increase the chances of bactobilia. Such maneuvers may also cause perforation of the gallbladder leading to increased risk of bile peritonitis, particularly in the setting of acute cholecystitis. The development of skin flaps circumferentially to accommodate a single large or multiple small ports is necessary with either a single large incision or multiple fascial incisions. Exertion of pressure by a single large port or multiple ports at a single site may potentially weaken the fascia thereby increasing the risk of hernias, especially on intentional creation of a "Swiss cheese" defect. The creation of skin flaps also raises the possibility of forming subcutaneous seromas or hematomas that would contradict the claimed intention of SILS to offer less bodily trauma as compared to conventional techniques.[16] Moreover, if SILS is associated with a higher rate of seroma or hematoma formation, these complications could jeopardize the cosmetic benefits that the procedure attempts to exploit.

Navarra et al.[10,42] have reported the largest series of 30 consecutive single-incision laparoscopic cholecystectomies. In their own unpublished prospective randomization of SILS versus a conventional four-trocar approach, no significant cosmetic advantages, cost-effectiveness, or difference in postoperative pain between the two techniques were observed. In addition, they noted that the average procedure time was considerably longer, and suggest that the single large umbilical incision may have resulted in a higher incidence of umbilical hernias among their patients. SILS operative times in some series were reported to be at par with conventional laparoscopy (see Table 1), but a majority of the procedures were lengthy which may only be justified in patients who have special cosmetic interest.

Conclusion

NOTES and SILS are promising techniques in the field of minimally invasive surgery. Clinical data in the area of NOTES and SILS are too preliminary to draw any meaningful conclusions. Low success rates and avoidable complications as reported in some published studies raise doubts as to the future of both techniques using current technology. However, we are only at the beginning of a new minimally invasive revolution and modifications in the

technological aspects of these procedures will likely yield better outcomes. Randomized studies comparing natural orifice endoscopic surgery and single-incision laparoscopy with traditional laparoscopy are necessary to evaluate the safety, efficacy, complication rates, and potential benefits, if any, that these innovative techniques may provide.

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GI IMAGE

Multiseptate Gallbladder

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Abstract
Introduction Multiseptate gallbladder is a rare congenital condition that may be asymptomatic or may lead to symptoms consistent with biliary colic, even in the absence of cholelithiasis.
Discussion We present the case of a 19-year-old female who underwent an extensive gastrointestinal workup before she was referred for cholecystectomy, which led to resolution of her symptoms. The distinct imaging features of this entity are presented.

Keywords Gallbladder · Multiseptate · Biliary colic

Case Report

A 19-year-old previously healthy woman initially presented to an urgent care center with a several week history of watery diarrhea not associated with fever, weight loss, or recent travel. She complained of loose stools three to four times per day and periumbilical pain. Her initial workup included a complete blood count, urinalysis, chemistry, amylase, lipase, human chorionic gonadotropin, *Helicobacter pylori* profile, fecal leukocytes, and test for fecal blood, all of which were normal or negative. She was treated with diphenoxylate/atropine and dicyclomine without relief. She was referred to a gastroenterologist with persistent complaints of abdominal pain and several loose bowel movements per day. By that time, her diarrhea had slightly improved and the abdominal pain had become intermittent and localized to the right upper quadrant, associated with occasional nausea. The gastroenterologist's clinical evaluation included stool studies for ova and parasites, bacterial culture, and clostridium difficile toxin assays, which were all negative.

Nine months after the initial onset of symptoms, she returned to her gastroenterologist due to recurrence of disabling symptoms. Since her last visit, she had received care at several institutions without substantial relief of symptoms. A right upper quadrant abdominal ultrasound was obtained, which revealed multiple thin septations within the gallbladder with no associated cholelithiasis, bile duct dilatation, gallbladder wall thickening, or pericholecystic fluid. Esophagogastroduodenoscopy, as well as an upper gastrointestinal (GI) contrast study with small bowel follow-through, were normal. Computed tomography of the abdomen revealed multiple septations within the gallbladder without stones or sludge (Fig. 1). A cholecystokinin hepatobiliary iminodiacetic acid (CCK-HIDA) scan was normal with a gallbladder ejection fraction of 99%. Thirteen months after the onset of symptoms, the patient was referred to the General Surgery clinic for laparoscopic cholecystectomy. The patient underwent the procedure without complica-

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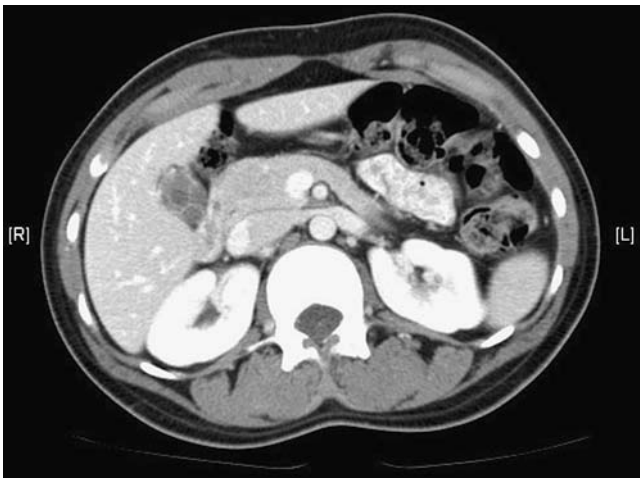

Figure 1 Computed tomography of the abdomen revealing a multiseptate gallbladder.

tions. Her pathology report was significant for multiseptate gallbladder (MSG) without any evidence of cholelithiasis (Fig. 2). Since surgery, her presenting gastrointestinal complaints have resolved.

Discussion

Multiseptate gallbladder is a rare congenital anomaly. In 1952, Knetsch published radiologic findings of three patients with MSG.[1] Simon and Tandon in 1963 published the first thorough case report with clinical, radiological, and surgical findings with follow-up.[2]

Although there is no proven theory as to how MSG develops, several theories have been proposed. Incomplete cavitation of the solid embryonic gallbladder bud may result in MSG or stricture of the gallbladder.[2,3] The wrinkling theory and the "Phrygian cap" theory attempt to explain the smooth muscle presence in the septa.[4] The wrinkling theory suggests that during the solid stage of gallbladder development, the bud takes an irregular wrinkled appearance. The wrinkled gallbladder creates invaginations that fuse with the solid intraepithelial structures. These fusions may prevent coalescence of intraepithelial tissue to properly form the gallbladder cavity. The "Phrygian cap" theory suggests that the solid gallbladder may develop faster than the surrounding structures such as the gallbladder bed and the peritoneum. Gallbladder wrinkling and kinking are created due to lack of space, which may cause fusion to the intraepithelial tissue preventing coalescence.

Two theories have been postulated to describe how MSG causes biliary colic. Bhagavan et al. theorized that the transient inability or resistance of the thick viscid bile to pass through small openings in the septa results in stasis and incomplete emptying, thereby causing biliary colic.[4] The normal gallbladder ejection fraction by CCK-HIDA scan in our patient provides evidence to dispute this theory. Toombs et al. postulated that multiseptate gallbladders have uncoordinated contractions which raise intraluminal pressure and produce biliary colic.[5]

There is a female preponderance of this anomaly, and most patients present with abdominal symptoms, often of long duration.[6–8] The absence of cholelithiasis or biliary sludge in many cases may be indicative of delay in diagnosis or delay in referral for surgery, as most patients have no other biliary pathology. However, MSG has been reported in association with hypoplasia of gallbladder, ectopic gallbladder, cholelithiasis, choledochal cyst, Phrygian cap, cholecystitis, and pancreaticobiliary ductal union.[4,6,9–13] Unsuspected carcinoma of the gallbladder was reported in a 70-year-old patient.[14]

The ultrasonographic appearance of MSG is described as honeycomb in nature, with septa crossing the lumen of the gallbladder, which has fine echogenic bands without acoustic shadowing.[7,10,15] Ultrasound evaluation of the gallbladder is usually sufficient to diagnose MSG, although other modalities, including computed tomography, have been described to establish the diagnosis.[16,17]

In conclusion, MSG is a rare anomaly that general surgeons should be aware of, as cholecystectomy in symptomatic patients is curative. Cholecystectomy should also be considered in elderly, asymptomatic patients in whom MSG is incidentally discovered, due to the possibility of undetected carcinoma of the gallbladder. Extensive GI workup in patients with MSG and symptoms of biliary colic is unnecessary and should be reserved for those patients with atypical symptoms or recurrent symptoms following cholecystectomy.

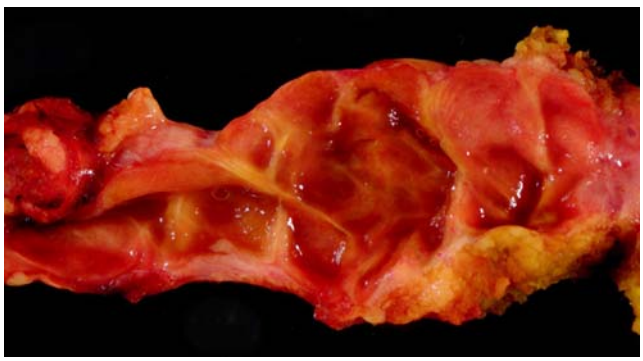

Figure 2 Gross pathology specimen showing the multiple septations within the gallbladder.

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LETTER TO THE EDITOR

Biliary Colic Preceding Acute Gallstone Pancreatitis

Alejandro Oría · Gustavo Kohan

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Dear Sir,

We read with much interest the article by Besselink et al.[1] on the "warning" episodes of biliary colic preceding "complicated" gallstone disease. Up to 58% of patients with acute gallstone pancreatitis had experienced episodes of biliary colic prior to onset of the attack. Patients' delay or reluctance of the general practitioner to refer the patient for imaging studies or specialist consultation precluded timely treatment of gallstone disease.

Biliary colic is a poor descriptor for biliary pain due to "uncomplicated" gallstone disease. Although biliary colic is most commonly due to cystic duct obstruction, identical pain may be secondary to main bile duct obstruction. In the absence of jaundice, differentiation between cystic duct obstruction due to gallbladder gallstones and main bile duct obstruction due to choledocolithiasis cannot be made without radiologic and laboratory studies. A clear distinction between these two conditions is important for the prevention of acute gallstone pancreatitis.

Gallstone migration through the papilla of Vater is the triggering event for acute gallstone pancreatitis. We investigated gallstone migration in 39 patients admitted to the hospital with upper abdominal pain due to gallstone disease and a distal bile duct measuring 7 mm or more on ultrasound examination.[2] None of the patients had acute pancreatitis or acute cholangitis. Using stool screening and ultrasound monitoring for diameter changes of the biliary and pancreatic duct, migration of small gallstones was detected in ten patients; of these, six exhibited total serum bilirubin values below 2 mg/dL throughout migration. All of the six patients had experienced recent episodes of "biliary colic" and had been treated symptomatically elsewhere. This high prevalence of anicteric episodes of gallstone migration was confirmed in another study using a greater number of patients.[3] In contrast to a widely held view, gallstone migration does not occur after a brief impaction of the stone at the distal bile duct. Even the smallest stone may obstruct the upper segment of the sphincter for several days or even weeks before reaching the papilla.[2] In order to prevent acute gallstone pancreatitis, early identification of patients undergoing anicteric episodes of gallstone migration is essential. At present, however, many of these patients are labeled "biliary colic" and managed on an outpatient basis.

We agree with Besselink et al.[1] on the importance of increasing awareness of the general public and the general practitioner for the warning aspect of upper abdominal pain. It is our opinion, however, that another important issue is the use of the term biliary colic to describe any episode of upper abdominal pain due to presumed uncomplicated gallstone disease. Biliary colic is a confounding term that should be substituted for a precise descriptor of the site of biliary obstruction. In the present evidence-based medicine era, inaccurate terms should be removed from medical language.[4]

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LETTER TO THE EDITOR

Biliary Colic is a Valuable Clinical Descriptor for Biliary Pain Due to "Uncomplicated" Gallstone Disease

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We thank Drs Oria and Kohan for their interesting comments on our article: "Is complicated gallstone disease preceded by biliary colic?"[1] We found that 57% of 175 patients with complicated gallstone disease (including pancreatitis) had experienced biliary colics before the complication. In these cases, the complication could probably have been prevented by early cholecystectomy. However, significant patient's and general practitioner's delays had occurred after the "warning" colic (especially if the pain was located in the epigastric region), thus precluding this option in practice. We agree with Drs Oria and Kohan that it is not possible to differentiate between biliary colic due to cystic duct obstruction by gallbladder stones and biliary colic caused by stones migrated to the bile duct. In fact, the term "biliary colic" does not pretend to make such differentiation. Although considered "a confounding term" by the authors, "biliary colic" is used frequently to describe biliary pain due to "uncomplicated gallstone disease," not only by this journal[2] but also by other key journals[3, 4] and the Cochrane database.[5]

Nevertheless, the "a priori" chance that gallbladder stones are the cause of biliary colic is much higher than bile duct stones, provided that significant abnormalities in liver biochemistry and clear bile duct dilatation by ultrasound are absent. Indeed, most episodes of biliary colic resolve spontaneously, without subsequent complications. Using various techniques including routine intraoperative cholangiography during cholecystectomy, frequency of unexpected bile duct stones in patients who have experienced biliary colics varies between 5% and 12%.[6,7] These data indicate that bile duct stones are relatively rare in patients with biliary colics and/or that most bile duct stones migrate spontaneously to the duodenum. Oria and Kohan report interesting data on migration of bile duct stones in 39 patients with prior biliary pain, using the time-honored technique of stool screening.[8–10] In fact, their patients all had dilated bile ducts by ultrasound and may thus not be entirely representative of the entire population of patients with biliary colics. In addition, there is no solid evidence that early detection or bile duct stones by endoscopic ultrasound or magnetic resonance cholangiopancreatography would lead to a more beneficial outcome in the entire group of patients who have experienced biliary colics. If one assumes an a priori chance of 5% for bile duct stones under these circumstances and endoscopic ultrasound to have a sensitivity and specificity of 95%, positive predictive value of finding bile duct stones by endoscopic ultrasound would be only 50%. Subsequent endoscopic retrograde cholangiopancreatography would thus expose 50% of the patients to unnecessary risks of this procedure. In addition, the natural history of bile duct stones under these circumstances is uncertain.[6, 7]

The authors further state that "in order to prevent acute gallstone pancreatitis, early identification of patients undergoing anicteric episodes of gallstone migration is essential." However, the evidence for this statement is lacking. No study has shown a reduction in incidence of biliary pancreatitis by differentiating between cystic and main duct obstruction. In our opinion, additional investigations and treatment of bile duct stones in patients with biliary colics should be performed depending on the chance that bile duct stones are indeed present (for useful risk factors see Abboud et al.[11]) In contrast, as we conclude in our paper, a policy of

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timely referral and cholecystectomy of patients with biliary colic could prevent complicated gallstone disease, including biliary pancreatitis in up to 50% of cases.

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