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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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REVIEW

Perforated peptic ulcer - an update

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Abstract

Peptic ulcer disease (PUD) affects 4 million people worldwide annually. The incidence of PUD has been estimated at around 1.5% to 3%. Perforated peptic ulcer (PPU) is a serious complication of PUD and patients with PPU often present with acute abdomen that carries high risk for morbidity and mortality. The lifetime prevalence of perforation in patients with PUD is about 5%. PPU carries a mortality ranging from 1.3% to 20%. Thirty-day mortality rate reaching 20% and 90-d mortality rate of up to 30% have been reported. In this review we have summarized the current evidence on PPU to update readers. This literature review includes the most updated information such as common causes, clinical features, diagnostic methods, non-operative and operative management, post-operative complications and different scoring systems of PPU. With the advancement of medical technology, PUD can now be treated with medications instead of elective surgery. The classic triad of sudden onset of abdominal pain, tachycardia and abdominal rigidity is the hallmark of PPU. Erect chest radiograph may miss 15% of cases with air under the diaphragm in patients with bowel perforation. Early diagnosis, prompt resuscitation and urgent surgical intervention are essential to improve outcomes. Exploratory laparotomy and omental patch repair remains the gold standard. Laparoscopic surgery should be considered when expertise is available. Gastrectomy is recommended in patients with large or malignant ulcer.

Key words: Peptic ulcer; Perforation; Laparoscopy; Surgery

Core tip: The classic triad of sudden onset of abdominal pain, tachycardia and abdominal rigidity is the hallmark of perforated peptic ulcer. Early diagnosis, prompt resuscitation and urgent surgical intervention are essential to improve outcomes. Exploratory laparotomy and omental patch repair remains the gold standard and laparoscopic surgery should be considered when expertise is available. Gastrectomy is recommended in patients with large or malignant ulcer to enhance outcomes; however the outcomes of patients treated with gastric resections remain inferior.

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INTRODUCTION

Peptic ulcer disease (PUD) results from an imbalance between stomach acid-pepsin and mucosal defense barriers. It affects 4 million people worldwide annually[1]. The incidence of PUD has been estimated at around 1.5% to 3%[2]. A systematic review of seven studies from developed countries estimated that the annual incidence rates of PUD were 0.10%-0.19% for physician-diagnosed PUD and 0.03%-0.17% when based on hospitalization data[3]. Although 10%-20% of patients with PUD will experience complications, only 2%-14% of the ulcers will perforate causing an acute illness[4,5]. Perforation is a serious complication of PUD and patients with perforated peptic ulcer (PPU) often present with acute abdomen that carries high risk for morbidity and mortality[6]. The lifetime prevalence of perforation in patients with PUD is about 5%[7]. PPU carries a mortality ranging from 1.3% to 20%[8-10]. Thirty-day mortality rate reaching 20% and 90-d mortality rate of up to 30% have been reported[11,12]. In this review we have summarized the current evidence on PPU and we hope our review will assist surgeons updated with evidence based practice.

AETIOLOGY

Although previous studies have indicated that seasonal variation did influence the incidence of PPU, other studies have failed to prove such a pattern[13-16]. In developing world, patients tend to be young male smokers while in developed countries; patients tend to be elderly with multiple co-morbidities and associated use of non-steroidal anti-inflammatory drugs (NSAIDs) or steroid[17,18]. NSAIDs, *Helicobacter pylori* (*H. pylori*), physiological stress, smoking, corticosteroids and previous history of PUD are risks factors for PPU[1,19-27]. In the presence of risk factors, recurrence of ulcer is common despite initial successful treatment. A systematic review of 93 studies has shown that the average long-term recurrence of perforation was 12.2% (95%CI: 2.5-21.9)[5].

NSAIDs

NSAIDs are widely used for its analgesic, anti-inflammatory and anti-pyretic effects. NSAID use is known to increase the risk of PPU[28,29]. About a quarter of chronic NSAID users will develop PUD and 2%-4% will bleed or perforate[30-33]. Drug interaction with steroids and selective serotonin reuptake inhibitors also increases the risks of PUD. Selective cyclo-oxygenase-2 inhibitors are less associated with PUD. A study in western Denmark showed that the standardized hospitalization rates for PPU reduced from 17 per 100000 population in 1996 to 12 per 100000 population in 2004 (HR 0.71; 95%CI: 0.57-0.88) after the introduction of selective cyclo-oxygenase-2 inhibitors into clinical practice[34].

H. pylori

H. pylori remain one of the commonest infections worldwide. The prevalence of *H. pylori* has decreased in developed countries due to improved hygiene and reduced transmission in early childhood. The mean prevalence of *H. pylori* in patients with PPU varies between studies due to different diagnostic methods and geographical variations. Recent studies using histopathological methods of *H. pylori* detection have shown that *H. pylori* prevalence in patients with perforated duodenal ulcers ranges from 50%-80%[22,35]. A randomized controlled trial in 2008 involving 65 patients who underwent simple closure of a perforated duodenal ulcer showed one year ulcer recurrence rate of 6.1% in *H. pylori* treated patients as opposed to 29.6% in the control group[36]. Recurrent PUD mainly occurs in patients with *H. pylori* infection suggesting that *H. pylori* play an important role in the development of PUD and its complications[22,37]. The risk of recurrent *H. pylori* infection is significantly reduced with proton pump inhibitor therapy, but proton pump inhibitors have only a modest efficacy for reduction in ulcers with NSAID users.

Smoking

Tobacco is thought to inhibit pancreatic bicarbonate secretion, leading to increased acidity in duodenum[38,39]. It also inhibits the healing of duodenal ulcers. A meta-analysis has indicated that 23% of PUD could be associated with smoking[40]. However, in some studies, there was no difference in tobacco use between patients with non-*H. pylori*, non-NSAID duodenal ulcers and those with *H. pylori* related ulcers, indicating a limited role of smoking[41]. This is in agreement with previous studies, which indicated that smoking did not increase the risk of ulcer recurrence once the *H. pylori* had been eradicated[42,43].

Others

A study involving 72 patients investigated the genetic differences between *H. pylori*-positive and negative duodenal ulcer patients. *DQA1*0102* allele were significantly more common in *H. pylori* negative patients[44]. This study indicated that genotypes might influence the ability of the host to resist *H. pylori* infection. A study involving 228 patients indicated that steroid use prior to hospital admission was associated with two fold increase in 30 d mortality amongst patients admitted for PPU[45]. Other risk factors may include excessive alcohol consumption and excessive acid production such as gastrinomas and Zollinger-Ellison syndrome (ZES)[18,46,47]. Alcohol consumption is known to damage gastric mucosa and stimulate *gastrin* secretion. Despite these acute effects, there is no evidence that alcohol causes PUD. ZES

is caused by a gastrin secreting tumor of the pancreas that stimulates the parietal cells in stomach to increase the acidity, resulting in gastrointestinal mucosal ulceration. Over 90% of patients with ZES develop peptic ulcers and typically these ulcers are refractory to proton pump inhibitor therapy. ZES should be suspected in patients with multiple or refractory peptic ulcers, jejunal ulcers, family history of PUD and associated diarrhea. All patients with ZES should be screened for Multiple Endocrine Neoplasia 1 (MEN1) syndrome.

CLINICAL FEATURES

In 1843 Edward Crisp stated that "the symptoms are so typical, I hardly believe that it is possible that anyone can fail in making a diagnosis"[48].

Symptoms of PUD include abdominal pain, upper abdominal discomfort, bloatedness and feeling of fullness. When PUD worsen and eventually perforate, gastric juice and gas enters the peritoneal cavity leading to chemical peritonitis. Sudden onset of abdominal pain or acute deterioration of the ongoing abdominal pain is typical of PPU. Typically the pain never completely subsides despite usual premedical remedies and forces the patient to seek medical attention. The chemical peritonitis due to efflux of gastroduodenal contents and severe pain lead to tachycardia. The classic triad of sudden onset of abdominal pain, tachycardia and abdominal rigidity is the hallmark of PPU.

The clinical manifestation can be divided into three phases[49]. In the initial phase within 2 h of onset, epigastric pain, tachycardia and cool extremities are characteristic. In the second phase (within 2 to 12 h), pain becomes generalized and is worse on movement. Typical signs such as abdominal rigidity and right lower quadrant tenderness (as a result of fluid tracking along the right paracolic gutter) may be seen. In the third phase (more than 12 h), abdominal distension, pyrexia and hypotension with acute circulatory collapse may be evident.

A study involving 84 patients with PPU reported that the commonest presenting symptoms were sudden onset of severe epigastric pain (97.6%), abdominal distention (76.2%) and vomiting (36.9%)[50]. Abdominal tenderness and classical signs of peritonitis could be elicited in 88.1% and 66.7% of the patients with PPU in this study. Other symptoms also included nausea (35.7%), severe dyspepsia (33.3%), constipation (29.8%) and fever (21.4%)[50]. In our experience of managing 332 patients with PPU, the most common presenting symptom was acute onset of abdominal pain (61.7%)[51]. A recent study in Taiwan has shown that patients with PPU were more likely to present to emergency room on weekends and this needs to be validated[52].

Tachycardia and abdominal tenderness with rigidity are common clinical signs. Severe pain, systemic inflammatory response from chemical peritonitis and fluid deficit either due to poor intake or vomiting or pyrexia leads to compensatory tachycardia. In patients who delay seeking medical attention, hypotension ensues due to total body water deficit. If uninterrupted; this progresses to mental obtundation and acute kidney injury. This leads to a state where patient becomes physiologically unfit for operative intervention which is absolutely necessary. Hence it is important to establish prompt confirmatory diagnosis.

DIAGNOSIS

An urgent erect chest X-ray and serum amylase/lipase is basic essential test in a patient with acute upper abdominal pain. In modern era it is not prudent to perform an exploratory laparotomy and establish a diagnosis of acute pancreatitis. Seventy-five percent of PPU have free air under diaphragm on erect chest X-ray[53]. In our experience of managing 332 patients, erect chest X-ray revealed free air in 59.8% of patients[51]. This variation could reflect the earlier presentation and easy access to healthcare locally. Sixty-one point seven percent of our patients presented within 24 h of onset of abdominal pain. In a patient with upper abdominal symptoms, free air on an erect chest X-ray establishes a diagnosis of PPU. In some patients, an abdominal X-ray may have been performed by emergency physician or primary medical team. It can show signs such as appearance of gas on both sides of the bowel wall (Rigler's sign), a large volume of free gas resulting in a large round black area (Football sign) and gas outlining soft tissue structures such as liver edge or falciform ligament. It is authors' practice not to perform an abdominal X-ray in patients with suspected PPU when chest X-ray does not show free air under the diaphragm. CT scan is recommended as it has a diagnostic accuracy as high as 98%[54]. Besides, CT scan can exclude acute pancreatitis that would not need surgical intervention. CT scan is performed in supine position and free air is usually seen anteriorly just below the anterior abdominal wall. The falciform ligament can sometimes be visible when air is present on both sides. In resource poor healthcare facilities, oral gastrografin can be used to diagnose PPU. Water-soluble contrast leaking into the peritoneal cavity can confirm the diagnosis of PPU. Absence of a leak does not exclude PPU as the perforation may have sealed off spontaneously[55]. Barium study is contraindicated in gastrointestinal perforation and should be avoided as a tool to diagnose PPU. We consider lateral decubitis abdominal radiographs as obsolete and do not recommend. The traditional practice of instilling air *via* the nasogastric tube and repeating the erect chest X-ray after few minutes is not recommended except in resource poor facilities. It takes time and a repeat negative chest X-ray does not rule out the diagnosis of PPU and still a CT scan would be warranted. Rarely a CT scan is performed even when an erect chest X-ray reveals free air under diaphragm. The utility of this CT scan is justified when clinical presentation is not specific to upper gastrointestinal pathology or a malignancy is suspected and patients' hemodynamics is not deranged. In patients with acute

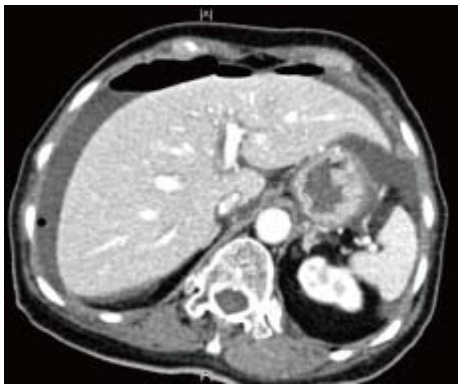

Figure 1 Computerized tomography scan shows free air under the diaphragm with peri-hepatic free fluid.

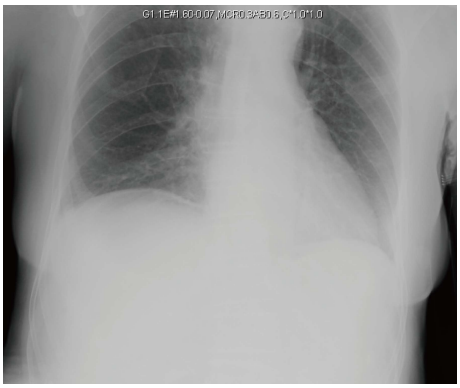

Figure 2 Erect chest X-ray image of the same patient with equivocal free air under the right hemidiaphragm.

kidney injury, a non-contrast CT scan is adequate to see free air. Oral contrast with CT scan is a useful tool and if free leak is seen, diagnosis is certain (Figures 1 and 2).

Laboratory tests are performed in PPU not to establish diagnosis but to rule out differential diagnosis and also to understand the insult to various organ systems. They are non-specific[56]. Serum amylase should be done at index presentation to emergency unit or after a normal chest X-ray. Raised serum amylase may be associated with PPU and it's usually raised less than four times its normal level[57]. Tests such as white cell count and C-reactive protein may be done as part of the investigation in PPU. Leukocytosis and raised C-reactive protein may be raised as a result of inflammation or infection[57]. Elevated creatinine, urea and metabolic acidosis reflects systemic inflammatory response syndrome (SIRS) and prerenal injury[58]. Serum gastrin levels are indicated in patients with history of recurrent ulcers or recalcitrant PUD and can help establish diagnosis of Zollinger Ellison syndrome. In patients with suspected parathyroid disorders, serum calcium levels are indicated.

MANAGEMENT

PPU is a surgical emergency associated with high mortality if left untreated. In general, all patients with PPU require prompt resuscitation, intravenous antibiotics, analgesia, proton pump inhibitory medications, naso-gastric tube, urinary catheter and surgical source control.

Drug treatment in PPU

Omeprazole and triple therapy for *H. pylori* eradication are useful adjuncts in treatment of PPU. Evidence has shown that omeprazole and triple therapy treatment reduces the recurrence rate significantly. Ulcer healing shown at 8-wk follow up with endoscopy was significantly higher in triple therapy eradication group[36]. Eighty-five point three percent of ulcers were healed in the triple therapy group as opposed to 48.4% in the omeprazole alone group. Several other studies from different countries have also proven triple therapy eradication after simple closure of PPU reduced the incidence of recurrent ulcer[37,59,60]. It is our practice to prescribe intravenous proton pump inhibitor for 72-96 h and start oral triple therapy immediately after. We perform urea breath test to establish *H. pylori* eradication after completion of medical treatment.

Non-operative management

Studies have shown that about 40%-80% of PPU will seal spontaneously with conservative management and overall morbidity and mortality are comparable[2,61,62]. Conservative management "Taylor method" consists of nasogastric suction, intravenous drip, antibiotics and repeated clinical assessment. A gastrograffin dye study is essential to confirm absence of leakage in patients selected for non-operative management. If patients are clinically stable and improving, especially with a sealed perforation, surgery may not be warranted. However, if they deteriorate, regardless of the presence and size of the leak, urgent operation is indicated. A Randomized controlled trial involving 83 patients compared the outcome of non-operative treatment with that of operative intervention in patients with PPU[61]. Cefuroxime, ampicillin and metronidazole were administered to all patients. Seventy-two point five percent (29/40) of patients in conservative group showed clinical improvement and were successfully managed without surgery. Covering with an appropriate antibiotic in patients with peritonitis is associated with an increased chance of resolution of the infection after primary surgery[63]. Another study looking at 82 patients who were treated conservatively also showed that 54% of the patients (44/82) showed clinical improvement and did not require a surgical intervention[64]. Study also suggests that patients do well without surgery if spontaneous sealing occurs[55]. A study has shown that about 40% of PPU had no evidence of leak on upper GI contrast studies, indicating that the perforation had sealed off spontaneously[65]. The mortality rate for non-operative management in patients with a sealed perforation was 3% as opposed to 6.2% where emergency surgery was performed for PPU[65]. This suggests that PPU with a sealed perforation can be managed conservatively. The advantages of conservative management include avoidance

of surgery, risks of general anaesthesia and post-operative complications. On the other hand, disadvantages include misdiagnosis and higher mortality rate if conservative management fails[61,66]. In clinical practice, non-operative management strategy is resource intensive and it requires a commitment of active regular clinical examination along with round the clock availability of a surgeon and if there is clinical deterioration, emergency surgery is warranted. The essential components of non-operative management of PPU can be grouped as "R"s: (1) Radiologically undetected leak; (2) Repeated clinical examination; (3) Repeated blood investigations; (4) Respiratory and renal support; (5) Resources for monitoring; and (6) Readiness to operate.

Operative management

Management of PPU is primarily surgical and different suture techniques for closure of the perforation are described. Johan Mikuliczradecki stated that "every doctor who is faced with a perforated ulcer of stomach or duodenum must consider opening the abdomen, sewing up the hole and averting a possible inflammation by a careful cleansing of the abdominal cavity"[4]. In 1992, Feliciano[67] also described 5 points of decision that surgeon needs to take into account. Those decisions include: (1) Is surgery indicated? (2) Is an omental patch sufficient or a definitive ulcer operation indicated? (3) Is the patient stable enough to undergo a definitive ulcer operation? (4) Which definitive ulcer operation should be done? (5) Should the availability of newer medical options influence the choice of operation? With the development of laparoscopic operation in the past few decades, a sixth decision point is proposed; and (6) Should the procedure be performed laparoscopically?[67,68]. Roscoe Graham described PPU to be not a local disease but a local manifestation of a constitutional disturbance[69]. There are many operative methods that could be used to treat PPU. Primary closure by interrupted sutures, closure by interrupted sutures covered with a pedicled omentum on top of the repair (Cellan-Jones repair) and plugging the perforation with a free omental plug (Graham patch) are the most common techniques.

VAGOTOMY

Vagus nerve plays an important role in the regulation of gastrin release and gastric acid secretion by stimulating parietal cells *via* cholinergic receptors[70]. Vagal stimulation also releases histamine and gastrin from enterochromaffin like cells and G-cells, which in turn, will stimulate the parietal cells to produce acid secretion. Vagotomy is a procedure that transects the vagal trunks (truncal vagotomy) or distal nerve fibers (highly selective vagotomy). Truncal vagotomy aims to reduce the gastric acid secretion, thus reducing the risks of recurrent PUD. Selective vagotomy, which spares the hepatic and celiac divisions of the vagal trunks, are associated with higher long-term recurrence rates[71]. Therefore, selective vagotomy is no longer performed. Studies have shown that the ulcer recurrence rate was as high as 42% in perforated duodenal ulcer patients who underwent simple omental patch repair[72,73]. Few prospective randomized studies also reported substantially less ulcer recurrence in patients who underwent vagotomy in addition to omental patch repair[37,74]. Nonetheless, vagotomy is now seldom performed for PPU due to the availability of medications such as histamine receptor antagonists, proton pump inhibitors and *H. pylori* eradication.

GASTRECTOMY

Rydiger did a partial gastrectomy for the management of PUD in 1880. Unfortunately, it was not successful[75]. A year later, Theodor Billroth performed a successful gastroduodenostomy in a 43-year-old woman with pyloric cancer. He was the first surgeon who did gastric resection for antral carcinoma[76]. Nowadays, emergency gastrectomy is reserved for a giant ulcer or a suspicion of malignancy when it is not safe to perform omental patch repair[77]. A retrospective study reported a mortality rate of 24% in 41 patients who underwent gastrectomy for perforated benign gastric ulcers[78]. A study comparing outcomes after gastrectomy and simple closure repair showed that there were no significant differences in patient recoveries[79]. Longer operating times, ventilation and postoperative blood transfusion are associated with increased mortality[80]. The larger size of perforation is associated with higher mortality and post-operative anastomotic leak[81]. In a study of 601 patients and including 62 patients treated with gastric resection, we have shown that serum albumin is the only preoperative factor predictive of mortality (OR 5.57) and outcomes of patients treated with gastric resection are inferior as compared to omental patch repair with mortality risk of 24.2%[82]. Gastric resections for acid reduction have become less favorable after proton pump inhibitors era and in our experience, up to 10% of PPU patients require gastric resection.

LAPAROSCOPIC REPAIR

Laparoscopic repair was first performed for a perforated duodenal ulcer in 1990[83]. Laparoscopic repair of PPU is believed to reduce the post-operative morbidity and mortality[84]. A recent systematic review of 3 randomized controlled trials with a total of 315 PPU patients compared laparoscopy with open surgery[85]. This study failed to demonstrate differences in abdominal septic complications, pulmonary complications, mortality and re-operation. However, the operative time was shorter in laparoscopic group in contrast with previous study[86]. A systematic review of 56 studies comparing laparoscopic *vs* open approach for PPU concluded that there was no consensus on the perfect operating techniques[87]. The overall conversion rate for laparoscopic surgery was 12.4% mainly due to the size of perforation. Ulcer size more than 9 mm is a significant risk factor for

conversion to open surgery[88]. The operating time was longer and recurrent leakage was higher in laparoscopic group. However, the laparoscopic group also showed less postoperative pain and a shorter hospital stay. Furthermore, the laparoscopic treatment is also associated with equivalent costs compared with the open surgery as it reduces duration of hospital stays[89]. The current evidence remains poor for choosing laparoscopic repair over open surgery for PPU. This review has suggested that patients with a Boey score of 3, age over 70 years and symptoms lasting longer than 24 h should have open surgical approach as these patients have higher morbidity and mortality. Laparoscopic repair of PPU has now been performed by trainee surgeons with acceptable results[90,91]. Our local experience also showed that strict selection such as Boey score of 0-1, ulcer size of less than 10 mm, ulcer located in pyloro-duodenal area, haemodynamic stable, no previous abdominal surgeries, not suspected malignant ulcer and excluding ASA 3 and above score were safe for training[92]. There were no conversions, complications or mortality.

Laparoscopic repair techniques mirror techniques of open surgery and in particular sutureless techniques are more prominently described. This may in part due to training in intra-corporeal knotting skills. Sutureless techniques involve gelatin sponge plug with fibrin glue sealing or endoscopic clipping[68]. A recent study has compared the effectiveness of a sutureless onlay omental patch with a sutured omental patch method[93]. Forty-three patients underwent laparoscopic repair of PPU with sutureless onlay omental patch and another 64 patients underwent laparoscopic repair of PPU with sutured omental patch. There were no leaks in either group. The operating time and length of stay were significantly shorter in sutureless onlay omental patch group. This study has indicated that both techniques are safe and effective for repair of PPU. Trainees can easily perform laparoscopic sutureless repair with limited experience in laparoscopic surgery. Laparoscopic gelatin sponge plug and fibrin glue sealing can be easily performed[94]. However, this technique has not been widely accepted as it has been reported to have a higher leak rate[95]. Endoscopic clipping of PPU is not widely practiced, as there are only few centers with technical expertise and experience is limited with reports showing high complications and mortality[96,97].

"Dilution with solution is the solution to pollution". Towards the end of surgery, some surgeons like to irrigate the peritoneal cavity with 6-10 litres and even up to 30 litres of warm saline although no evidence has been found in literature to support that irrigation can lower the risk of sepsis[98,99]. On the other hand, pneumoperitonuem induced during laparoscopic surgery may increase the risk of bacterial dissemination[100]. It also seems to be a surgeon's preference whether or not to leave a drain at the end of surgery[101]. There is no evidence to support that leaving a drain in can reduce the incidence of intra-abdominal collections[101,102]. On the contrary, it may lead to infection of drain site and increased risk of intestinal obstruction[102]. A questionnaire performed by Schein showed that eighty percent of the surgeons did not leave a drain in after surgery due to the reasons discussed above[63]. Nowadays, the tire test (watch for bubbles after submerging patch repair under water) and the dye test (to inject dye *via* nasogastric tube) to look for leakage after closure of PPU are rarely used (Figure 3).

SELF-EXPANDABLE METAL STENTS

Primary stenting and drainage may be used as new treatment option for PPU[103]. Eight patients with PPU were treated with self-expandable metal stents[103]. Two patients were treated with stenting due to postoperative leakage after initial surgical closure and six patients were treated with primary stenting. Seven out of 8 patients recovered without complications and were discharged 9-36 d after stenting. Another study involving 10 patients with PPU who were treated with stenting also showed good clinical results[104]. This study has indicated stent treatment as a minimal invasive alternative with fewer complications compared to surgical treatment. These studies indicate that patients with PPU may be treated with primary stenting and drainage where training and expertise is available. More data is required to prove the effectiveness of this method.

MARGINAL ULCER PERFORATION

Any form of gastroenteric reconstruction can lead to the development of ulcer at the margins of the gastrojejunal anastomosis, known as marginal ulcer. The incidence of marginal ulcer is around 1% to 16%[105,106]. The ulcer tends to develop on the jejunal side of the stoma since it is directly exposed to the gastric acid[107]. Local ischemia, NSAIDS, anastomotic tension, chronic irritation due to the suture material and duodenal reflux are implicated in the aetiopathogenesis of marginal ulcer[108]. Marginal ulcer can rarely lead to perforation[109]. The presentation of patients with marginal ulcer perforation should be similar to PPU, however it may not be so. The small bowel contents has increased bacterial load and will also neutralize the gastric acid. A prospective study has shown that 28% of patients with marginal ulcers were asymptomatic[110]. Operative management for marginal ulcer perforation includes anastomotic revision such as converting Billroth Ⅱ gastro-jejunostomy reconstruction into a Roux-en-Y. It can also be treated with simple omental patch repair[109,111]. In recent time, majority of the published studies describe marginal ulcer and its perforation following bariatric procedures. We have reported a series of nine patients with marginal ulcer perforation following previous gastric resections for benign and malignant diseases[112]. We have concluded that patients with marginal ulcer do not present with septic shock. Also, revision of Billroth Ⅱ gastro-jejunostomy to Roux-en-Y anastomosis is not mandatory and omental patch repair is sufficient[112].

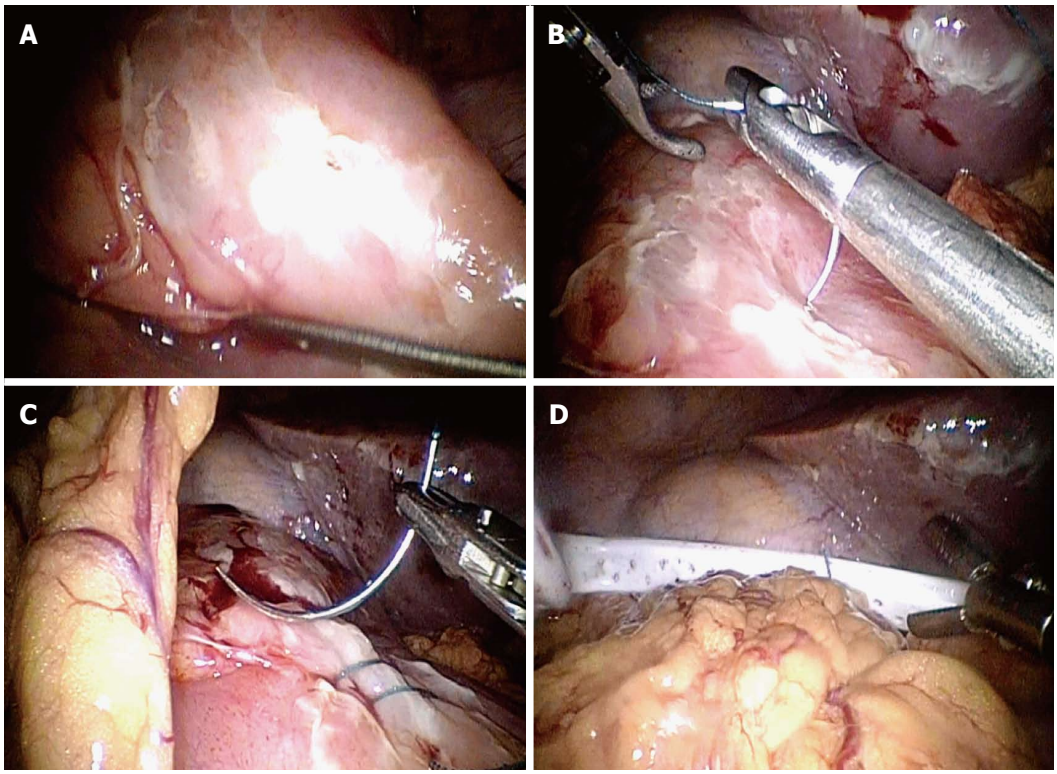

Figure 3 Shows laparoscopic omental patch repair. A: Anterior duodenal perforation; B: Laparoscopic suturing; C: Omental patch; D: Abdominal drain placement.

POST-OPERATIVE COMPLICATIONS

PPU treatment is associated with a significant post-operative morbidity and mortality regardless of whether laparoscopic or open repair is performed[113]. Post-operative mortality for PPU is estimated to be 6%-10%[114]. Age more than 60 years old, delayed treatment greater than 24 h, shock at presentation with systolic blood pressure less than 100 mmHg and concomitant diseases are the main risk factors influencing outcome[2,115]. Post-operative mortality in elderly is 3 to 5 times higher[116]. This may be due to the presence of medical comorbidities, delayed presentation, atypical presentation or delay of > 24 h in diagnosis[116].

Post-operative complications have been reported at around 30%[50,117]. Complications after surgical closure of PPU include surgical site infection, pneumonia, intra-abdominal collection/abscess, wound dehiscence, entero-cutaneous fistula, peritonitis, incisional hernia and ileus. A study has shown the commonest post-operative complications were surgical site infections (48%) and pneumonia (28%)[50]. However, this study only involved 25 patients and may not be representative. A more recent study involving 726 PPU patients between 2011 and 2013 in Denmark indicated the most common post-operative complications were post-operative leak (5.9%) and wound dehiscence (4.7%)[118]. Around 1 in every 5 patients underwent re-operation due to post-operative complications. This study also indicated that laparoscopic repair was associated with lower risk of re-operation than laparotomy or laparoscopic surgery converted to open surgery. Another study assessing postoperative complications in 96 patients reported that a total of 29 patients developed a total of 50 events of postoperative complications[119]. The most common complications were surgical site infection (32%), respiratory complications (30%), wound dehiscence (12%) and postoperative fistula (8%). Each additional complication was estimated to prolong hospital stay by 1.25 d. This study also reported that age > 40 years, larger size of perforation and history of shock significantly increased the rate of postoperative complications.

In our local study involving 332 patients who underwent surgery for PPU, post-operative complications included intra-abdominal collection (8.1%), leakage (2.1%) and re-operation (1.2%)[51]. Intra-abdominal abscess remains a serious postoperative complication after PPU surgery. Therefore, good surgical technique must be adopted to prevent this complication. Our low leak rates (2.1%) could be explained by early presentation, prompt diagnosis, early resuscitation and appropriate surgery. Our data on 30 d mortality was 7.2% which is comparable to a recent study from South Korea[120]. The lower mortality in our local study could be due to younger age (54.7), less co-morbidity (16.2%) and less patients with pre-operative shock (7.2%).

A recent study looked at the association of mortality with out of hours admission in patients with PPU[121]. A total of 726 patients who were surgically treated for PPU were included in this study. This study did not show statistically significance between 90-d mortality and out-of-hours admission in patients surgically treated for PPU.

In order to allocate resources appropriately and

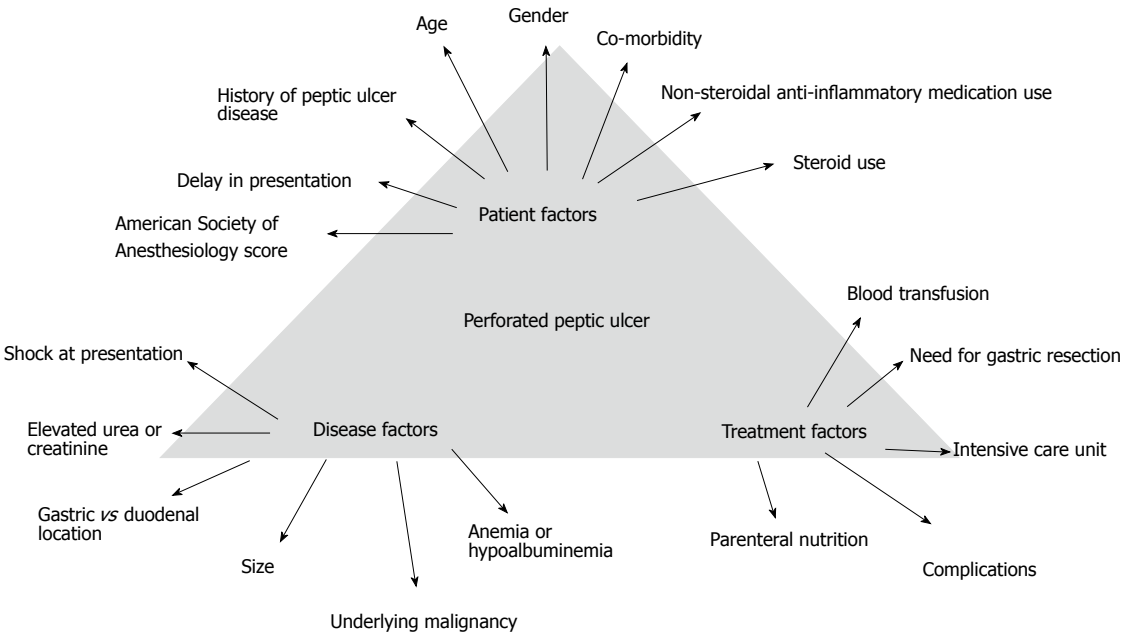

Figure 4 Determinants of outcomes in patients with perforated peptic ulcer.

provide optimal care, it is important to stratify patients into low and high risk of mortality. There are many scoring systems available to predict the mortality.

SCORING SYSTEMS TO PREDICT OUTCOMES IN PPU

About 11 different scoring systems used to predict outcome in PPU can be identified through the literature: the Boey score, the Americal Society of Anesthesiologists (ASA) score, the Sepsis score, the Charlson Comorbidity Index, the Mannheim Peritonitis Index (MPI), the Acute Physiology and Chronic Health Evaluation Ⅱ (APACHE Ⅱ), the Simplified Acute Physiology Score Ⅱ (SAPS Ⅱ), The Physiology and Operative Severity Score for the Enumeration of Mortality and Morbidity Physical Sub-score (POSSUM-phys score, the Mortality Probability Models Ⅱ (MPM Ⅱ), Peptic Ulcer Perforation (PULP) score, the Hacettepe score and the Jabalpur score[121]. Amongst these 11 scoring systems, the Boey score and ASA score are the most commonly validated systems[8,80,122-124]. Other scoring systems are not widely used due a lack of validation or their complexity in clinical use. We have validated ASA score, Boey's score, MPI and PULP score and found that all the four systems have moderate accuracy of predicting mortality with area under the receiver operator curve of 72%-77.2%[51]. In a recent study including 148 patients from two university affiliated hospitals in Singapore, Lee *et al*[125] has reported that in selected patients with presentation within 48 h and ulcer size < 2 cm, laparoscopic repair reduces length of hospital stay compared to open surgery in patients with MPI > 21.

A recent study was looking at 62 patients who underwent emergency surgery for PPU[126]. This study was investigating the correlation between the amount of peritoneal fluid and clinical parameters in patients with PPU. Using the methods described by Ishiguro *et al*[126], it was possible to predict the amount of accumulated intraperitoneal fluid by CT scan. This study has shown that the method of Ishiguro *et al*[126] was useful for predicting the amount of intraperitoneal fluid in patients with PPU. It is believed that it will be useful for predicting the severity of postoperative complications and also helpful for treatment decision-making (Figure 4).

MORTALITY

Mortality is a serious complication in PPU. As we mentioned before, PPU carries a mortality ranging from 1.3% to 20%[9,10]. Other studies have also reported 30-d mortality rate reaching 20% and 90-d mortality rate of up to 30%[11,12].

Significant risk factors that lead to death are presence of shock at admission, co-morbidities, resection surgery, female, elderly patients, a delay presentation of more than 24 h, metabolic acidosis, acute renal failure, hypoalbuminemia, being underweight and smokers[11,127-131]. The mortality rate is as high as 12%-47% in elderly patients undergoing PPU surgery[132-134]. Patients older than 65 year-old were associated with higher mortality rate when compared to younger patients (37.7% *vs* 1.4%)[131]. A study involving 96 patients with PPU also showed that there was a ninefold increase in postoperative complications in patients with comorbidities[119]. In another large population study, patients with diabetes had significantly increased 30-day mortality from PPU[135].

CONCLUSION

PUD can now be treated with medications instead of elective surgery. However, PUD may perforate and PPU carries a high mortality risk. The classic triad of sudden

onset of abdominal pain, tachycardia and abdominal rigidity is the hallmark of PPU. Erect chest radiograph may not establish the diagnosis and an index of suspicion is essential. Early diagnosis, prompt resuscitation and urgent surgical intervention are essential to improve outcomes. Non-operative management should be conducted by experienced teams with optimal resources and ideally under trial conditions. Exploratory laparotomy and omental patch repair remains the gold standard and laparoscopic surgery should be considered when expertise is available. Gastrectomy is recommended in patients with large or malignant ulcer to enhance outcomes; however the outcomes of patients treated with gastric resections remain inferior. Gelatin sponge plugs, fibrin glue sealants, self-expandable stents and endoscopic clipping techniques deserve to be tested in a controlled trial setting.

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MINIREVIEWS

Practice, training and safety of laparoscopic surgery in low and middle-income countries

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Abstract

Surgical management of diseases is recognised as a major unmet need in low and middle-income countries (LMICs). Laparoscopic surgery has been present since the 1980s and offers the benefit of minimising the morbidity and potential mortality associated with laparotomies. Laparotomies are often carried out in LMICs for diagnosis and management, due to lack of radiological investigative and intervention options. The use of laparoscopy for diagnosis and treatment is globally variable, with high-income countries using laparoscopy routinely compared with LMICs. The specific advantages of minimally invasive surgery such as lower surgical site infections and earlier return to work are of great benefit for patients in LMICs, as time lost not working could result in a family not being able to sustain themselves. Laparoscopic surgery and training is not cheap. Cost is a major barrier to healthcare access for a significant population in LMICs. Therefore, cost is usually seen as a major barrier for laparoscopic surgery to be integrated into routine practice in LMICs. The aim of this review is to focus on the practice, training and safety of laparoscopic surgery in LMICs. In addition it highlights the barriers to progress in adopting laparoscopic surgery in LMICs and how to address them.

Key words: Laparoscopic surgery; Global surgery; Low and middle-income countries; Laparoscopic training; Patient safety; Laparoscopy; Minimally invasive surgery

Core tip: The rate of laparoscopic surgery in low and middle-income countries (LMICs) is gradually increasing. In this review we highlight the practice of laparoscopic surgery in LMICs from diagnostic procedures to complex resections. Training in laparoscopic surgery is inherently variable in LMICs, however innovative teaching methods with inexpensive materials have been developed. Safety data on laparoscopic surgery in LMICs is minimal and more research needs to be done. It is essential to establish safe practices that must be contextualized to serve the population in various LMICs.

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INTRODUCTION

Surgical management of diseases are now recognized as major unmet needs in low and middle-income countries (LMICs)[1]. These countries are defined by the World Bank as having a gross national income (GNI) per capita of $1045 or less for low-income countries and more than $1045 but less than $12736 for middle income countries[2]. High-income countries (HICs) by definition have a GNI per capita of more than or equal to $12736[2].

Laparoscopic surgery was first introduced in the 1980s and is the preferred approach to a number of surgical procedures in HICs[3]. There are growing numbers of global surgery initiatives that have acknowledged surgical need and volume will continue to rise in LMICs[4-6]. Laparoscopic surgery offers the benefit of minimizing the morbidity and potential mortality associated with laparotomies. Several studies have shown that laparoscopic surgery is feasible in LMICs with reports of laparoscopy reducing laparotomy rates from fourteen to six percent[7-11]. Particular advantages of minimally invasive procedures are lower surgical site infection rates, ileus, earlier return to work, better pain control and cosmesis[12,13]. Decreasing the length of stay in hospital is of paramount importance to patients in LMICs, where days lost working translates into lack of food for some families. Hence, laparoscopic surgery seems attuned to serve such communities.

There has been sporadic and marginal adoption of laparoscopic surgery in LMICs for various reasons. Some of the obstacles are intrinsically health care system related, others financially driven such as inadequately trained personnel and lack of equipment. The cost of initial set up and maintenance of laparoscopic surgery equipment has been reported in some studies as the main inhibitory factor for minimally invasive surgery being commonly used in LMICs[9,10]. Nevertheless, laparoscopic procedures are performed in a number of surgical specialties in LMICs such as general surgery, urology, paediatric surgery and gynaecology. Laparoscopic procedures such as hysterectomies, tubo-ovarian surgery, cholecystectomies, appendicectomies, herniorrhapies and diagnostic laparoscopies are well established and performed routinely mainly in private centres in LMICs[7,10,14,15]. The aim of this review is to highlight the practice, training and safety of laparoscopic surgery in LMICs.

PRACTICE OF LAPAROSCOPIC SURGERY

The benefits of laparoscopic surgery in LMICs are parallel to those of HICs. Diagnostic laparoscopy has the value of decreasing laparotomy rates. Furthermore, laparoscopy in certain LMICs has replaced radiological diagnosis due to the lack of radiologisits and radiological facilities. A study from Nigeria by Adisa *et al*[16] reported neoplastic lesions identified in 64 patients through diagnostic laparoscopy, which aided further management of their cancers in some cases with chemotherapy or palliative procedures. The study highlighted only six computed tomography (CT) scanners and three magnetic resonance imaging (MRI) scanners were serving a population of approximately 15 million in Southwestern Nigeria as at 2012[16].

The challenges of the adoption and use of new technology or ideas are common to any health care setting. The initial reservations of laparoscopic surgery not being "orthodox" surgery in LMICs are gradually disappearing. Interestingly, hierarchical surgical culture has been quoted as a hindrance for laparoscopic surgery being performed in some hospitals, as senior surgeons "did not feel comfortable with it" due to lack of engagement[17]. Some patient driven factors due to deficiencies in communication or education also contribute to the hurdles of the acceptance of laparoscopic surgery in LMICs[18,19].

Equipment donated by charitable organisations has enabled the practice of laparoscopic surgery in numerous LMICs. Minimally invasive procedures are being used in LMICs for both emergency and elective procedures. In many parts of Africa, laparoscopic surgery is much more common in private hospitals due to the availability of funding for equipment and maintenance. Diagnostic laparoscopy in particular has taken center stage in LMICs where radiological facilities are lacking. Udwadia[9] reported performing approximately 3000 diagnostic laparoscopies over an 18 year period with no mortalities and a complication rate of 0.1%. These procedures had been used for the evaluation of abdominal tuberculosis, peritoneal pathology and abdominal trauma[9]. Shehata *et al*[20] reported 36 successful laparoscopic inguinal hernia operations with no recurrences or conversions to open surgery in a paediatric cohort. Day case procedures in LMICs are feasible provided set discharge criteria are in place to ensure patient safety[18,19]. Laparoscopic appendicectomies have been performed with 87% of patients being discharged on the same day successfully from a cohort of thirty in India[21].

Studies on certain specialised laparoscopic procedures such as colorectal, endocrine and urological surgery are scarce. Laparoscopic colorectal surgery as a whole is not commonly performed in African countries[10], this may be a reflection of the low incidence of colorectal disease. An Egyptian study however has reported successful outcomes in 37 patients with colorectal cancer managed laparoscopically[22]. Laparoscopic urological procedures in sub-Saharan Africa are usually performed by visiting surgeons from HICs during voluntary work or by sponsored invitations.

Spinal and regional rather than general anaesthesia has been safely used in LMICs for laparoscopic surgery[9,23,24]. Insufflation with carbon dioxide alone is an expensive venture in LMICs. Therefore, the development

and use of "gasless" laparoscopy in LMICs has been revolutionary[25]. Inventive strategies such as insufflation with room air, extracorporeal knot tying and hand assisted techniques have evolved in LMICs[26,27]. Adisa *et al*[10] used tube drapes that can be autoclaved as camera covers. Such innovative measures make laparoscopic surgery more attainable in LMICs.

TRAINING IN LAPAROSCOPIC SURGERY

In certain LMICs, visiting surgeons and some nationals who have relocated from HICs work on the expansion and further development of laparoscopic surgery. Moreover, as part of their continuing professional development, some surgeons from LMICs travel to centres in the United States and Europe to gain more laparoscopic experience[28]. This also stimulates practice on box trainers where available on their return. Laparoscopy is not suited to the old surgical mantra of "see one, do one, teach one". Under this traditional model, some local surgeons in LMICs have acquired and developed laparoscopic abilities in an unstructured way. This has the potential for unsafe practices being learnt by surgeons in training.

The challenges for the surgeon of learning to decipher two to three dimensional images, hand eye co-ordination; past pointing and haptic feedback are universal. Learning and practicing outside the operating theatre is crucial for acquiring laparoscopic skills. The resource-limited environment in LMICs also hampers the progress of laparoscopic training, with the lack of expert trainers. Laparoscopy is not taught in postgraduate residency training programmes in several LMICs and hence simulated laboratories are not readily available due to equipment costs. Lack of animal laboratories or wet labs as aids to practice in a safe location also add to the training constraints. Nevertheless, innovative measures have been developed to counteract the simulation problem with low fidelity but effective trainers. Ingenious low technology and cost laparoscopic trainers have evolved from both LMICs and HICs. Low cost trainers vary in price in different countries ranging from $0 (if using already available materials) to $85[29,30]. For example, Mir *et al*[4] reused an empty dextrose solution cardboard box to make an inexpensive trainer. Home laparoscopic trainers have been made from recyclable materials such as storage and shoe boxes[29,31]. Simulation based training even with low cost equipment requires investing time and sustainability[32]. Locally sourced materials are key to the success of making low cost laparoscopic training tools.

Andreatta *et al*[33] developed a training programme in Ghana with laparoscopic exercises such as cutting or peeling a tangerine into as few pieces as methods to assist in learning dissection and haptic feedback[33] American surgeons have used validated training tools such as the McGill Inanimate System for Training and Evaluation of Laparoscopic Skills in Tanzania to assess the use of a low-cost laparoscopic box trainer, which they found to be effective when an expert trainer was present[29].

The recording of commonly performed procedures such as appendicectomies and cholecystectomies for teaching and training is significantly underutilized in both LMICs and HICs. This can allow nurses, medical students, surgical and anaesthetic trainees to understand the processes involved in these laparoscopic operations. Access to the Internet can also aid learning as a number of laparoscopic operations are freely available online. Curricular can facilitate learning of laparoscopic skills in LMICs using low cost trainers and these need to be developed.

Both surgeons and nurses need to be trained in the principles and practical aspects of laparoscopic surgery. Knowledge of the instruments is essential when performing laparoscopic surgery. The training and practice of laparoscopic surgery in LMICs, could be improved and made more widely available through postgraduate medical education. In Nigeria for example, a group of general surgeons have recently formed the Laparoscopic Surgery Society of Nigeria to assess the scope of practice, basic competency, proficiency, and outcomes of laparoscopic surgery, so as to develop training.

SAFETY OF LAPAROSCOPIC SURGERY

Variability in safety and quality exists with laparoscopic surgery in LMICs[34]. Although a number of studies have reported safely preforming laparoscopic surgery, studies on the early complication rates may however be under reported in the literature. Mortality associated with anaesthesia is a major concern in LMICs, with reports ranging from 1 in 100 to 500[35,36]. The direct relationship of anaesthetic risks during laparoscopic surgery in LMICs is scarce in the literature. This may be because in a number of LMICs, spinal rather than general anaesthetic is used for laparoscopic surgery. Furthermore, the numbers of laparoscopic cases in most units have not reached a level whereby complications directly related to laparoscopy are reported such as respiratory compromise secondary to a pneumothorax or pulmonary odema.

In a comparative study, Manning *et al*[37] reported major complications such as bile leaks and duodenal perforations in patients following laparoscopic cholecystectomy in a large patient series from Afghanistan. More advanced laparoscopic procedures are being undertaken in certain LMICs. Senthilnathan *et al*[38] reported long-term results of a 130 patients following a laparoscopic pancreaticoduodenectomy for pancreatic cancer. This included a 5-year actuarial survival of 29%, a mortality rate of 2% and a positive margin rate of 9%[38]. Adequate training is crucial for patient safety. The inability to easily recognise the complications associated with laparoscopic surgery is a potential safety concern. In LMICs, there are significant implications with morbidity and mortality risks that can be associated with laparoscopic surgery such as bile duct injury in laparoscopic cholecystectomies, as facilities such as

endoscopic retrograde cholangiopancreatography are lacking[39].

The use of reusable laparoscopic instruments has helped in reducing the financial load in LMICs compared with disposable instruments. Studies have reported instruments being used for over 10 years, as well as reusing disposable instruments[9,40]. However, safety data about such usage is unknown. Nonetheless, no short-term safety concerns or suboptimal function have been described post sterilization. The upkeep and repairs of laparoscopic equipment is a significant challenge in LMICs. Part of the problems with donated instruments and equipment is the unavailability of trained personnel to undertake servicing. To counteract this, the manufacture and maintenance of low-cost equipment should be part of the future projects for industries to cater for LMICs.

DISCUSSION

Laparoscopic surgery has been a paradigm shift in surgical practice. Global surgical diseases have been estimated at eleven percent, although this may be an underestimate[41-44]. Only four percent of surgical procedures are carried out in low-income countries[45]. Lower life expectancy and infant mortality, which could partly be related to surgical need in terms of trauma and obstetric care respectively, remain a major issue in LMICs[46,47]. Therefore, there is a rising trend to develop surgical treatment in LMICs[48-50] with laparoscopic surgery playing a central role.

Surgical cultures and behaviours have been narrated as having an impact on the introduction and progress of new technology. Therefore a mindshift towards laparoscopic surgery and other new surgical techniques needs to be encouraged in LMICs to challenge the status quo. The time taken for some laparoscopic procedures, because of the set up, is much longer than open surgery. Therefore in LMICs where demand for high output surgical procedures is great, the throughput ability of laparoscopic surgery may be questioned. The specialist "general surgeon" is fast disappearing in HICs due to sub-specialisation. In LMICs however, the general surgeon is still very necessary given the array of conditions he or she is required to treat. Controversially, the generalist laparoscopic surgeon may be too demanding to have among a personnel limited and population heavy setting that exists in many LMICs.

Inequalities in health with regards to access and affordability are wider in LMICs, where the more affluent are more likely to have their operations performed laparoscopically. The payment plans of health care services vary in LMICs. They may be self-financed, government subsidized or insurance based and this has the potential effect of influencing the choices in procedures carried out specifically with regards to cost such as in laparoscopic surgery. A number of units in LMICs have acquired their laparoscopic instruments through donations or following surgical missions from HICs. A way of accessing materials is for surgeons, healthcare service providers and governments to engage in the development process for laparoscopic surgery to be more accessible in LMICs.

Cost is a major barrier to healthcare access for a significant number of individuals in LMICs. The financial afflictions that face some LMICs may have been the result of war, conflict, corruption and other humanitarian crises. Thus, understanding the baseline operative capabilities in these countries is paramount before embarking on an improvement operation[51]. It is also key for surgical mission trips to endeavour to build, adapt and tailor practices that are sustainable for LMICs, rather than perform procedures with considerations only for the standards of HICs. The focus of these mission trips should be goal directed with long-term planning for continuous teaching, training and supervision of new initiatives.

The price of equipment is a major obstacle to laparoscopy being routine in LMICs. This was one of the initial factors hindering rapid uptake of laparoscopic surgery in a number of hospitals in HICs. Although some studies have reported diagnostic laparoscopy to be more cost effective in some African countries, others have reported laparoscopy costs to be similar to that of laparotomy[7-9]. Remarkably laparoscopic equipment per case has been reported to be as low as $20, with the cost of the procedures themselves ranging from approximately $55 to $300 in some LMICs[9,10,15]. Lowering the cost of the equipment, maintenance and surgery itself will increase the endorsement of laparoscopic surgery in LMICs. This could be achieved through collaborative work with governments and medical equipment suppliers.

Bal *et al*[18] have shown that day case laparoscopic procedures such as laparoscopic cholecystectomies are feasible in LMICs. Chauhan *et al*[19] on the other hand argue that day surgery is not cost effective in LMICs compared with HICs because of infrastructural constraints. The practice of day case surgery to negate the cost of hospital stay would be variable in LMICs. As patients sometimes have come from long distances and for safety reasons a period of in-patient observation may be necessary. However with the advent of global mobile phone technology, telephone and video based reviews and follow-ups may be the way forward to offset this problem.

The Fundamentals of Laparoscopic Skills, which involves web-based and technical skills training in the United States, is a good example of a method for standardizing skills. A low cost version of such a program would be appropriate in a resource-limited environment to provide education, training and accreditation. The training programmes should be structured to include lectures and workshops rather than just short-term courses. Global connectivity though technology can also facilitate teaching and training methods with the development of Google glasses, Face Time and Skype for example, to allow communication, consultation and feedback.

International organizations provide a lot of surgical

care in LMICs; therefore, cooperative efforts are crucial to the success of safe laparoscopic operations in LMICs. The benefit of experience from visiting or locally trained surgeons will provide insight into potential short and long-term problems with solutions, as well as the economic contingency measures. Centralization of laparoscopic surgery maybe better for infrastructure planning in the initial stages of service provision in LMICs. This may curtail the differences in the quality of health care delivery and integrate various concepts such as patient selection, safety, re-cycling of equipment and resource allocation. It could also help in training surgeons and nursing staff from different peripheral hospitals to a certain standard.

This review has a number of limitations that we acknowledge such as the difficultly in generalizing the differences between LMICs in terms of health care budgets and the surgical needs of the population. Therefore, some of the solutions we suggest may not be suitable for all LMICs. Most of the studies reported in the literature were retrospective, non-comparative with short-term follow-up periods. More research needs to be encouraged into data collection, formation of registries and reporting of outcomes of laparoscopic surgery in LMICs.

CONCLUSION

The management of surgical conditions in LMICs are now of great interest to health care funders and researchers in HICs. We believe laparoscopic surgery in LMICs offers the same advantages as in HICs - reduced surgical site infections, length of stay; and should be promoted as such. Social and economic change alongside with manufacturers and health ministries are the main drivers for cost effective healthcare in LMICs to enable deprived individuals access to surgical care. The global economic picture for better healthcare should include the manufacture of robust, durable and affordable surgical instruments that can be used by LMICs.

The realms of safety in surgery in certain LMICs still lies in the ability to obtain basic amenities such as clean water and electricity as well as having adequately trained medical, nursing and allied health professional staff. The culture of guidelines, regulation and monitoring also needs to be adopted in LMICs in line with accountability for complications. The trend of laparoscopic surgery is here to stay for a few years before robotic surgery or other means take over. It is therefore vital to establish safe practices that must be contextualized to serve the population in various LMICs.

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ORIGINAL ARTICLE

Prospective Study

Triple tube drainage for "difficult" gastroduodenal perforations: A prospective study

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Abstract

AIM

To prospectively study the outcome of difficult gastroduodenal perforations (GDPs) treated by triple tube drainage (TTD) in order to standardize the procedure.

METHODS

Patients presenting to a single surgical unit of a tertiary hospital with difficult GDPs (large, unfavourable local and systemic factors) were treated with TTD (gastrostomy, duodenostomy and feeding jejunostomy). Postoperative parameters were observed like time to return of bowel sounds, time to start enteral feeds, time to start oral feeds, daily output of all drains, time to clamping/removal of all drains, time for skin to heal, complications, hospital stay, and, mortality. Descriptive statistics were used.

RESULTS

Between December 2013 and April 2015, 20 patients undergoing TTD for GDP were included, with mean age of 44.6 ± 19.8 years and male:female ratio of 17:3. Mean pre-operative APACHE Ⅱ scores were 10.85 ± 3.55; most GDPs were prepyloric (9/20; 45%) or proximal duodenal (8/20; 40%) and mean size was 1.83 ± 0.59 cm (largest 2.5 cm). Median times of resumption of enteral feeding, removal of gastrostomy, removal of duodenostomy,

removal of feeding jejunostomy and oral feeding were 4 d (4-5 IQR), 13 (12-16.5 IQR), 16 (16.25-22.25 IQR), 18 (16.5-24 IQR) and 12 d (10.75-18.5 IQR) respectively. Median hospital stay was 22 d (19-26 IQR) while mortality was 4/20 (20%).

CONCLUSION

TTD for difficult GDP is feasible, easy in the emergency, and patients recover in two-three weeks. It obviates the need for technically demanding and riskier procedures.

Key words: Peptic ulcer; Perforation peritonitis; APACHE; Triple tube drainage; Duodenostomy

Core tip: Generalised peritonitis secondary to hollow viscous perforation is common in India, with poor outcomes in many patients. Gastroduodenal perforations (GDPs), commonly treated by pedicled omental patch repair, have high leak rates and consequent high mortality, especially with advancing age, large perforations, and other systemic insults. Described strategies for leakage like jejunal patches or grafts, or pyloric exclusion are actually fraught with more risk. To emphasize minimizing time and skill, the concept of damage control from trauma is extrapolated and triple tube drainage is proposed for sick and difficult GDP patients. This study is prospective and demonstrates the ease and utility of this procedure, in an attempt to standardize it.

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INTRODUCTION

Generalised peritonitis secondary to hollow viscous perforation continues to be one of the most common surgical emergencies in India. In fact, the most common cause of exploratory laparotomy in the emergency setting is intestinal perforation peritonitis[1,2]. In most Indian series, small bowel and gastroduodenal perforations are the predominant causes[1,3]. Gastroduodenal perforations (GDPs) in India occur in younger patients and have a worse outcome than in developed countries[1,3,4]. The most common and easily performed procedure for GDP is the pedicledomental patch repair[4,5].

The leak rates after patch repair are 8%-10% in Indian series, while the mortality rates are also high (10%-15%). Leakage leads to a significant increase in morbidity and mortality[1,5,6]. The factors reported to be associated with high leak rates and mortality in gastroduodenal perforations are advancing age, large perforation size (≥ 1.5 cm diameter), presence of malignancy or immunocompromised status, delay in treatment, pre-operative hypotension, and raised serum creatinine levels[4,7]. Up to 25% of GDPs are more than 1 cm in size; about 2%-3% are more than 2 cm. These are particularly predisposed to leakage[5,6]. In our hospital, almost 20% of patients of GDPs have two or more of these adverse factors.

Operative strategies to treat or prevent leakage have included jejunal serosal patch, jejunal or omental pedicle graft, pyloric exclusion with gastrojejunostomy, gastrectomyand vagotomy, and, novel techniques like myocutaneous flaps or gastric disconnection[5,6,8,9]. However, many authors now feel that adding more suture lines in these sick and septic patients is fraught with more risk and poorer results. These procedures need high degree of surgical expertise and may prolong operative time, and none of the above technique is immune to postoperative leak[6]. The emphasis should be on minimizing time and surgical skill.

The concept of damage control surgery for the treatment of complex pancreatico-duodenal injuries has led to the acceptance of diversion and decompression of all enteric secretions. This is mostly performed as "triple tube ostomy" or "triple tube drainage (TTD)". The components are tube gastrostomy, retrograde tube duodenostomy, and, feeding jejunostomy[10,11].

Duodenal decompression is also recommended for the protection of the duodenal stump after gastrectomy for malignancy[12]. Some authors have extrapolated the concept of damage control for GDPs, especially the large or "giant" subtypes and in re-operations after leakage. However, the reported experience of TTD for GDP is small, with only a few case series. There is only one study from India, despite the high prevalence of the condition here. The proponents of TTD feel it to be a significantly underutilized procedure[6,12-14].

This prospective observational study was performed as a pilot study in patients with difficult GDPs treated by triple tube drainage, to study outcomes and standardize this procedure.

MATERIALS AND METHODS

This prospective observational pilot study was conducted in the department of surgery of a teaching tertiary hospital in north India, from December 2013 to April 2015, after getting clearance from the institutional ethics committee. Patients undergoing triple tube drainage for difficult duodenal perforation were included in the study. Difficult gastroduodenal perforations, for the purpose of our study, were defined as cases with two or more of the following features: Perforation size ≥ 1.5 cm, late presentation (≥ 3 d), unfavorable systemic factors (APACHE Ⅱ score ≥ 10), unfavorable local factors (copious pus, friable bowel, indurated or friable margins), and, re-operated patients (leakage after omental patch repair).

The aim of the study was to observe the postoperative

Table 1 Mean/median hematological/laboratory parameters (n = 20)

Parameter	Mean/median ± SD	IQR (1st to 3rd)
Haemoglobin (g/dL)	11.76 ± 2.59	
Total leukocyte counts (/mm^3)	12550	4675 - 19425
Platelet (× 10^5/mm^3)	1.80 ± 1.05	
Blood urea (mg/dL)	47.15	39.75- 67.5
Serum creatinine (mg/dL)	1.49 ± 0.68	
Serum sodium (meq/L)	135.7 ± 7.70	
Serum potassium (meq/L)	4.33 ± 0.90	
pO_2 (mmHg)	93.8 ± 33.20	
pH	7.37 ± 0.07	

IQR: Inter quartile range.

course and outcome of patients undergoing triple tube drainage for difficult gastroduodenal perforations. The primary outcome variables were: Time to oral feeding, time to removal of drains, hospital stay, complications (leakage, surgical site infections, and respiratory complications), and, mortality. As a secondary objective, this was proposed as a pilot study to compare two techniques of duodenal decompression, namely T-tube duodenostomy and retrograde duodenostomy in terms of hospital stay and leak rate.

Flow of study

After a provisional diagnosis of gastroduodenal perforation peritonitis in the emergency room, the patients were admitted for investigations and treatment. Informed written consent was obtained from the patients. The relevant biochemical, haematological and radiological tests were performed; the APACHE Ⅱ score was recorded. After optimization, exploratory laparotomy was performed. Copious lavage with normal saline was followed by identification of perforation site, and assessment of suitability for patch repair. In patients who fulfilled the inclusion criteria for difficult gastroduodenal perforations, the gastroduodenal perforation was first repaired using the standard omental patch technique. This was followed by TTD, consisting of: (1) Gastric decompression using 12-14 Fr tube brought out as gastrostomy; (2) duodenal decompression by retrograde duodenostomy (RD) using 12-14 Fr tube brought out through the jejunum, 10 cm from duodeno-jejunal flexure; and (3) feeding jejunostomy (FJ) using 10-12 Fr tube introduced into jejunum 20 cm from duodeno-jejunal flexure.

All tubes were fixed internally to parietal peritoneum by double purse-string absorbable polygalactin (Vicryl) 2-0 sutures, and fixed externally using purse-string suture with silk No.1. Polydiaxanone sutures would offer less friction, but are more expensive. The feeding jejunostomy and gastrostomy tubes were pulled up till the parietal wall and bowel sutured to peritoneum to ensure a controlled fistula. A sub-hepatic drain (28-32 Fr) was placed near the duodenostomy tube to act as a sump drain.

The abdomen was closed using interrupted far-near technique with polypropylene No. 1 suture. Skin was sutured loosely with packs soaked in antiseptic solution.

Table 2 Pre-operative physiological profile

Parameters	Mean ± SD
Temperature (℃)	37.46 ± 0.87
Mean arterial pressure (mmHg)	78.40 ± 18.60
Pulse rate (beats/minute)	116.7 ± 20.63
Respiratory rate (/minute)	22.3 ± 2.77
Pre-op APACHE-II score	10.85 ± 3.55

Postoperative assessment

Patients were assessed on daily basis in the postoperative period using the following outcome parameters: time to return of bowel sounds, time to start enteral feeds, time to start oral feeds, daily output of all drains, time to clamping/removal of all drains, time for skin to heal, complications, hospital stay, and, mortality. All outcome parameters were analysed using descriptive statistics with SPSS software.

RESULTS

Between December 2013 and April 2015, 20 patients undergoing TTD for difficult gastroduodenal perforation were included in the study. Mean age of the patients was 44.6 ± 19.8 years (range: 10-73 years) with a male: female ratio of 17:3. Table 1 shows the mean/median hematological and laboratory parameters for the 20 patients.

Five patients (25%) were anaemic (Hb < 10 g/dL) at presentation, while five (25%) had total leukocyte counts within the normal range (4000/mm^3-11000/mm^3). Most had leukocytosis, while 4 (20%) had leucopenia. The slightly deranged mean renal functions reflect the state of prerenal/renal azotemia secondary to sepsis. Table 2 reflects the common physiological parameters and mean APACHE-II scores.

Intra-operative findings

Peritoneal contamination with more than 1.4 L of purulent fluid was present in all the cases. The perforation was prepyloric in 9 patients (45%), in the first part of duodenum (D1) in 8 (40%), present in the body of stomach in 2 (10%), and, in the duodenum distal to D1 in 1 (5%). Friable irreparable edges were noted in 11 (55%) perforations (excluding the 2 cases where the patients were re-explored after leak). The mean diameter of the perforations in our cases was 1.83 ± 0.59 cm (largest 2.5 cm).

Seven patients (35%) with perforation size of 0.5 cm were included, due to fulfillment of other inclusion criteria. All patients underwent TTD with the retrograde duodenostomy technique, as none were found suitable for T-tube duodenostomy. The reasons were: friable and edematous duodenal wall (8), and, dense adhesions around lateral duodenal wall (13).

Table 3 Postoperative course (n = 20)

Observations	Postoperative days (mean/median)	Standard deviation OR IQR (1st-3rd)
Time to return bowel sounds	3.53	± 0.91
Time to start feeding *via* FJ	4	4-5
Time to start oral feed	12	10.75-18.5
Time of clamping of Gastrostomy	9.87	± 3.75
Time of clamping of RD	13	± 4.18
Time of removal of Gastrostomy	13	12-16.5
Time of removal of RD	16	16.25-22.25
Time of removal of FJ	18	16.5-24
Total hospital Stay	22	19-26
Wound healing time	15.75	± 1.91

IQR: Inter quartile range; FJ: Feeding jejunostomy; RD: Retrograde duodenostomy.

Table 4 Postoperative outcomes/complications n (%)

Outcomes/complications	n = 20
Surgical site infection	9 (45)
Respiratory complications	4 (20)
Peritubal leakage	4 (20)
Peritubal excoriation	2 (10)
Burst abdomen	5 (25)
Bed sore	2 (10)
Postoperative leak	1 (5)
Mortality	4 (20)

Postoperative course

All patients were observed till discharge or death, in terms of parameters listed in Table 3.

The gastrostomy tube was accidentally pulled out in one patient, while the retrograde duodenostomy came out in two patients. These patients were excluded for the determination of time of removal of tubes.

The total hospital stay ranged from 17 to 139 d. Out of 20 patients included in the study, four (20%) died in the postoperative period. One patient underwent Whipple's procedure on postoperative day (POD) 29 for duodenal neuroendocrine tumor reported on histopathological examination of the perforation edge. Table 4 lists the various complications in the postoperative period.

DISCUSSION

Despite the proven advantages of TTD in pancreatico-duodenal trauma, it is an underused strategy for peptic perforations. This is despite the high morbidity (> 30% mortality; up to 50% leak rates) of certain types of peptic perforations. Less than 5 case series (largest about 40 patients) have been published on triple tube drainage for gastroduodenal perforations; most published data is retrospective. There is no standardization regarding postoperative management[6,11-14].

Though classical pedicled omental patch repair remains gold standard for the gastro-duodenal perforations[5,6], patients with difficult gastro-duodenal perforations are associated with poor outcome in terms of postoperative complications, postoperative leak, morbidity and mortality. Most authors have labeled large (> 1.5-2.5 cm) GDPs as difficult; however, we have included poor physiological performance also as "difficult" due to the known propensity for leak and mortality (vide infra). In our study, we have prospectively observed 20 cases of difficult gastroduodenal perforation undergoing triple tube drainage (Cellan-Jones omental patch repair with gastrostomy, retrograde duodenostomy and feeding jejunostomy) during December 2013-April 2015. Lal *et al*[6] compared 20 cases of controlled tube duodenostomy (primary repair of perforation with nasogastric tube or gastrostomy, retrograde duodenostomy and feeding jejunostomy) with 20 cases of classical omental patch repair over a period of 10 years. Fujikuni *et al*[13] studied 3 patients over 18 mo (between November 2009 and March 2011) undergoing triple-tube-ostomy for iatrogenic duodenal perforations. The higher number of patients in the present study could possibly be due to increased occurrence of difficult duodenal perforations in the study group or due to different inclusion criteria, which were not limited only to the size of perforation.

The higher mean age of patients in the present study is consistent with results of Svanes *et al*[15] who have shown that median age of the patients has increased from 38 years in 1935-44 to 60 years in 1985-90 for men and 55 to 69 years for women (Table 5). The authors have also observed that the relative incidence of duodenal perforation as has decreased, while pyloric and prepyloric perforations have increased from 1935-1990 in 1483 patients[15]. Male predominance in the cases is also consistent with available literature, which can be attributed to the higher incidence of smoking in males.

There is no clear-cut definition of giant gastroduodenal perforation in literature; it has varied from 1.5 to 3 cm[5,6,16]. Most authors would accept that a perforation of > 2 cm is fraught with more risk of leakage and mortality, and needs more specific intervention that just primary closure. Many of our patients are referred from far-off hospitals and present late; we have added physiological scoring (APACHE-Ⅱ) along with perforation size to improve the accuracy of the risk assessment. This has been shown to be consistent for prediction of outcome in GDPs[17,18].

In our view, the most crucial part of the procedure is the adequate decompression of the duodenal C-loop, as it is retroperitoneal in position and cannot be brought out as a stoma. The duodenum is also an unfriendly organ in terms of repair, as it lacks a proper serosal wall. Hence, in our mind, tube decompression of right side of the duodenal segment seemed like the most attractive option, as demonstrated by a few authors[11-14]. A T-tube, as used by Isik *et al*[12] seems ideal. Unfortunately, in our patients, extensive inflammation in the right upper quadrant precluded the use of this technique, and we used the retrograde duodenostomy inserted more

Table 5 Comparison between age, gender, and intra-operative findings

Study	Most common age group (yr)	Gender distribution (M:F)	Size of perforation	Site of perforation
Present study	46-70	5.6:1	1.83 ± 0.59	Prepyloric 45%, Duodenal 40%
Lal *et al*[6]	30-50	4:1	60% 2 to 3 cm; 40% > 3 cm	
Jani *et al*[16]	21-50	7.3:1	> 2 cm	
Menekse *et al*[17]	39-62	6.1:1	13% with > 1 cm	
Berleff *et al*[19]	40-50	3.7:1		
Chaudhary *et al*[20]	18-40	4.3:1	> 1 cm in 7.29%	Duodenal 69.7%, Gastric 30.2%

distally. The latter technique is limited by the maximum calibre possible though such a circuitous route, and is more prone to blockage and failure. We actively endeavoured to keep it patent with frequent flushes, and would prefer to perform T-tube decompression when possible.

Postoperative course

It is evident that a reliable inpatient protocol should be in place to manage these multiple tubes without complications. Unfortunately, due to the scant research on the subject, no clear guidelines are available. The prospective study which most closely resembles our design was conducted by Lal *et al*[6] at a nearby center. The postoperative course in the two studies has been compared. In present study, mean time of return of bowel sounds was 3.53 ± 0.91 d. Lal *et al*[6] observed that bowel sounds returned in 72 h, after which enteral feed could be attempted through the jejunostomy tube. It is consistent with other emergency procedures that small bowel peristalsis returns in 48-72 h. We clamped the gastrostomy and retrograde duodenostomy tubes at was 9.87 ± 3.75 d and 13 ± 4.18 d respectively, while it was 7 d and 9-10 d respectively in the Lal study. These tubes are safely removed once the patient resumes a normal oral diet 3-4 d later. The removal of tubes may vary by 24-72 h, at the discretion of the treating physician.

It would be needless to emphasize the importance of fluid and electrolyte balance during the recovery period. Our patients are thin-built and nutritionally poor; the high output from controlled fistulae can be the "tipping point" towards a poorer outcome. It is also imperative to ensure the patency of the tubes too, as any undrained collections could cause crippling sepsis. Since the entire assembly works as a proximal diversion of gastric, duodenal and pancreatic secretions (at least 2-2.5 L/d), patency is important (vide supra).

Damage control procedures are performed in the most critical patients. In the present study, median hospital stay was 22 d (17-139 d) while the mortality was 20%. The incidence of postoperative complications was also higher than similar series[6,15-17,19,20]. Poorer outcomes can be explained by the fact that all the patients included in our study had "difficult" gastroduodenal perforations in the truest sense, with higher predicted deaths.

We have thus shown in a prospective group of patients that TTD is feasible, easy to perform in the emergency setting, and is followed by two-three weeks of easy convalescence. The patients usually accept oral diet after the second week.

Limitations

Some limitations are evident in our study. A larger sample size over a longer duration would allow better recommendations to be put forward. We had hypothesized before the start of our study that TTD would be useful in both GDPs and also some very proximal jejunal perforations with tuberculous etiology. The latter are commonly seen in our scenario; and are difficult to treat due to high leak rate and an unmanageable short bowel if exteriorized. However, in the present study, we did not include such patients in order to enable comparison of "like with like". Also, a well-described technique of TTD, namely, T-tube decompression of the lateral wall of the duodenum, could not be evaluated as all our patients demonstrated intense fibrosis in that area. With a larger study duration and more number of patient, the next stimulus for research would be a more analytical study comparing the two types of TTD.

COMMENTS

Background

Generalised peritonitis secondary to hollow viscous perforation continues to be one of the most common surgical emergencies in India. In fact, the most common cause of exploratory laparotomy in the emergency setting is intestinal perforation peritonitis.

Research frontiers

Operative strategies to treat or prevent leakage have included jejunal serosal patch, jejunal or omental pedicle graft, pyloric exclusion with gastrojejunostomy, gastrectomyand vagotomy, and novel techniques like myocutaneous flaps or gastric disconnection.

Innovations and breakthroughs

In authors' mind, tube decompression of right side of the duodenal segment seemed like the most attractive option, as demonstrated by a few authors. A T-tube, as used by Isik *et al* seems ideal. Unfortunately, in the patients, extensive inflammation in the right upper quadrant precluded the use of this technique, and the authors used the retrograde duodenostomy inserted more distally. The latter technique is limited by the maximum calibre possible though such a circuitous route, and is more prone to blockage and failure. The authors actively endeavoured to keep it patent with frequent flushes, and would prefer to perform T-tube decompression when possible.

Peer-review

This is a very comprehensive review of the literature on NETs, also being very well written.

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Uncommon presentation of a common disease - Bouveret's syndrome: A case report and systematic literature review

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Abstract

AIM

To investigate and summarise the current evidence surrounding management of Bouveret's syndrome (BS).

METHODS

A MEDLINE search was performed for the BS. The search was conducted independently by two clinicians (Yahya AL-Habbal and Matthew Ng) in April 2016. A case of BS is also described.

RESULTS

A total of 315 articles, published from 1967 to 2016, were found. For a clinically meaningful clinical review, articles published before 01/01/1990 and were excluded, leaving 235 unique articles to review. Twenty-seven articles were not available (neither by direct communication nor through inter-library transfer). These were also excluded. The final number of articles reviewed was 208. There were 161 case reports, 13 reviews, 23 images (radiological and clinical images), and 11 letters to editor. Female to male ratio was 1.82. Mean age was 74 years. Treatment modalities included laparotomy in the majority of cases, laparoscopic surgery, endoscopic surgery and shockwave lithotripsy.

CONCLUSION

There is limited evidence in the literature about the appropriate approach. We suggest an algorithm for management of BS.

Key words: Bouveret's syndrome; Biliary anomalies; Endoscopy; Digestive system; Duodenal obstruction diagnosis; Gallstones surgery; Gallstones complications; Duodenal obstruction etiology; Duodenal obstruction surgery; Intestinal fistula diagnosis; Humans

Core tip: Bouveret's syndrome is gastric outlet obstru-

ction secondary to an impacted gallstone in the duodenum or stomach. There is limited evidence surrounding management of this rare syndrome. Here we systematically review the published cases and recommend a treatment algorithm to clinicians facing this syndrome in future.

AL-Habbal Y, Ng M, Bird D, McQuillan T, AL-Khaffaf H. Uncommon presentation of a common disease - Bouveret's syndrome: A case report and systematic literature review. *World J Gastrointest Surg* 2017; 9(1): 25-36 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i1/25.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i1.25

INTRODUCTION

Bouveret's syndrome (BS) was first described by Beaussier in 1770, but reported in the literature first by Leon Bouveret in 1896, where he had two cases[1]. Leon Bouveret was actually an internist but supported surgery[2]. BS is gastric outlet obstruction secondary to a gallstone impacted in the duodenum or stomach.

We report a 39-year-old lady who presented with upper abdominal pain and vomiting. She was diagnosed with BS after scans and endoscopy. Her gallstone was successfully removed by gastroscopy. Though her symptoms continued, a literature review was sought to manage her according to the recent evidence. Almost all the case reports and limited case series were in favour of conservative management. She was managed expectantly, but represented with ongoing pain.

The patient underwent laparoscopic cholecystectomy. The fistula was dissected and closed laparoscopically. On intra-operative cholangiogram, she had more bile duct stones which were treated by laparoscopic bile duct exploration and stone extraction. She did well in the post-operative course.

MATERIALS AND METHODS

MEDLINE and PubMed searches were performed for the terms BS. The search was conducted in April 2016. Three hundred and fifteen articles, published between 1967 and 2016, were identified. For a clinically meaningful clinical review, articles published before 01/01/1990 and were excluded, leaving 235 unique articles to review. Twenty-seven articles were not available (neither by direct communication nor through inter-library transfer). The final number of articles reviewed was 208 (Figure 1A).

Data from retrieved articles were independently reviewed by the two authors (Yahya AL-Habbal and Matthew Ng) and data was extracted using a standardised collection tool. Data was analysed with descriptive statistics. In contrast to classic meta-analyses, statistical analysis was performed where the outcome was calculated as the percentages of an event (without comparison) in pseudo-cohorts of observed patients.

RESULTS

Articles comprised 161 case reports[3-163], 13 reviews[164-176], 23 images reports (radiological and clinical images[177-198] and 11 letters to the editor[199-209], as illustrated in (Figure 1F).

Articles were written in multiple languages. English articles constituted the main bulk of the literature (176 articles, 77%). The rest were Spanish (20 articles, 9%), Italian (7 articles, 3%) French (5 articles, 2%), and other languages (13%). These other languages include: Bulgaria, South Korean, Japanese, German, Romanian, Turkish, Hungarian, Ukrainian, and Czech. Articles not in English were translated to English using dependable medical dictionaries (Figure 1D and E).

A 39 years old lady presenting to the emergency department with two-week history of epigastric and right upper quadrant pain. The pain was constant, dull, and radiating to the back, she had acidity and reflux symptoms, nausea and vomiting. There was no history of jaundice, or weight loss.

On examination she was mildly dehydrated. Pulse rate was 92 beats/min and temperature was 37.3°. She was tender in the epigastrium and right upper quadrant, with a negative Murphy's sign.

Initial blood tests showed high white cells count 13.9 $\times$ 10^9. Her liver functions were deranged. Bilirubin was 14 IU/L, ALP 285 IU/L, ALT 335 IU/L, GGT 445 IU/L, and ALT 0f 205 IU/L. Her lipase was mildly raised at 455 IU/L (normal range < 45 IU/L).

With this mixed picture the initial differential diagnosis was cholangitis or pancreatitis, or Mirrizzi syndrome.

The patient was referred for an ultrasound (US) scan. The images were degraded by pneumobilia and, while difficult to characterize, demonstrated a contracted gallbladder without stones. Common bile duct was 10 mm with mild intrahepatic biliary tree dilatation (Figure 2). CT scan obtained to further characterize the gallbladder demonstrated large-volume pneumobilia, a fistula between the distal stomach and the collapsed gallbladder, and oral contrast in the region of the gallbladder neck.

There was an opacity in the stomach that was interpreted as hypo-dense gallstone in the stomach (Figures 3 and 4). At this point the diagnosis of cholecysto-gastric fistula secondary to gallstone disease with subsequent intermittent gastric outlet was made.

Upper GI endoscopy confirmed the presence of gallstone in the stomach and fistula orifice (Figure 5). The stone was successfully retrieved by snare (Figure 6). Patient's symptoms improved significantly and ultimately discharged home after 2 d. Her liver functions normalized before discharge. Given that there was no evidence of any further gallstones, and after reviewing the current evidence and practice, we decided to manage her expectantly.

Upon follow up, it was found that the patient was

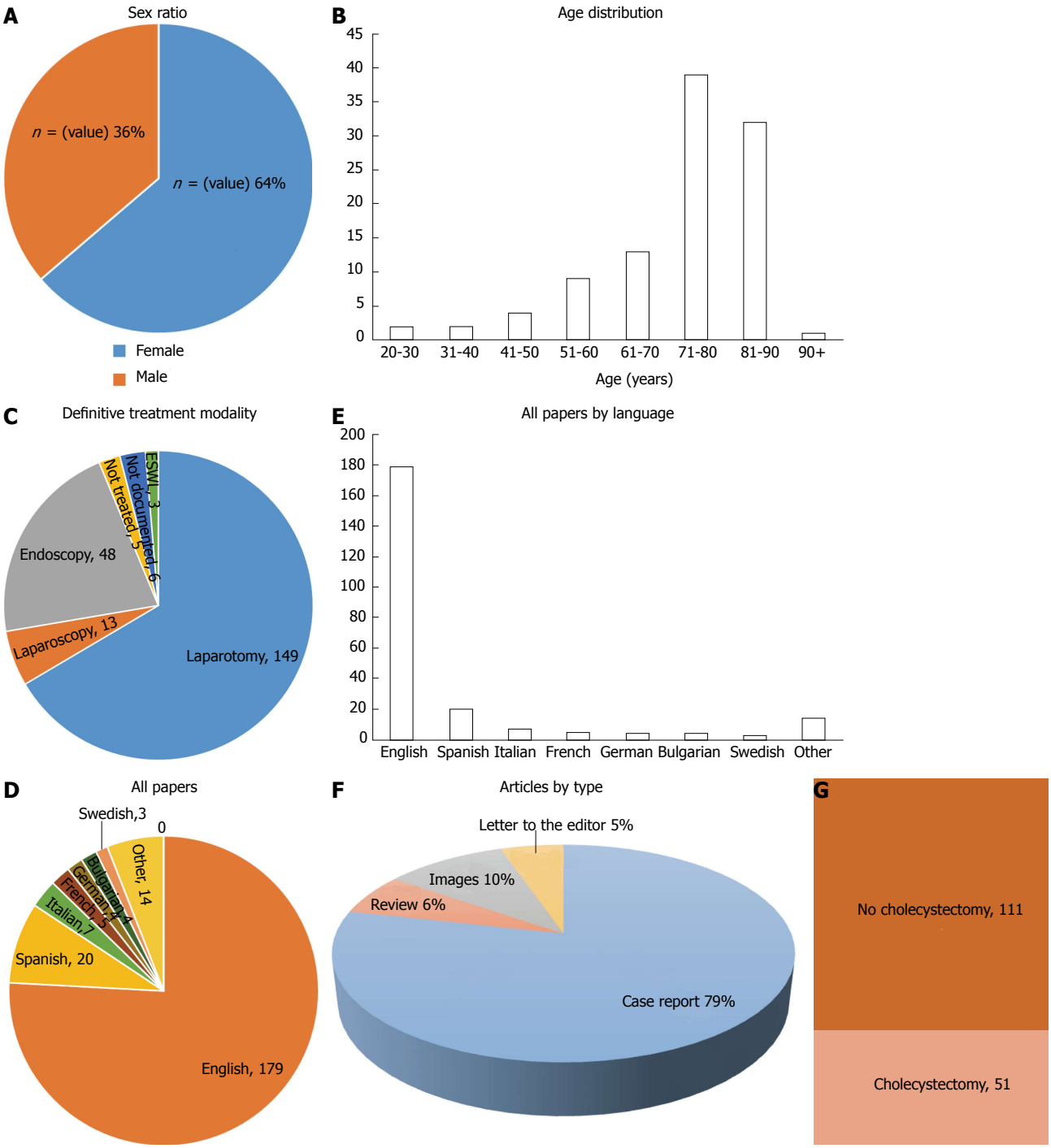

Figure 1 MEDLINE and PubMed searches were performed for the terms Bouveret's syndrome. A: Sixty-four percent of the identified cases in the literature were female; B: Bouveret's syndrome is more common in elderly patients, with the majority of cases occurring above 71 years of age; C: While some cases were successfully treated endoscopically, the majority of cases require open surgical management; D and E: Articles not in English were translated to English using dependable medical dictionaries; F: Results of the literatures; G: In patients receiving surgical stone retrieval, the majority did not receive a concurrent or delayed cholecystectomy.

still complaining of abdominal pain. An MRCP done at this point that showed more gallstones have fallen into the bile duct.

She underwent a laparoscopic cholecystectomy. The operation revealed adhesions between the gallbladder and distal stomach. No real fistular tract was seen, but dense adhesions were ligated by an Endoloop. Intra-operative cholangiogram confirmed bile duct stones. These were difficult to be retrieved by trans-cystic exploration. A laparoscopic bile duct exploration was performed. Several stones were successfully retrieved. Bile duct repaired primarily by 4/0 monofilament non-absorbable suture material. The postoperatrive course has been uneventful.

DISCUSSION

BS is a rare cause of gastric outlet obstruction caused

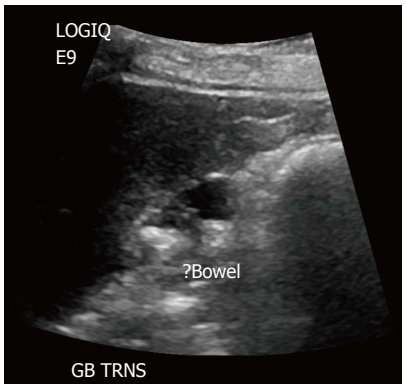

Figure 2 Common bile duct was 10 mm with mild intrahepatic biliary tree dilatation.

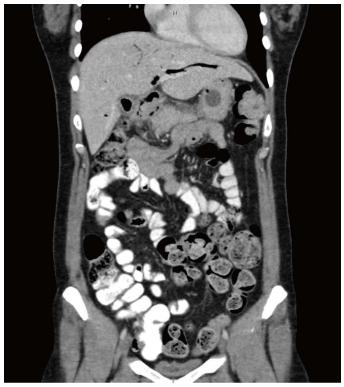

Figure 3 Coronal section of computed tomography scan.

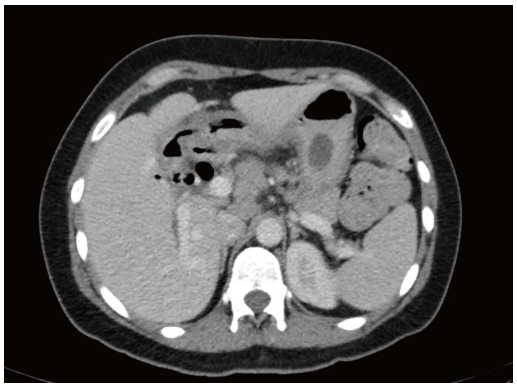

Figure 4 Cross section of computed tomography scan showing gallstone in the stomach and pneumobilia. The gallbladder is contracted and gas-filled.

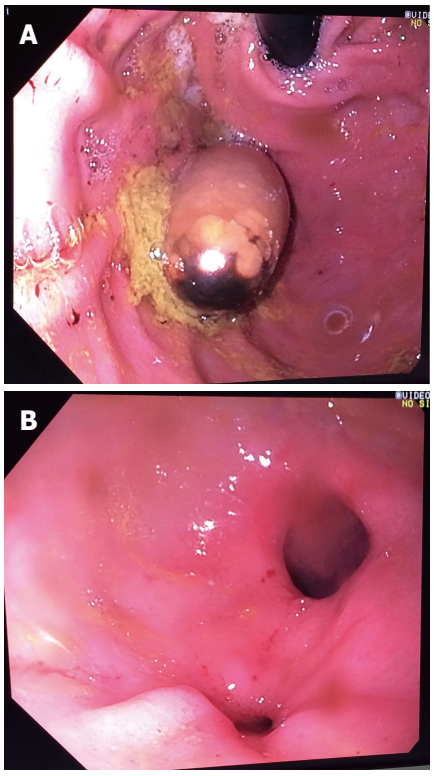

Figure 5 Upper gastrointestinal endoscopy confirmed the presence of gallstone in the stomach (A) and fistula orifice (B).

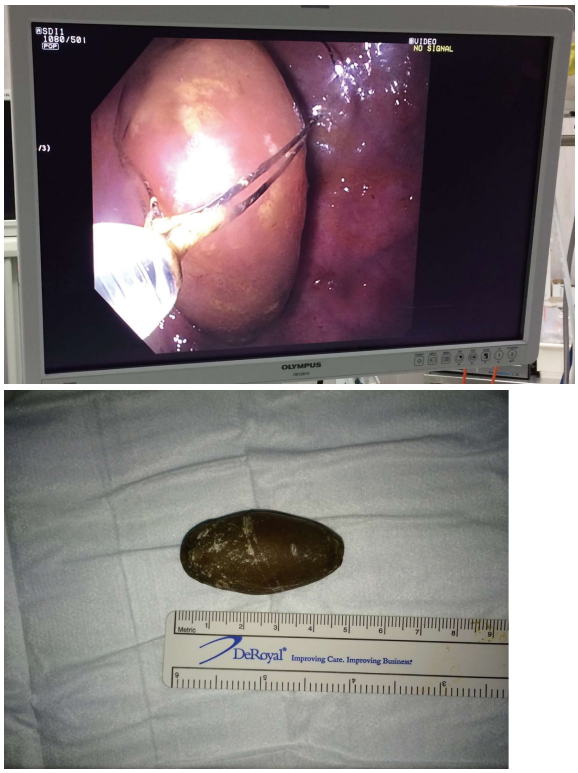

Figure 6 The stone was successfully retrieved by snare.

by gallstones. The stone(s) tend to migrate secondary to fistulation. The fistula can be cholecystogastric (less common) or more commonly, cholecystoduodenal. BS constitutes 1%-3% of cases of gall stone ileus which in turn complicates only 0.3%-4% cases of cholelithisasis[91,107]. BS can be associated with high mortality (up to 12%) mainly due to the frailty of patients[136]. The pathophysiology is usually caused by prolonged pressure, ischemia, and then fistulation and stone migration. The stone(s) then obstruct the gastric outlet or duodenum. A collection of small stones can produce the same picture[210]. Malignancy can also produce fistulation and stone migration. This has

been reported by Sharma *et al*[35] where the patient underwent laparotomy and stone extraction with gastro-jejunostomy to relieve the obstruction, while Shinoda *et al*[34] offered a curative cancer resection and fistula repair in a similar case of fistulating cancer.

In one interesting variant of BS, a patient presented with upper abdominal pain 10 years after Roux-en-Y Billroth Ⅱ resection for benign disease. A stone retrieved from the duodenum after laparotomy[64]. There have been a few cases in the literature where BS presented with pancreatitis[33,122]. The stone(s) can be lodged tightly in the duodenum causing necrosis and intra or extra-peritoneal perforation[109].

BS has been reported many times as a single case report. A few reports included more than one case[99,130,153,160,163,173,188]. These patients usually present with abdominal pain and vomiting as universally reported. There was one case in which the vomiting was severe to the point of causing Boerhaaves oesophageal rupture[63]. The diagnosis is usually late given the uncommon and vague nature of its symptoms. In about one-third of cases the diagnosis can be made by a plain abdominal film that demonstrates the classical Rigler's triad of a dilated stomach, pneumobilia, and a radio-opaque shadow in the region of the duodenum representing the ectopic gallstone[47,209-213]. There have been some reported cases of migrating stone into the mediastinum after relieving an obstructed duodenum of BS *via* endoscope[71]. Ultrasound can be helpful as indicated in some papers[184], but the study can be greatly degraded by the presence of gas in the biliary tree. Historical data shows that the diagnosis has only been made preoperatively in 50% of cases[80]. Due to the nearby inflammation, the gallbladder can be FDG/PET positive[178].

Spontaneous resolution can occur when the impacted stone falls back away from the pyloric orifice[16], but this can be associated with further bowel obstruction distal to the stomach and duodenum (gall stone ileus)[114,141]. On the other hand, the condition can be fatal due to the profound metabolic derangement[13], and later by sepsis and multi-organ failure[62].

In our review, the sex (female to male) ratio was (1.82), female being 64% and male being 36% (Figure 1A). Age distribution of these cases showed majority of cases being elderly patients above 60 years old with the average age of (74 ± 13), and minority less than 30 years old (Figure 1B).

There are multiple available treatment modalities. This includes laparotomy, laparoscopy, endoscopy and ESWL (Figure 1C). Majority of cases were treated with laparotomy and stone extraction through either an enterotomy or gastrotomy (146 cases, 71%). Successful laparoscopic treatment was also possible (13 cases, 6%). Some of patients had a radical procedure where the procedure was combined with cholecystectomy (51 cases, 25%), as illustrated in (Figure 1G). The advantages of doing cholecystectomy is not only removing the source of stones, but eliminating the theoretical carcinogenic risk of gastro-intestinal juices contacting the biliary tree[212]. Cholecystectomy has been described as a single procedure combined with fistula dissection and closure, or as a separate procedure done later on elective or semi-urgent basis (like our case).

With the recent advents in endoscopic technology, endoscopic treatment was tried in 160 cases (77%) and was successful in removing the stone in 46 cases of patients (29%). This was either through direct visualization and retrieval of the stone or combined with a lithotripsy method (laser, mechanical, shockwave). This is more than the reported 10% success rate in earlier narrative review of BS[168]. In recent years, therapeutic endoscopy has been more frequently and successfully used to extract the obstructing stone(s). This might be attributed to improved lithotripsy, better optical instruments and improved graspers and nets to extract gallstones.

Extracorporeal shock-wave lithotripsy (ESWL) has been described by Gemmel *et al*[115], Chick *et al*[181], Dumonceau *et al*[130] and Tanwar *et al*[23] which was successful combined with either endoscopy alone or laparotomy to remove stone fragments from distal bowels. Intracorporeal lithotripsy using water jet[6], or other mechanical methods[139], have been described.

It is estimated that up to 90% of patients will need some form of surgical intervention[173]. These interventions can vary but mainly depend on the patient's age and co-morbidities. The vast majority of these stones pass spontaneously without producing obstruction. Stones that obstruct the digestive tract are usually greater than 2-2.5 cm in diameter[175]. Cholecystostomy has been tried to treat associated cholecystitis but this has not been associated with a great deal of success[145]. Sometimes, to alleviate the obstruction and allow patients to eat and drink, an interim bypass procedure has been described[53]. Subtotal cholecystectomy and drain tube insertion is another option which is safe and successful[8,178].

A minority of cases in the literature were not treated due to either severely compromised patients or spontaneous resolution (5 cases, 2%). In addition, there were some reports where the treatment modality was not mentioned (6 cases, 3%).

After reviewing the (review) articles of BS, it was noted the majority of these reviews are more or less narrative reviews and not systematic, except three reviews[165,166,170]. A summary of these articles can be found in Table 1. There were issues with the previously done reviews being either limited to English language (thus excluding almost 15% of the literature) or incomplete not including all the papers. The limitation of our paper is the fact that we excluded 27 articles as we could not get them through multiple available channels. But almost all of these articles were published prior to 1995 and are case reports including single cases, or images for doctors.

Finally, the term pseudo BS has been used in the literature once to describe the condition of gall stones

Table 1 Review articles

Ref.	Year	No. articles	No. cases	Age (mean ± SD)	%Female	Endoscopy performed	Nonsurgical treatment success	Enterolithotomy	Cholecystectomy	Mortality/ major complications
Cappell *et al*[165]	2006	111	128	74.1 ± 11.1	65.10%	63%	18.00%	98/128 = 76.6%	40/98 = 40.8%	16/98 = 16.3%
Lowe *et al*[170]	2005	39	44	73 ± 13.5	68%	51%	13.60%	40/44 = 90.9%	36%	19%-24%
Frattaroli *et al*[166]	1997	79	79	68.6	65%	60%	14%	93%	Not reported	12%-33%

and gastric outlet obstruction due to external duodenal or pyloric compression (akin to Mirizzi's type I)[213].

In conclusion, with the current paucity of high level of scientific evidence about BS, the management remains highly arbitrary. Here we present a young patient with BS who failed conservative measures, and suggest a treatment algorithm for these patients. The management of this uncommon condition should be tailored to the patient's clinical presentation and morbidities. Perhaps a more radical treatment (which might include cholecystectomy) should be offered to young patients and patients with ongoing symptoms. Whenever possible, endoscopic approach should be offered first after immediate resuscitation, with stone extraction and lithotripsy as two options. If that fails, surgical management with enterolithotomy or gastrolithotomy depended on stone position. We do not recommend immediate cholecystectomy or fistula dissection as this can be associated with significant morbidity and mortality. Delayed cholecystectomy and fistula repair should be offered electively to patients with persistent symptoms or patients younger than 50 years old.

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COMMENTS

Background

Bouveret's syndrome (BS) is a rare complication of gallstone disease, where a gallstone erodes into the duodenum and causes gastric outlet obstruction following impaction in the stomach or duodenum. The stone must be removed to restore normal function of the gastrointestinal tract. This may be done *via* laparotomy or laparoscopic stone removal, or more recently, using lithotripsy with or without endoscopic retrieval to dislodge the stone.

Research frontiers

The literature surrounding BS is sparse and consists mainly of case reports and series. Reviews of these cases have been few and far between, with the most recent dating back to 2006. In this time, endoscopy, endoscopic interventions, and laparoscopy have improved, potentially offering new options for managing these patients.

Innovations and breakthroughs

In this study the authors systematically reviewed the published cases of BS from 1990 to the present. While laparotomy and laparoscopy were performed in a significant number of cases, endoscopic treatment has become much more successful with the advent of improved lithotripsy, improved endoscopic retrieval devices, and improved visualisation. Extracorporeal shockwave lithotripsy has also been successfully used in multiple cases.

Applications

They recommend that patients presenting with BS should be initially managed with attempted endoscopic retrieval, with or without lithotripsy, followed by open or laparoscopic surgical retrieval *via* enterotomy or gastrotomy if unsuccessful. In younger, healthier patients, a delayed cholecystectomy may be performed, however in older or multiply comorbid patients, this may be omitted from the treatment algorithm.

Terminology

BS is gastric obstruction due to an impacted gallstone in the duodenum or gastric outlet. Lithotripsy is the act of breaking a stone into multiple smaller pieces. This may be effected with extracorporeal shock waves, using a mechanical lithotripter, or a laser device.

Peer-review

In this systematic review, the authors have presented a thorough and critical analysis of the published cases of BS, and recommended an appropriate treatment algorithm for future cases.

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World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJGS covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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MINIREVIEWS

Enhanced recovery after surgery: Current research insights and future direction

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Abstract

Since the concept of enhanced recovery after surgery (ERAS) was introduced in the late 1990s the idea of implementing specific interventions throughout the peri-operative period to improve patient recovery has been proven to be beneficial. Minimally invasive surgery is an integral component to ERAS and has dramatically improved post-operative outcomes. ERAS can be applicable to all surgical specialties with the core generic principles used together with added specialty specific interventions to allow for a comprehensive protocol, leading to improved clinical outcomes. Diffusion of ERAS into mainstream practice has been hindered due to minimal evidence to support individual facets and lack of method for monitoring and encouraging compliance. No single outcome measure fully captures recovery after surgery, rather multiple measures are necessary at each stage. More recently the pre-operative period has been the target of a number of strategies to improve clinical outcomes, described as prehabilitation. Innovation of technology in the surgical setting is also providing opportunities to overcome the challenges within ERAS, *e.g.*, the use of wearable activity monitors to record information and provide feedback and motivation to patients peri-operatively. Both modernising ERAS and providing evidence for key strategies across specialties will ultimately lead to better, more reliable patient outcomes.

Key words: Enhanced recovery after surgery; Laparoscopic surgery; Prehabilitation; Outcome measures; Technology

Core tip: Enhanced recovery after surgery (ERAS) together with laparoscopic surgery improves clinical outcomes in patients post-operatively. Prehabilitation is gaining evidence as a further method of enhancing post-operative recovery. Pre-operative programmes to improve physical function have been used and we review this early literature as well as some current issues within ERAS. Technology, which is already in use in the peri-operative period for interventions and

monitoring could be used to further complement ERAS. Small, non-invasive devices which can monitor activity levels could help monitor compliance and post-operative patient activity levels as well as act as an intervention to encourage patients to increase their physical activity and thereby their post-operative outcomes.

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INTRODUCTION

The concept of enhanced recovery after surgery (ERAS) was initially proposed by Kehlet[1] who explored the possible determinants of post-operative morbidity in the late 1990s. He identified potential risk factors that needed to be recognised and treated peri-operatively to minimise the effects of surgical stress on the patient. He also championed the idea of working within a multi-disciplinary framework. Together these have led to a series of interventions which have been formulated into standardised protocols to span a patient's entire journey through the surgical process with distinct elements in the pre-operative, intra-operative and post-operative phase (Table 1).

Colorectal surgery was the first specialty to implement ERAS in the early 2000s. Early studies proved feasibility and demonstrated that patients benefited from shorter length of hospital stay and reduced post-operative ileus and cardiopulmonary complications, compared with standard care[2-4]. ERAS has also been shown to be feasible and safe in the emergency colorectal setting, leading to shorter length of stay and faster recovery of bowel function[5].

A 2012 consensus review of ERAS guidelines for colonic surgery examined the evidence base for each ERAS intervention and provided graded recommendations[6]. Though given strong recommendation grading, not all the interventions have high levels of evidence for their efficacy (Table 2).

Minimally invasive surgery is one element that has been strongly recommended with a high level of evidence for oncological outcomes and moderate evidence in terms of patient recovery.

ERAS and laparoscopic surgery

Minimally invasive surgery has been shown to reduce post-operative pain, length of hospital stay and complications[7-9]. Recent studies have examined the use of laparoscopic techniques within an enhanced recovery programme. For example, the LAFA-study[10] showed that laparoscopic surgery, as part of an enhanced recovery programme, significantly shortened length of hospital stay compared with open surgery. Other outcomes including morbidity, readmission rates and quality of life were similar between the groups. The EnROL Trial[11] found a statistically significant difference between length of hospital stay and 30 d readmissions favouring the laparoscopic group compared with the open surgery group, but no differences between groups for physical fatigue or other secondary outcomes.

Newer minimally invasive techniques in the form of single incision laparoscopic surgery (SILS), robotic surgery and natural orifice transluminal endoscopic surgery have recently emerged. Although still in the early stages with ongoing research in progress, SILS has been shown to reduce conversion rate to laparotomy and reduce length of hospital stay[12]. Robotic surgery has advantages over purely laparoscopic surgery including the ability for seven degrees of freedom and tremor filtration which could benefit more demanding surgery, *e.g.,* rectal resections. Robotic surgery has been shown to be both safe and feasible with short term outcomes comparable to conventional laparoscopic surgery but longer operative time and higher costs[13,14]. ROLARR (Robotic *vs* Laparoscopic Resection for Rectal cancer) is an RCT which aims to compare the benefits of robotic *vs* laparoscopic surgery, the results of which have not yet been published.

The ultimate benefits of laparoscopic surgery and ERAS are essentially the same; improved outcomes and faster recovery. Given that laparoscopic surgery has been shown to improve outcomes both separately from, and as a part of ERAS, it can be seen as a significant and integral component to any ERAS protocol where minimally invasive surgery is applicable.

Specialty specific ERAS

The principles of ERAS have been adopted by most specialties, each formulating their own specific protocols and guidelines. The generic overarching ideas of pre-operative, intra-operative and post-operative elements are included, but the actual interventions and evidence base are specialty specific. Specialties with similar operative procedures, *i.e.*, those within the lower abdominal/pelvic cavity, tend to have similar elements within their protocols, for example colonic surgery[6] and gynaecological oncology surgery[15,16] recommend no pre-operative bowel preparation, avoidance of nasogastric tube insertion and use of minimally invasive surgical techniques when expertise is available. Similar recommendations exist for urological surgery[17], however long-term oncological results following use of minimally invasive techniques are still awaited.

A review of enhanced recovery in pancreatic surgery highlighted placement of intraperitoneal drains as a controversial and highly debated element within ERAS protocols for pancreatectomy[18]. Intraperitoneal drains have been used historically to help in the recognition of a pancreatic fistula or anastomotic leak. This leak of pancreatic fluid can cause erosion of vessels, haemorrhage and sepsis. A recent meta-analysis concluded that those patients without drains had higher mortality

Table 1 An example of a generic enhanced recovery after surgery protocol

Pre-operative	Intra-operative	Post-operative
Pre-admission counselling	Short acting anaesthetic agents	Mid-thoracic epidural anaesthesia
Fluid and carbohydrate loading	Mid thoracic epidural anaesthesia	No Nasogastric tubes
No prolonged fasting	No drains	Prevention of nausea and vomiting
No/selective bowel preparation	Avoidance of salt and water overload	Avoidance of salt and water overload
Antibiotic prophylaxis	Maintenance of normothermia	Early removal of catheter
Thromboprophylaxis		Early oral nutrition
No Premedication		Early mobilisation
		Non-opioid oral analgesia
		Stimulation of gut motility
		Audit of compliance and outcomes

Table 2 Enhanced recovery after surgery society recommendations for colonic surgery and their evidence level[6]

ERAS element with high/moderate level evidence	ERAS element with low level evidence
Stopping smoking 4 wk prior to surgery	Pre-operative information and counselling
No routine use of bowel preparation	Stopping drinking alcohol 4 wk prior to surgery
Allowing clear fluids up until 2 h before and solids 6 h before anaesthetic induction	Peri-operative oral nutritional supplements and carbohydrate loading
No routine use of sedative premedication	Standard anaesthetic that allows rapid awakening
Routine thromboprophylaxis	Post-operative nausea and vomiting prophylaxis
Antimicrobial prophylaxis and skin preparation	Routine urinary drainage
Balanced intravenous fluids guided by flow measurements	Using stress reducing elements of ERAS to minimise hyperglycaemia
Use of mid thoracic epidural blocks in open surgery	Early mobilisation
Us of spinal analgesia or PCA in laparoscopic surgery	
Laparoscopic surgery	
No routine use of nasogastric tubes	
Maintenance of normothermia	
No routine intra-abdominal drains	
Early post-operative enteral feeding	
Insulin treatment of severe hyperglycaemia in ICU	
Use of chewing gum to prevent post-operative ileus	

ERAS: Enhanced recovery after surgery; PCA: Patient controlled analgesia; ICU: Intensive care unit.

but lower overall complications[19]. Current ERAS guidelines recommend systemic post-operative drainage with early removal in patients at low risk of pancreatic fistula, but these recommendations could change as further evidence is highlighted in future studies[20]. Within bariatric surgery pre-operative factors have been suggested to have important post-operative benefits, these include pre-operative weight loss, pre-operative exercise and adequate nutritional supplementation[21]. Studies have shown that pre-operative weight loss is a positive predictor of post-operative weight loss[22]. Together with adequately improving known nutritional deficiencies, which are common in obese patients, these elements seem essential additions to any bariatric ERAS protocol.

Other specialty specific elements include pre-operative respiratory physiotherapy prior to thoracic surgery[23]. This improves exercise capacity and lung function in patients who will lose lung volume after surgery. Use of pre-emptive analgesia and local anaesthetics infiltration within orthopaedic surgery is thought to allow early mobilisation and increased limb movement secondary to decreased somatic sensation[24,25].

Using generic elements as a basis for specialty guidelines with added specific interventions allows for a more comprehensive ERAS protocol with improved outcomes and recovery for each specialty.

CURRENT RESEARCH INSIGHTS AND CHALLENGES

Barriers to the implementation of ERAS

Despite the evidence of improved post-operative outcomes and recovery, ERAS implementation varies in different centres. McLeod *et al*[26] reported that of the 18 specific ERAS guideline recommendations, only two reached a compliance rate of greater than 75%. Pędziwiatr *et al*[27] implemented an ERAS protocol over a period of time and found that although only 65% compliance was reached for the first cohort, compliance rose to 89.6% by the third cohort, *i.e.*, a gradual improvement was shown over time. Recently the ERAS Compliance Group found that ERAS protocol compliance in elective colorectal cancer resections were around 75%, but there was variation between centres and elements[28]. Compliance with ERAS protocols was associated with better outcomes and exhibited a form of "dose-dependency" whereby, as compliance increased, complications decreased. Laparoscopic surgery and balanced intravenous fluid therapy were

specifically shown to be associated with a reduced risk of complications.

Certain elements are easier to implement than others, for example if they already form part of routine practice, *e.g.,* prophylactic antibiotics, thromboprophylaxis and using minimally-invasive techniques. Some elements are more difficult to implement despite increased efforts[27], including: No bowel preparation, early urinary catheter removal, no opioids and restrictive fluid therapy. An early study into ERAS protocol compliance indicates that compliance with post-operative factors significantly influenced outcomes[29], but it was difficult to determine which specific elements had an independent influence on outcomes. Conversely, a review by Ahmed *et al*[30] found that studies achieved similar outcomes despite not including all components of recommended ERAS protocols. Furthermore, a systematic review[31] looking at RCTs of ERAS *vs* standard care was unable to show that ERAS protocols with more elements were more successful than those with fewer elements.

Given the barriers to implementation and the difficulty in determining the relative importance of each individual component within the ERAS protocol the idea of a flexible and individualised method rather than a rigid protocol has been postulated, with each centre and hospital determining which elements to include for their specific protocols[29,31,32]. Factors thought to encourage the implementation of ERAS and improve compliance include; appointment of specific ERAS coordinators, use of engaged multidisciplinary teams, specific ERAS units/wards, specific teaching sessions about the benefits of ERAS and regular auditing[27,29,30].

Whichever elements are included, auditing compliance with the ERAS protocol, as well as measuring patient outcomes, form an essential part of the ERAS audit cycle[6].

Outcome measures

The impetus behind ERAS is improving post-operative recovery therefore it is necessary to measure recovery objectively. Many outcome measures have been used, yet the most frequently reported is length of hospital stay[33]. However, this surrogate measure of recovery can be influenced by external circumstances, for example patients' expectations of discharge date, social or support networks not being in place or even hospital administration issues with inability to process discharge summaries or dispense necessary medications. Furthermore, despite meeting the necessary clinical markers required for discharge, *e.g.,* blood tests and physiological observations, the patient is unlikely to be back to their functional baseline, since hospital discharge is based on the patient being safe to convalesce in the community. Other clinical outcomes studied include thirty-day mortality, thirty-day re-admission and post-operative complications[34,35]. These outcomes are often recorded as part of the clinical notes and can be used in conjunction with length of hospital stay. However, they only offer insight into the major complications or post-operative issues in patients who are readmitted or treated. There is little information to represent how patients are recovering at home in the long term.

Since 2009 the NHS in the United Kingdom has invited patients to fill in a patient reported outcomes questionnaire after hip replacement, knee replacement, groin hernia and varicose vein surgery. Such questionnaires measure a patient's health status and health related quality of life at a single point in time is collected before and after the procedure. This has been introduced to provide an indication of the quality of care being delivered. These outcome measures are more patient-focused, relating to daily living within their own environment and their return to normal function. King *et al*[33] assessed the influence of an ERAS protocol on quality of life. A validated QOL questionnaire (EORTC QLQ-C30) was used by patients undergoing surgery with an ERAS protocol compared to a historic control group. No statistically significant difference between the two groups in terms of quality of life was found. Another study measured post-operative fatigue as a long-term outcome to compare ERAS *vs* conventional care[36]. It was shown that post-operative fatigue levels increased in both groups significantly, which reached a maximum level just before discharge. However, the peak level reached was significantly smaller in the ERAS group. They also exhibited a significantly smaller Fatigue Consequence Score during the first thirty post-operative days. More recently proponents of ERAS have started to focus research on the theme of patient experience[37], and qualitative studies undertaken have highlighted areas for improvement including post-discharge support and follow-up[38].

Another consideration is the economic potential of ERAS. Studies have shown that implementing an ERAS protocol is cost effective[39]. Recent systematic reviews by Lemanu *et al*[40] and Lee *et al*[41] note however, that there are few RCTs documenting cost data, there are inconsistencies in the reporting of cost data, and suggest the need for well-designed trials in order to fully determine the true cost-effectiveness of ERAS.

A recent systematic review by Neville *et al*[42] aimed to identify useful recovery parameters within ERAS, noting that validated outcome measures were lacking for this complex recovery process. It was found that multiple different outcome measures are in use and that they tend to reflect short term recovery focusing on biological and physiological outcomes. The paucity of outcomes in the longer term was highlighted, for example few studies actually report any outcomes after thirty days post-surgery. A suggestion has been made for longer-term follow-up for post-surgical patients with a focus on patients' functional status including physical activity measurement and exercise capacity to help quantify recovery more fully. Another review by Feldman *et al*[43] postulates that phases of recovery overlap and cannot be defined as a single event within a specific time frame. This means that different outcome

measures are relevant at different time periods, but that no single outcome measure is perfect to quantify total recovery. Instead, a core set of outcome measures for each stage of recovery is proposed which reflect the perspectives of each member of the multi-disciplinary team as well as the patient.

It is now clear that different outcomes are relevant at different stages of the recovery process. One measure of recovery that is poorly represented by current outcome measures is physical activity. This is an important indicator of functional recovery both in hospital and back at home whilst convalescing. There is a potential to fill this gap by providing means of continual measurement in a non-invasive and objective manner.

Prehabilitation

Physiotherapy and mobilisation recommendations are frequently given in the post-operative period with a view to improving recovery and function. However, physical "conditioning" prior to operative stresses have been considered with the idea of enhancing patients' functional capacity and thus improving outcomes post-operatively[44,45]. For example, studies have implemented pre-operative exercise regimens and assessed subsequent post-operative functional activity and outcomes[46].

However, the benefit of prehabilitation is uncertain with systematic reviews reporting contradictory evidence. The review by Valkenet *et al*[47] included twelve studies [orthopaedic surgery, cardiac surgery and open abdominal aortic aneurysm (AAA) repair]. The risk of developing post-operative pulmonary complications was lower in those patients receiving inspiratory muscle training prior to cardiac and AAA surgery (RR = 0.40, 95%CI: 0.23-0.72). Conversely, there was no significant difference between post-operative complication rates or length of stay in joint replacement surgery. Lemanu *et al*[48] included eight studies in their review (cardiothoracic surgery, abdominal surgery and orthopaedic surgery), which found that there was poor adherence with the prehabilitation interventions with little evidence of physiological and clinical outcome improvements. One review focused more specifically on total body exercise as a prehabilitation intervention[49]. In this review of twenty one studies, improvements were seen in post-operative pain, length of stay and physical function in those undergoing the prehabilitation intervention. These differing conclusions may be due to the heterogeneity of the included studies with different physiological outcomes recorded and different prehabilitation interventions being used.

A tri-modal prehabilitation intervention was used in a randomised controlled trial with patients undergoing colorectal resection[44]. The intervention consisted of fifty minutes' total body exercise, alternating between aerobic and resistance training three times a week, nutrition counselling with protein supplementation and provision of stress reducing strategies. The trial found that the prehabilitation group had increased functional walking capacity both pre-operatively and at eight weeks post-operatively compared with the rehabilitation group. There was no difference in self-reported physical activity, health related quality of life, thirty day complications, anxiety or depression between groups.

The evidence for prehabilitation is in its preliminary stages, with mainly low powered, observational studies. It is difficult to quantify or characterise the benefits of a prehabilitation programme, or indeed which interventions should be included. Randomised controlled trials looking at prehabilitation in colorectal cancer patients[50] and in vascular patients undergoing elective abdominal aortic aneurysm repair[51] are currently underway, which will help towards informing the decision of whether or not prehabilitation should become part of the ERAS protocol.

FUTURE DIRECTIONS

Use of technology

A variety of technologies have been used within the peri-operative period as helpful adjuncts within ERAS, for example oesophageal Doppler for monitoring fluid balance[52], pneumatic calf compression to provide thromboprophylaxis[53] and the use of forced air warming units to maintain normothermia[54]. Furthermore, recent advances in technology have led to the emergence of small, wearable sensors that can measure, store and transmit large amounts of patient and environmental data[55,56]. These sensors have been used to objectively and continuously monitor physical activity in the home environment following discharge from hospital[57] and within the hospital setting[58].

Studies in the early post-operative period have offered insight on patient mobility and functional recovery[59]. Cook *et al*[60] monitored patient steps after elective cardiac surgery. An association was found between number of steps taken by a patient and their length of hospital stay and post-operative discharge destination. Wasowicz-Kemps *et al*[61] measured daily physical activity following laparoscopic cholecystectomy in a controlled study where advice was given to resume normal activity quickly following their operation. Recovery to baseline daily activity took more than one week in 64% of patients but women in the intervention group resumed normal daily activity quicker than those in the control group. One study comparing laparoscopic *vs* open distal gastrectomy used an objective physical activity monitor to evaluate post-operative recovery[62]. Recovery of activity on each post-operative day was higher in the laparoscopic group. Studies assessing longer term physical activity monitoring[63,64] have shown this is both feasible and beneficial for collecting data on longer-term outcomes.

Providing feedback on activity levels to participants has been shown to increase physical activity in a randomised controlled trial in young healthy Finnish men[65]. A randomised controlled trial assessing interventions for patients with intermittent claudication[66]

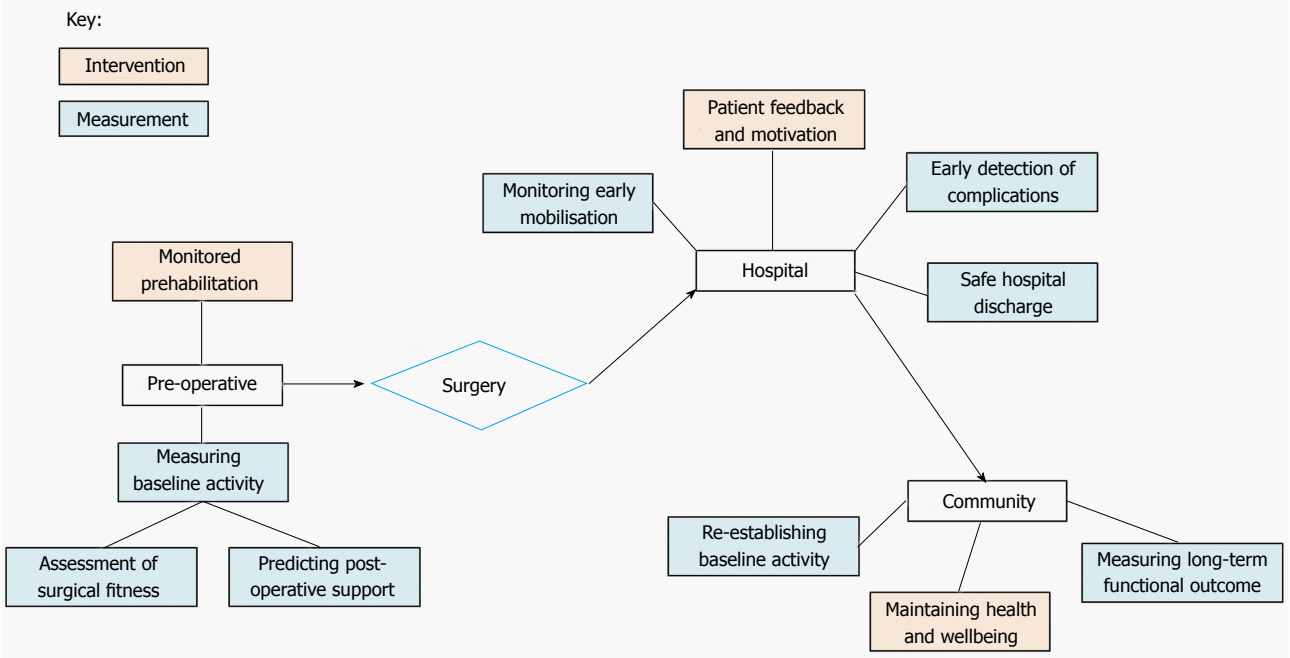

Figure 1 Uses of physical activity monitoring in the peri-operative period. Multiple opportunities exist for implementation of activity monitors in the peri-operative period. Pre-operatively, this includes the assessment of surgical fitness, and guiding a prehabilitation programme. Post-operatively there are multiple options for intervention and measurement in the hospital setting, as well as longer term assessments of functional outcome and encouraging an active lifestyle for overall physical and mental wellbeing.

Table 3 Additional enhanced recovery after surgery elements using sensor technology

Additional ERAS element	What this adds
Pre-operative physical activity monitoring	Measuring patient's baseline function to assess for surgical fitness and to predict support required post operatively
Prehabilitation	Exercise training prescribed to patients to improve their baseline functional capacity, together with nutritional advice and psychological support
Post-operative physical activity monitoring	Providing feedback to clinicians of patient recovery, monitoring compliance with mobilisation recommendations and picking up complications/allowing safer hospital discharge
Activity feedback	Providing motivation to patient to encourage them to mobilise in the initial post-operative phase, thereby reducing complications and enhancing recovery

ERAS: Enhanced recovery after surgery.

showed that wearing a feedback-enabled physical activity monitor improved claudication and walking distance as well as quality of life scores at three months.

There is therefore the potential to use sensor technology to complement and augment ERAS, leading to improved patient experience and outcomes. Knowing patients' pre-operative activity levels might correlate to their baseline function and wellbeing, which could provide an indication of anticipated support the patient may require post-operatively. Monitoring physical activity in the hospital post-operatively can help monitor compliance with post-operative mobilisation recommendations as well as measure inpatient activity providing an indication of functional recovery and screening for complications. Over time, monitoring physical activity unobtrusively can give useful long-term outcome measures that truly reflects a patient's recovery in the community[67]. Activity feedback to patients both in hospital and in the community may help to encourage an increase in their activity levels, as well as motivate them to be more engaged in their own recovery and care (Figure 1).

Sensor technology could, therefore, help overcome the current barriers to ERAS and help assess and improve patient outcomes and experience throughout the surgical period, in keeping with Kehlet's initial ERAS concept. Additional elements to add to specialty specific protocols could include pre-operative activity monitoring, prehabilitation and post-operative activity monitoring with feedback (Table 3).

CONCLUSION

Enhanced recovery after surgery is an evolving principle that aims to improve patient outcomes following surgery, with minimally-invasive surgery as an integral core. Current problems that are being discussed by ERAS proponents include barriers of implementation

of ERAS protocols and the difficulty of measuring post-operative outcomes and improvements. Evidence for prehabilitation is being explored in randomised controlled trials, as initial studies are contradictory and based on observational studies with few participants. Technological advances have enabled wearable devices to continuously and objectively collect data about the wearer's well-being. This could provide an opportunity to assess ERAS compliance, monitor patient outcomes and offer a variety of promising therapeutic interventions.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Perinatal risk factors in newborns with gastrointestinal perforation

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Abstract

AIM

To investigate correlation of perinatal risk factors in newborns with gastrointestinal perforation (GIP).

METHODS

Single-center retrospective cohort study was conducted between January 1990 and December 2012. Medical records on all newborns with GIP were reviewed (n = 35). Surgical records and histopathologic examination of all perforated intestine samples were also reviewed.

RESULTS

The most common cause of GIP was necrotizing enterocolitis (51.4%). The most common site of perforation was large intestine. Mortality rate was 31%. Infants with GIP more frequently had very low birth weight (< 1500 g), especially birth weight below 10th percentile

according to gestational age. Ponderal index was not differing between infants with GIP and control subjects. In infants with GIP anemia was more frequently found than in control group.

CONCLUSION

GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia.

Key words: Gastrointestinal perforation; Newborn; Necrotizing enterocolitis; Ponderal index

Core tip: Gastrointestinal perforation (GIP) in newborns is a severe and life threatening condition associated with high mortality. GIP usually occurs in prematures with necrotizing enterocolitis. GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia. The most common site of perforation was large intestine Mortality rate was 31%. Infants with GIP more frequently had very low birth weight (< 1500 g), especially birth weight below 10th percentile according to gestational age.

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INTRODUCTION

Gastrointestinal perforation (GIP) in newborns is a severe and life threatening condition associated with high mortality of 17%-60%[1-4]. GIP usually occurs in prematures with necrotizing enterocolitis[1-11]. The major causes of GIP are low gestational age, low birth weight, feeding with adapted formulas instead of breastfeeding, early and fast increase in meal volume, bacterial colonization and intestinal ischemia[5,6].

Although most frequently observed in prematures, necrotizing enterocolitis also occurs in term newborns. In the latter, it is clearly associated with perinatal factors, *i.e.,* intrauterine drug exposure, in particular cocaine, in mothers drug addicts; intestinal anomalies (aganglionosis or atresia); congenital heart disease; sepsis; polycythemia; asphyxia; respiratory distress syndrome; presence of umbilical catheter; and exsanguinotransfusion. These factors can affect blood flow through the mesenteric blood vessels of the newborn and lead to hypoperfusion and consequential intestinal hypoxia[7,8]. In prematures, necrotizing enterocolitis mostly develops in the second week of life, whereas in term newborns it usually occurs earlier, *i.e.,* in the first week of life[7,9,10].

Spontaneous intestinal perforation is a specific clinical entity that should be differentiated from necrotizing enterocolitis. Spontaneous intestinal perforation is a multifactorial disease of very low birth weight infants (< 1000 g), which is not related to the mode of feeding. Local intestinal ischemia is considered to be the major risk factor for the occurrence of spontaneous intestinal perforation. In addition, the following risk factors have hitherto been associated with spontaneous intestinal perforation: Neonatal hypotension, umbilical arterial catheter, dehydration, indomethacin and steroids[11,12]. The less frequent causes of perforation include intestinal obstruction, idiopathic gastric perforation and iatrogenic perforation[12-15].

To the best of our knowledge, ponderal index has not yet been assessed relative to the occurrence of GIP. Studies suggest low ponderal index or lean neonates to have been exposed to hypoxic-ischemic events during gestation, which then results in increased perinatal mortality and morbidity, in particular a higher prevalence of perinatal infection[16].

The aim of the study was to assess the correlation of ponderal index and other risk factors with GIP; the prevalence of GIP (according to causative disorder and site of perforation); and GIP mortality (according to causative disorder and site of perforation).

MATERIALS AND METHODS

Medical records of infants born at the niversity Hospital of Split from January 1, 1990 till December 31, 2012 were reviewed. There were 103852 live births, 5193 (13%) of them were prematures. Study group included 35 newborns (19 males, 16 females) with confirmed GIP, gestational age 25-40 wk. Control group comprised of all newborns admitted immediately before or immediately after study group subjects, matched by no more than plus or minus one gestational week (n = 76), free from neonatal intestinal perforation. Study group was compared to control group matched by gestational age (case-control study).

The following perinatal risk factors were observed: maternal age and parity; maternal edema, proteinuria, hypertension (EPH) gestosis-preeclampsia; prolonged amniotic sac rupture; fetus presentation; method of delivery termination; neonate sex; Apgar score at 1 min; birth weight (BW); birth length (BL); and ponderal index.

Considering particular population specificities for birth weight determination according to gestational age, sex and maternal parity, percentile curves developed for our population at the Department of Gynecology and Obstetrics, University Hospital of Split in 2005 were used[17,18]. Ponderal index (PI) was determined for each study subject using the following formula: PI (g/cm^3) = 100 × BW (g)/BL (cm^3).

The following postnatal risk factors were also ob-

Table 1 Perinatal risk factors *n* (%)

Perinatal risk factor	GIP *n* = 35	Control group *n* = 76
Maternal age (years, min-max)	26 (18-44)	28 (18-41)
Maternal parity		
Primipara	20 (58.8)	35 (46.7)
Secundipara	10 (29.4)	27 (36.0)
Multipara	4 (11.7)	13 (17.4)
EPH gestosis-preeclampsia	5 (15.2)	2 (2.6)
Prolonged membrane rupture	5 (15.2)	13 (17.1)
Breech presentation	5 (15.2)	7 (9.2)
Cesarean section	11 (32.4)	17 (22.4)
Sex (male)	19 (54.3)	38 (50.0)
Apgar score at 1 min		
0-3 (severe hypoxia)	2 (5.9)	1 (1.3)
4-7 (moderate hypoxia)	13 (38.2)	23 (30.3)
8-10 (normal vitality)	19 (55.9)	52 (68.4)
Birth weight (BW)		
< 1500 g (very low BW)	8 (22.9)	7 (9.2)[a]
1500-2499 g (low BW)	4 (11.4)	24 (31.6)
⩾ 2500 g (normal BW)	23 (65.7)	45 (59.2)
Birth lenght (cm)	47 (34-53)	48 (32-55)

[a]$P < 0.05$ (χ^2-test). GIP: Gastrointestinal perforation; EPH gestosis: Edema, proteinuria, hypertension (EPH) gestosis.

served: Respiratory distress syndrome; presence of central venous umbilical catheter; sepsis; polycythemia; and anemia. GIP was demonstrated radiologically by visualizing free air intraperitoneally.

The risk factors for GIP were divided into perinatal and postnatal variables. Ponderal index was analyzed by *t* test; qualitative variables and maternal parity were analyzed by use of χ^2 test; and maternal age was analyzed by Mann-Whitney *U* test. Epidemiological measures of correlation or measures of relations, *i.e.*, odds ratio, was employed on assessing the power of statistical relationship between a particular risk factor and the disease (GIP) and on drawing conclusions on the potential causative relationship. An approximate risk for the occurrence of GIP was obtained by calculating the probability of a particular risk factor exposure in study subjects and control group. Then the 95%CI was calculated. All data were interpreted at the level of significance of $P < 0.05$.

The prevalence of GIP was calculated using the following formulas: (1) number of children with GIP/total number of live births × 1000; (2) number of children with GIP/number of children treated at clinical department × 1000; and (3) number of prematures with GIP/number of prematures × 1000.

Mortality following GIP shows the ratio of newborns with GIP that died during the neonatal period (28 d) and total number of newborns with GIP. Neonatal mortality due to GIP was determined according to the cause and site of GIP.

RESULTS

During the 22-year study period, there were 103852 live births at the University Hospital of Split, and 5193 of them were preterm infants. During the study period 35 patients with GIP were identified, yielding a 0.34‰ GIP incidence and 3.66‰ incidence of prematures in overall live births. The matched control group consisted of 76 infants. The study and control infants were matched for gestational age.

Table 2 Number (%) of newborns according to ponderal index mean value: arithmetic mean ± SD, birth weight and birth length percentiles

Variable	GIP *n* = 35	Control group *n* = 76
PI, mean ± SD, g/cm^3	2.53 ± 0.3	2.52 ± 0.3
BW, %		
SGA (< 10th percentile)	31.4	13.2[a]
AGA (10th-90th percentile)	51.4	77.6
LGA (> 90th percentile)	17.1	9.2
BL, %		
< 10th percentile	18.2	9.2
10th-90th percentile	66.7	84.2
> 90th percentile	15.2	6.6

[a]$P < 0.05$ (χ^2-test). SGA: Small for gestational age; AGA: Appropriate for gestational age; LGA: Large for gestational age.

Perinatal risk factors of 35 infants with GIP compared with control subjects are shown in Table 1. There were trends toward a higher incidence of male infants in the study group compared with control subjects. There were no differences between groups in prolonged rupture of membranes, method of delivery, presentation at delivery and Apgar score. Mothers were young in both groups (mean age 26 and 28 years in study group and control group, respectively) and tended to be primiparae. Mothers of infants suffering from GIP showed a trend toward increased pregnancy-induced hypertension, but the number of mothers with pregnancy-induced hypertension was too small for statistical analysis.

The mean values of ponderal index, and number and percentage of newborns according to birth weight and birth length percentiles *per* gestational age are shown in Table 2.

Infants suffering from GIP were significantly more likely to have birth weight less than 1500 g (22.9% *vs* 9.2%, $P < 0.05$) and birth weight below 10th percentile according to gestational age (31.4% *vs* 13.2%, $P < 0.05$). There was no statistically significant difference between groups in the mean value of ponderal index.

Table 3 shows postnatal risk factors in the both groups. More infants in the study group had anemia (25.7% *vs* 3.9%), yielding a statistically significant difference ($P < 0.05$).

Additional statistical tests of logistic regression and multiple logistic regressions were employed to confirm birth weight less than 10th percentile and anemia as risk factors for GIP. The results obtained by logistic regression are shown in Table 4.

The likelihood of GIP development was threefold greater in the group of hypotrophic for gestational age infants as compared with the group of eutrophic and

Table 3 Postnatal risk factors *n* (%)

Variable	GIP (*n* = 35)	Control group (*n* = 76)
RDS	13 (38.2)	29 (38.1)
RDS + mechanical ventilation	12 (35.3)	14 (18.4)
CVUC	5 (14.7)	9 (11.8)
Positive blood culture	4 (11.8)	11 (14.5)
Polycythemia[1]	5 (14.3)	6 (7.9)
Anemia[2]	9 (25.7)	3 (3.9)[a]

[1]Polycythemia was defined as hematocrit > 0.60; [2]Anemia was defined as hemoglobin level < 140 g/L in venous blood; [a]$P < 0.05$ (χ^2-test). RDS: Respiratory distress syndrome; CVUC: Central venous umbilical catheter.

Table 4 Logistic regression results *n* (%)

Risk factor	GIP *n* = 35	Control group *n* = 76	OR (95%CI)
Hypotrophy	11 (31.4)	10 (13.2)	3 (1.14-8)[a]
Eutrophy and hypertrophy	24 (68.5)	66 (86.8)	
With anemia	9 (25.7)	3 (3.9)	8.4 (2.1-33)[a]
Without anemia	26 (74.3)	73 (96.1)	

[a]$P < 0.05$.

Table 5 Multiple logistic regression results

Risk factor	OR	95%CI
Birth weight < 10th percentile for gestational age (hypotrophy)	4.01[a]	1.45-11.2
Anemia	10.9[a]	2.6-45

[a]$P < 0.05$.

hypertrophic for gestational age infants, with 95%CI. The probability of GIP was 8.4-fold greater in infants suffering from anemia as compared to those without anemia, with 95%CI. Multiple logistic regression confirmed both risk factors, *i.e.*, birth weight below 10th percentile for gestational age (hypotrophy) and anemia to be statistically significant for GIP development (Table 5).

The infants suffering from GIP were diagnosed mostly during the first 7 d (60%), and the age at diagnosis ranged from 1 to 25 d of life. Enteral feeding was started in 57.1% of case patients and in all matched control subjects.

All case patients underwent exploratory laparotomy, except one patient who underwent thoracotomy because of esophageal perforation. Stoma was established in 80% of patients. Direct suture was performed in five infants. The most common location of perforation was large intestine (45.7%), followed by ileum (20.0%), jejunum (11.4%), multiple perforation of both small and large intestine (11.4%), duodenum (5.7%) and esophagus in one patient (2.9%).

The causes of perforation were divided into four categories according to pathological and intraoperative reports. Necrotizing enterocolitis was the predominant cause of perforation (*n* = 18; 51.4%), followed by intestinal obstruction (22.9%), meconium plug (14.3%), spontaneous perforation (8.6%) and iatrogenic perforation of the esophagus (2.8%).

The overall mortality rate was 31.4% (during the neonatal period of 28 d). In the early study period (1990-2000), seven of 17 (41.2%) infants with GIP died, but later a considerably lower mortality rate was recorded, *i.e.*, four of 18 (22.2%) infants with GIP died in the 2001-2011 period. Most of these deaths were due to perforated necrotizing enterocolitis (63.6%), and the most common site among the expired was small bowel (36.4%).

DISCUSSION

According to available data, the prevalence of GIP is low. There are few studies addressing and assessing all causes of GIP and their interplay leading to this severe disorder. Asabe *et al*[3] found 34 cases of GIP during a 30-year period[3]. Khan *et al*[19] report on 89 cases of GIP that accounted for 16.5% of all newborns admitted to the Department of Pediatric Surgery. In their multicenter study, Calisti *et al*[4] recorded 85 cases of neonatal GIP in the region of Lazio, Italy, during a ten-year period. The authors estimate the prevalence of GIP in newborns treated at neonatal intensive care units to range between 1% and 3%.

In our study, necrotizing enterocolitis was the most common causative entity leading to GIP (51.4%), followed by intestinal obstruction (22.9%). This is consistent with literature data, where necrotizing enterocolitis is also reported as the most common cause of GIP[1-4,19,20]. A low prevalence of necrotizing enterocolitis (0.2%) has only rarely been reported[21]. According to the literature, spontaneous or idiopathic intestinal perforation has been postulated as the second leading cause of GIP, and less frequently meconium peritonitis[2-4,14]. Gastrointestinal obstruction as the cause of GIP is more common in term newborns. In our study, the rate of intestinal obstruction was high, as expected considering the high proportion of term newborns.

In our study, the most common site of GIP was large intestine (45.7%), whereas small intestine perforation was recorded in 37.1% of cases. In the literature, the most common site of GIP is small intestine, in particular distal ileum[22-24]. Colon perforation is considered a rare event; however, in a recent study, Sakellaris *et al*[25] found colon perforation in 18.5% of newborns. According to literature reports, colon perforation is more common in high birth weight newborns (> 2500 g), which predominated in our study sample (65.7%)[26].

Considering maternal characteristics, we found no statistically significant between-group difference in maternal age and parity. However, there are literature reports on the newborns with GIP to be born to young mothers (22 to 28 years on average) with a lower number of previous deliveries In our study, mothers in both case and control groups were young (26 and 28 years on average, respectively) and most of mothers in

both groups were primiparae[22,27].

In all previous studies, GIP was more common among male newborns, with a rate ranging from 59% to 89% of cases[5,6,19,22,24,27]. In our study, the rate of male newborns with GIP was 54.3%.

The group of newborns with GIP included a significantly higher proportion (22.9%) of very low birth weight (< 1500 g) infants. Literature reports reveal GIP to occur more frequently in very low birth weight newborns[4-6,10,20,22-24]. In our study, the group of newborns with GIP also included a high proportion of hypotrophic infants (31.4%). Thus, the likelihood of GIP was threefold greater in the group of hypotrophic infants as compared to other study subjects.

According to literature reports, intrauterine growth retardation (IUGR) leads to hypotrophy but has been rarely tackled specifically as a risk factor for GIP. Some studies dealing with IUGR failed to confirm its association with necrotizing enterocolitis or spontaneous intestinal perforation, whereas others compared case and control groups matched by gestational age and found IUGR to be a potential clinical risk factor for necrotizing enterocolitis as the most common cause of GIP[22,27,28]. Recently, however, there are ever more studies observing IUGR by fetal and neonatal blood flow Doppler monitoring. These studies recorded a higher prevalence of necrotizing enterocolitis in infants with impaired umbilical artery or superior mesenteric artery blood flow[29].

In our study, anemia was the major risk factor for GIP. The likelihood of GIP was 8.4-fold greater in neonates with anemia as compared with those without anemia. In the literature, anemia is sporadically associated with individual cases of GIP. Pelizzo *et al*[30] describe intrauterine anemia with consequential fetal hydrops and signs of meconium peritonitis caused by distal ileum perforation. On the other hand, others report on anemia detected by laboratory testing, along with thrombocytopenia and elevated C-reactive protein, in infants with GIP caused by necrotizing enterocolitis[31,32].

Recent studies confirm the association of deplasmatized red blood cell transfusion for anemia and necrotizing enterocolitis[33-35]. Other studies assessing the effect of administering erythropoietin and iron agents for anemia found a lower incidence of necrotizing enterocolitis[33]. In our study, anemia was an important risk factor for GIP; the more so, it also proved important for the prognosis after GIP. In more than half of the study subjects (54.5%) that died from GIP, anemia had been diagnosed even before the clinical signs of the diseases that caused GIP. In their recent study, Bracho-Blanchet *et al*[35] also identified anemia as a prognostic factor associated with mortality in newborns with necrotizing enterocolitis.

In our study, 57.1% of infants were fed per oral, as a rule with adapted formulas, until GIP onset. In necrotizing enterocolitis, perforation generally occurs upon switching to oral feeding[6]. It is considered that there is no causative relationship between oral feeding and spontaneous intestinal perforation. Ragouilliaux *et al*[22] report on enteral nutrition to have been introduced before the onset of GIP in 69% of newborns. As necrotizing enterocolitis was the most common cause of GIP in our study, the proportion of newborns on oral feeding before GIP occurrence was high, as expected.

Our study results showed that 31.4% of the newborns died from GIP. However, in the last 11 study years, the mortality was nearly half that recorded in the first 11 study years (22% *vs* 41%). Search of the literature yielded a mortality following GIP to range from 17% to 60%[2,4,19]. A 31.6% mortality rate has been reported for newborns with GIP in Japan in 2003. However, the same authors report on 50% mortality among 34 newborns during a 30-year period[3]. These figures correspond to the trend observed in our study on the mortality decline in the past decades. Advances in operative techniques, anesthesiology procedures and intensive care measures probably have contributed to the GIP mortality decline.

In our study, necrotizing enterocolitis was the most common cause of GIP in deceased infants (63.6%). Other studies also report on the highest mortality following GIP to be associated with necrotizing enterocolitis[2,19,25]. Although colon was the most frequent site of perforation, small intestine perforation was found in the majority of deceased neonates (36.4%). According to literature reports, the small intestine perforation mortality is also higher than colon perforation mortality[26]. Exploratory laparotomy is considered as the surgical method of choice in newborns with intestinal perforation, in particular the one caused by necrotizing enterocolitis. Most studies report on laparotomy with intestinal segment resection to be performed in all or nearly all infants with GIP[4,25]. Primary management with peritoneal drainage instead of laparotomy is less frequently described[19]. However, definite recommendations in favor of either laparotomy or peritoneal drainage are still lacking. In our study, percutaneous stoma after intestinal segment resection was established in 80% of newborns with GIP. According to literature data, stoma formation following resection is associated with better survival than primary anastomosis after resection[4,35].

In conclusion, Based on our study results, newborns with anemia and hypotrophic newborns, along with all very low birth weight newborns should be considered at high risk of GIP. The pattern of fetal growth (neonatal proportions, *i.e.*, birth weight to birth length ratio) as determined by ponderal index is not a risk factor for GIP development.

COMMENTS

Background

Gastrointestinal perforation (GIP) in newborns is mostly associated with necrotizing enterocolitis. Congenital anomalies with obstruction can also be the cause of GIP. There are little informations in literature about perinatal risk factors,

and ponderal index in infants with GIP has not been reported.

Research frontiers

A single institutional retrospective study of patients undergoing surgery because of GIP from 1990 to 2012 was performed.

Innovations and breakthroughs

GIP in newborns is mostly disease of infants with birth weight below 10th percentile according to gestational age. GIP occurs more often in infants with anemia.

Applications

Newborns with very low birth weight and anemia should be monitored carefully for GIP.

Terminology

Ponderal Index is a measure of leanness of a person calculated as a relationship between mass and height.

Peer-review

The manuscript is well written and important in its field.

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ORIGINAL ARTICLE

Retrospective Study

Critical analysis of feeding jejunostomy following resection of upper gastrointestinal malignancies

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Abstract

AIM

To assess nutritional recovery, particularly regarding feeding jejunostomy tube (FJT) utilization, following upper gastrointestinal resection for malignancy.

METHODS

A retrospective review was performed of a prospectively-maintained database of adult patients who underwent esophagectomy or gastrectomy (subtotal or total) for cancer with curative intent, from January 2001 to June 2014. Patient demographics, the approach to esophagectomy, the extent of gastrectomy, FJT placement and utilization at discharge, administration of parenteral nutrition (PN), and complications were evaluated. All patients were followed for at least ninety days or until death.

RESULTS

The 287 patients underwent upper GI resection, comprised of 182 esophagectomy (n = 107 transhiatal, 58.7%; n = 56 Ivor-Lewis, 30.7%) and 105 gastrectomy [n = 63 subtotal (SG), 60.0%; n = 42 total (TG), 40.0%]. 181 of 182 esophagectomy patients underwent FJT, compared with 47 of 105 gastrectomy patients (99.5% *vs* 44.8%, $P < 0.0001$), of whom most had undergone TG (n = 39, 92.9% *vs* n = 8 SG, 12.9%, $P < 0.0001$). Median length of stay was similar between esophagectomy and gastrectomy groups (14.7 d *vs* 17.1 d, $P = 0.076$). Upon discharge, 87 esophagectomy patients (48.1%) were taking enteral

feeds, with 53 (29.3%) fully and 34 (18.8%) partially dependent. Meanwhile, 20 of 39 TG patients (51.3%) were either fully (n = 3, 7.7%) or partially (n = 17, 43.6%) dependent on tube feeds, compared with 5 of 8 SG patients (10.6%), all of whom were partially dependent. Gastrectomy patients were significantly less likely to be fully dependent on tube feeds at discharge compared to esophagectomy patients (6.4% *vs* 29.3%, P = 0.0006). PN was administered despite FJT placement more often following gastrectomy than esophagectomy (n = 11, 23.4% *vs* n = 7, 3.9%, P = 0.0001). FJT-specific complications requiring reoperation within 30 d of resection occurred more commonly in the gastrectomy group (n = 6), all after TG, compared to 1 esophagectomy patient (12.8% *vs* 0.6%, P = 0.0003). Six of 7 patients (85.7%) who experienced tube-related complications required PN.

CONCLUSION

Nutritional recovery following esophagectomy and gastrectomy is distinct. Operations are associated with unique complication profiles. Nutritional supplementation alternative to jejunostomy should be considered in particular scenarios.

Key words: Feeding jejunostomy; Esophagectomy; Gastrectomy; Nutritional recovery; Outcomes

Core tip: Adequate nutrition following major upper gastrointestinal cancer resection is critical in order to achieve optimal recovery. However, feeding jejunostomy tube placement should not be considered obligatory as part of upper gastrointestinal resection. Alternative methods of nutritional supplementation are available and perhaps better-tolerated.

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INTRODUCTION

Upper gastrointestinal malignancy, comprised of esophageal and gastric cancer, represents nearly 42000 new diagnoses per year in the United States. These diagnoses carry a high disease-related mortality, causing an estimated 26000 deaths annually[1]. Patients with esophageal and gastric malignancies often present in a malnourished state, with significant unintentional weight loss a common sign of disease. Such weight loss has been associated with worse outcomes following resection[2]. Adequate nutrition for patients undergoing resection is critical in order to recover from the operation and to successfully undergo adjuvant therapy.

Nutritional support modalities include enteral nutrition *via* feeding tubes and parenteral nutrition (PN) *via* central venous catheters. Enteral feeding is preferred as it has been shown to maintain the epithelial lining of the gut in animals, with limited evidence of the same in humans[3,4]. However, enterally-fed patients are often unable to meet prescribed caloric goals due to postoperative dysmotility, tube malfunctions, missed feedings, or other reasons[5,6]. Parenteral nutrition has been used postoperatively when patients demonstrate that they are unable to orally or enterally achieve adequate caloric intake, with the benefit of consistent nutritional support. However, parenteral nutrition has been associated with a higher incidence of infectious complications[7]. Regarding oncology patients, Bozzetti *et al*[8] randomized 317 patients undergoing major gastrointestinal cancer resection to either enteral or parenteral nutritional support immediately postoperatively, finding lower overall, and specifically infectious, complication rates in enterally-supported patients.

Options for nutritional support following upper gastrointestinal resection include needle catheter jejunostomy, Stamm or Witzel jejunostomy, or nasojejunal feeding tube placement[9-14]. In some centers, feeding jejunostomy (FJT) is routinely performed following esophagectomy or total gastrectomy, with more selective utilization with subtotal gastrectomy. However, other groups advocate selective use of FJT to minimize tube-related complications[15]. This study examined parenteral nutrition administration and feeding tube utilization rates at the time of discharge in order to better assess the need for enteral support following upper gastrointestinal resection.

MATERIALS AND METHODS

The medical records for all patients who underwent esophagectomy and total or subtotal gastrectomy with curative intent from January 2001 to December 2014 were identified from a prospectively-maintained database. Patients' demographic information, procedure performed, utilization of nutritional support, post-operative length of stay, and post-operative complications were obtained from the medical record. Surgical complications within 30 d after the operation were graded using a surgical secondary events grading system, as described elsewhere, in which grade 1 complications required local or bedside care; grade 2 complications required invasive monitoring or intravenous medication; grade 3 complications required an operation, interventional radiology procedure, intubation, or therapeutic endoscopy; grade 4 complications resulted in a persistent disability or required major organ resection; and grade 5 complications resulted in death[16].

Nutritional support was considered to have been utilized if the patient was not able to achieve adequate oral intake during hospital admission and therefore (1)

received PN post-operatively while an inpatient and/or home PN at time of discharge or (2) required tube feeds to meet caloric goals at the time of discharge. PN was administered *via* triple-lumen subclavian or internal jugular venous lines or peripherally-inserted central catheters. Of note, all PN in our institution is managed by a physician-led multi-disciplinary team in conjunction with the primary service. All of the surgeons performing upper GI resections were observed by a second attending for a minimum of five cases to ensure technical uniformity and quality of feeding jejunostomy placement in order to confirm that the complications were not technical in nature. Jejunostomy was performed in conjunction with upper gastrointestinal resection in order to gain enteral access to (1) provide nutritional support in the immediate post-operative phase or (2) supplement caloric intake in the event that the patient could not meet nutritional goals with oral intake. Feeding jejunostomy-related complications were considered as such when an invasive intervention was required, such as interventional radiology procedure or reoperation; improper tube function such as clogging was not considered a complication.

Our institutional esophagectomy protocol is to keep the patient *nil per os* for seven days after resection, with nasogastric tube decompression of the conduit until post-operative day six. Trophic tube feeds are started on post-operative day two and slowly advanced to goal. Patients undergo thin barium swallow to evaluate for anastomotic leak on post-operative day seven, and if negative they are advanced first to clear liquids, then full liquids, and finally post-esophagectomy diet. If calorie counts demonstrate adequate intake, the patients are discharged without tube feeds. Tube feeds are continued on discharge if patients are unable to take oral diet or do not meet caloric requirements by mouth.

Our institutional subtotal gastrectomy protocol is to keep the patient *nil per os* with nasogastric tube decompression until the patient has return of bowel function. The tube is removed and the patient's diet is advanced as tolerated from clear liquids to post-gastrectomy diet. The total gastrectomy protocol is to keep the patient *nil per os* with nasogastric tube decompression until they undergo diatrizoic acid swallow to evaluate for anastomotic leak, on post-operative day seven. If the study is negative, the nasogastric tube is removed and the patient is advanced first to clear liquids, then full liquids, and finally post-gastrectomy diet. Enteral feeds are started in patients who are unable to tolerate oral feedings within the seven to ten days following operations. If calorie counts demonstrate adequate intake, the patients are discharged without tube feeds. Tube feeds are continued on discharge if patients are unable to take oral diet or do not meet caloric requirements by mouth.

All patients meeting inclusion criteria were identified and followed up for a minimum of 180 d or until death. Data were analyzed using SAS statistical software, version 5.0 (SAS Institute, Inc., Cary, NC). Data were expressed as percentages in the case of categorical variables. Frequencies were compared by the χ^2 test. Means of continuous variables were analyzed using *t* test or ANOVA. All reported *P* values were two-tailed and for all tests values less than 0.05 were considered significant. This study was approved by the institutional review board at Rhode Island Hospital.

RESULTS

Resection of an upper gastrointestinal malignancy was performed in 287 patients. The median patient age and proportion of males were similar between the esophagectomy and gastrectomy groups. There was no significant difference in mean length of stay groups (14.7 d *vs* 17.1 d, $P = 0.076$). Within the gastrectomy group, the median length of stay was significantly longer for the TG group compared to the SG group (16 d *vs* 10 d, $P = 0.0002$). Patients were more likely to be fully dependent on tube feeds at discharge following esophagectomy than gastrectomy ($n = 53$, 29.3% *vs* $n = 3$, 6.4%; $P = 0.0006$). Within 30 d of operation, 52.4% of TG and 29.6% of SG patients experienced complications, compared to 91 patients (50.0%) from the esophagectomy group. Major complications (grade 3-5) occurred in 59 esophagectomy patients and 26 gastrectomy patients (32.6% *vs* 24.8%, $P = 0.18$). Feeding tube-specific complications requiring reoperation within 30 d of operation occurred in 6 of 47 gastrectomy patients (12.8%), all within the TG group ($P = 0.23$). Complications were comprised of closed-loop obstruction around the feeding tube ($n = 2$), feeding tube leak ($n = 2$), small bowel perforation ($n = 1$), and multi-organ failure after initiation of tube feeds ($n = 1$). Conversely, within the esophagectomy group, only one jejunostomy tube-related major complication presented in follow-up, a small bowel obstruction at the jejunostomy site in a patient who had undergone transhiatal esophagectomy who required reoperation (Table 1).

Between January 2001 and June 2014, 182 patients underwent esophagectomy for esophageal malignancy with curative intent (Figure 1). Patients' median age was 64.0 years and 145 were male (79.7%). The predominant tumor type consisted of adenocarcinoma ($n = 158$, 86.8%), followed by squamous cell carcinoma ($n = 15$, 8.2%), high grade dysplasia ($n = 8$, 4.3%), and neuroendocrine tumor ($n = 1$, 0.5%). The primary tumor was located in the middle third of the esophagus in 11 patients (6.0%), lower third in 144 patients (79.1%), and at the gastroesophageal junction in 27 patients (14.8%). One hundred and seven patients (58.7%) underwent transhiatal esophagectomy, 56 patients (30.7%) had Ivor-Lewis esophagectomy, 10 patients (5.4%) underwent three-incision esophagectomy, and 9 patients (4.9%) had thoracoabdominal esophagectomy. Endoscopic ultrasound was used during pre-operative staging in 70 patients (38.4%). Neo-adjuvant induction therapy was administered to 114 patients (62.6%).

Between January 2004 and December 2013,

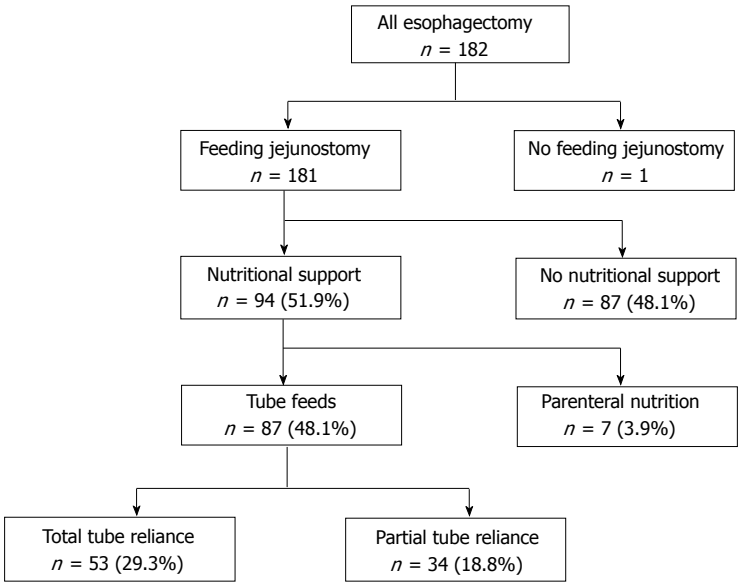

Figure 1 Flow chart of nutritional support for esophagectomy patients.

Table 1 Comparison of complications within thirty days by grade *n* (%)

Complication	Subtotal gastrectomy (*n* = 63)	Total gastrectomy (*n* = 42)	Esophagectomy (*n* = 182)
None	45 (71.4)	20 (47.6)	91 (50.0)
Low-grade	10 (15.9)	4 (9.5)	32 (17.6)
High-grade	8 (12.7)	15 (35.7)	54 (29.7)
Overall mortality	0 (0.0)	3 (7.1)	5 (2.7)
Tube-related complications	0	6	1

Low-grade denotes grade 1-2; high-grade denotes grade 3-4.

Table 2 Clinical characteristics of esophagectomy in relation to tube feed requirement *n* (%)

Characteristic	Total (*n* = 182)	Tube feeds used	Tube feeds not used	*P* value
Age > 65 yr	93	40 (43.0)	53 (57.0)	0.24
Male sex	145	69 (47.6)	76 (52.4)	0.91
Tumor type				
Adenocarcinoma	158	76 (48.1)	82 (51.9)	
Squamous cell carcinoma	15	7 (46.7)	8 (53.3)	0.99
High-grade dysplasia	8	4 (50.0)	4 (50.0)	
Neo-adjuvant therapy	114	52 (45.6)	62 (54.4)	0.54
Post-operative complication	91	66 (72.5)	25 (27.5)	< 0.0001
Esophagectomy approach				
Transhiatal	107	64 (59.8)	43 (40.2)	< 0.0001
Ivor-Lewis	56	14 (25.0)	42 (75.0)	

105 patients underwent total gastrectomy (TG) (*n* = 42, 40%) or subtotal gastrectomy (SG) (*n* = 63, 60%) (Figure 2). The TG and SG groups had similar proportions of males (66.7% each), however, the TG group was younger compared to the SG group (66.6 years *vs* 72.7 years, respectively, *P* = 0.018). Pre-operative albumin was obtained from the medical record in 36 TG patients (85.7%) and 41 SG patients (65.1%); mean albumin was higher in the TG group compared to the SG group (3.5 *vs* 3.2, *P* = 0.024).

A feeding jejunostomy tube was placed in 181 of the 182 esophagectomy patients (99.5%). At the time of discharge, 87 esophagectomy patients (48.1%) required tube feeds for nutritional supplementation, of whom 53 (29.3%) were fully and 34 (18.8%) were partially reliant (Table 2). There was no association between tube feed requirement and age, gender, tumor type, or administration of induction therapy. Patients who had undergone transhiatal esophagectomy were more likely to require tube feeds at discharge than patients who underwent Ivor-Lewis esophagectomy (64 of 107 transhiatal, 59.8% *vs* 14 of 56 Ivor-Lewis, 25.0%; *P* < 0.0001) (Table 3). Meanwhile, seven patients (3.9%) were discharged on parenteral nutrition, four for chylothorax and three having had the feeding tube removed on reoperation (for hemoperitoneum, evisceration, and anastomotic leak). Of the patients with transhiatal esophagectomy, 56 of 107 patients (52.3%) had a complication, of which 34 were cervical anastomotic leak (31.8%). Fifteen of 56 patients (26.8%) with Ivor-Lewis esophagectomy experienced complications, of which four were anastomotic leaks (7.1%). The difference in anastomotic leak rate between the two approaches was statistically significant (*P* = 0.0003).

A feeding jejunostomy tube was placed for 47 of the 105 gastrectomy patients (44.8%), of which significantly more were performed for the TG than the SG group (92.9% *vs* 12.9%, *P* < 0.0001). After TG with feeding tube, 20 of 39 patients (51.3%) were fully (*n* = 3, 7.7%) or partially (*n* = 17, 43.6%) dependent on tube feeds at the time of discharge, whereas after SG with feeding tube, 5 of 8 (62.5%) were partially dependent and no patients were fully dependent on tube feeds (Table 4). Need for tube feed-based nutritional support in gastrectomy patients was not associated with extent of resection (51.3% TG *vs* 62.5% SG, *P* = 0.56). During

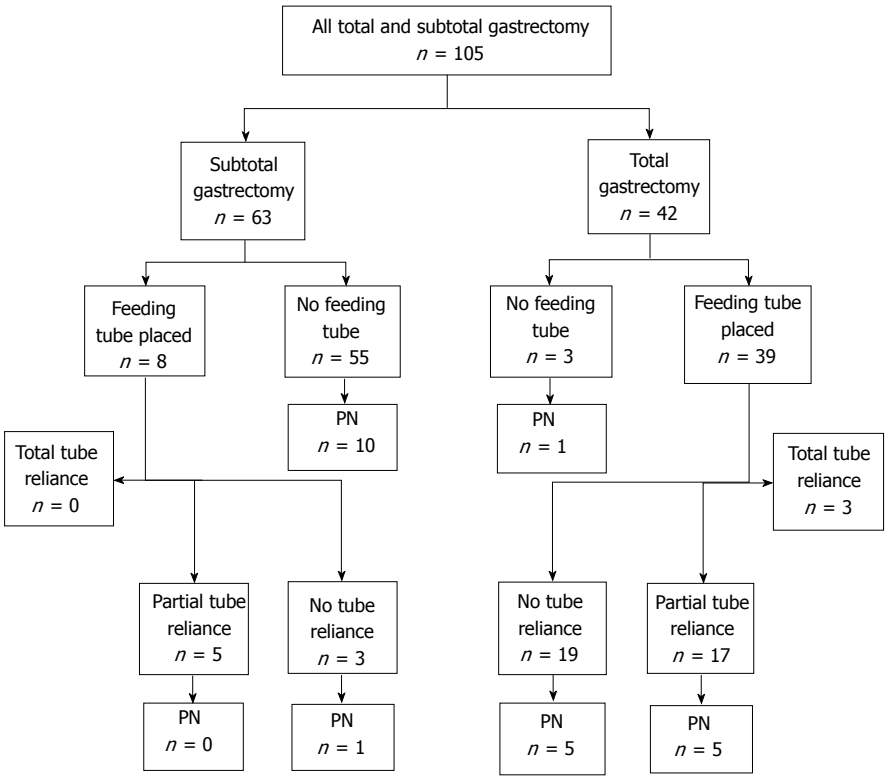

Figure 2 Flow chart of feeding tube placement, tube utilization and parenteral nutrition administration for gastrectomy patients. PN: Parenteral nutrition.

Table 3 Tube feed reliance by esophagectomy approach *n* (%)

Tube feed reliance	Transhiatal (*n* = 107)	Ivor-lewis (*n* = 56)	Other (*n* = 19)
None	43 (40.2)	42 (75.0)	10 (52.6)
Partial	20 (18.7)	10 (17.6)	4 (21.1)
Total	44 (41.1)	4 (7.1)	5 (26.3)

admission, 11 TG and 11 SG patients (26.2% *vs* 17.4%, respectively) required PN as a bridge to adequate oral or enteral intake. Following TG with feeding tube placement, 10 of the 39 patients (25.6%) required PN, whereas one of the SG with feeding tube placement patients required PN. Three patients (2.9%) required home parenteral nutrition, of whom two had had tube-related complications and one had persistent feeding intolerance. For TG and SG patients, PN administration was not associated with extent of resection (11 of 42 TG, 26.2%, *vs* 11 of 63 SG, 17.5%; $P = 0.28$), feeding tube placement (11 of 47 with tube, 23.4% *vs* 11 of 58 without tube, 19.0%; $P = 0.58$), or feeding tube utilization (5 of 25 with tube utilization, 20.0% *vs* 6 of 22 without tube utilization, 27.3%; $P = 0.56$).

DISCUSSION

Although both esophageal and gastric malignancies are classified as being upper gastrointestinal, nutritional recovery after resection of each is significantly different. The surgeon must consider not just the patient's pre-operative nutritional status but the planned resection, the potential complications, and the various methods of nutritional support available. This study illustrates those tenets, with variable reliance on enteral supplementation between transhiatal and Ivor-Lewis esophagectomy and between subtotal and total gastrectomy, as well as a substantial feeding-tube related major complication rate. Older literature has suggested that feeding jejunostomy placement is a well-tolerated, low-risk additional procedure that secures enteral access following esophagectomy and total gastrectomy[9].

The operative approach to esophagectomy has its attendant risks and complication profiles. The transhiatal esophagectomy is thought to accept a higher rate of lower-grade morbidity in that a cervical anastomosis is more likely to leak but is less detrimental to the patient. Meanwhile, the Ivor-Lewis approach is believed to provide a lower likelihood of anastomotic leak with the understanding that such a leak is more devastating given the resultant mediastinitis. Of note, randomized controlled trials have not borne out such beliefs[17]. In our series, the Ivor-Lewis approach to esophagectomy was associated with lower feeding tube utilization rates at discharge compared to the transhiatal approach (25.0% *vs* 59.8%, respectively; $P < 0.0001$). As the inability to use the reconstructed conduit is the most likely reason for need for nutritional support following esophagectomy, the difference in tube utilization rates was most likely related to lower leak rates of intrathoracic anastomoses (7.1%) *vs* cervical anastomoses (31.7%).

The extent of gastric resection determines the reconstruction approach, typically either Billroth II

Table 4 Feeding tube placement and utilization and overall need for nutritional support in relation to extent of gastric resection *n* (%)

Variable	Overall (*n* = 105)	Subtotal (*n* = 63)	Total (*n* = 42)	*P* value
Feeding tube placed	47 (44.8)	8 (12.7)	39 (92.9)	< 0.0001
Tube placed, utilized	25 (53.2)	5 (62.5)	20 (51.3)	0.71
Tube placed, utilized, PN utilized	5 (10.6)	-	5 (12.8)	0.57
Tube placed, not utilized	22 (46.8)	3 (37.5)	19 (48.7)	0.71
Tube placed, not utilized, PN utilized	6 (12.8)	1 (12.5)	5 (12.8)	1.0
PN utilized	22 (21.0)	11 (17.5)	11 (26.2)	0.28
PN utilized with feeding tube	11 (10.5)	1 (9.1)	10 (90.9)	0.42
PN utilized without feeding tube	11 (10.5)	10 (90.9)	1 (9.1)	0.51
No nutritional support used regardless of feeding tube placement	63 (60.0)	47 (74.6)	16 (38.1)	0.0004

PN: Parenteral nutrition.

gastrojejunostomy following subtotal gastrectomy or Roux-en-Y esophagojejunostomy following total gastrectomy. The lack of a gastric remnant eliminates the accommodating reservoir function of the stomach and requires a second anastomosis involving the small bowel. For these and other reasons, feeding jejunostomy placement is often routinely performed in conjunction with total gastrectomy and more selectively done with subtotal gastrectomy. In our series, feeding jejunostomy tube placement was more frequently placed during total than subtotal gastrectomy (92.9% *vs* 12.7%, $P < 0.0001$). Despite the significant difference in the frequency of feeding tube placement, tube utilization rates at the time of discharge were similar (51.3% *vs* 62.5%, respectively; $P = 0.56$). While the majority of patients who undergo subtotal gastrectomy will recover without requiring nutritional support, the relatively high tube utilization rate likely reflects a preference for enteral nutritional support instead of parenteral support when enteral access has already been established. This is evidenced in that no patient who underwent subtotal gastrectomy with feeding tube placement also received parenteral nutrition.

Our traditional institutional practice has been to routinely place FJT at the time of esophagectomy, while tube placement at the time of gastric resection has been more selective, with a higher rate of feeding jejunostomy following total gastrectomy than subtotal resection. Intra-operative feeding jejunostomy placement does not guarantee consistent enteral access or obviate the need for parenteral nutrition for post-operative supplementation. In the esophagectomy group, seven patients (3.9%) received parenteral nutrition to meet caloric goals since four patients developed chylothorax and three patients had their feeding jejunostomy removed at reoperation for intra-abdominal complications. Following gastrectomy, eleven of forty-seven patients (23.4%) who underwent feeding tube placement required parenteral nutrition. Six of these patients were given parenteral nutrition as a direct result of having developed tube-related major complications requiring reoperation. Of the remaining five patients, three had other intra-abdominal complications precluding tube feed administration and two demonstrated tube feed intolerance. Meanwhile, eleven of fifty-eight patients (19.0%) who underwent gastric resection without feeding jejunostomy placement required parenteral nutrition as a bridge to adequate oral caloric intake.

Feeding tube-specific complication rates within 30 d were identified in seven of 228 patients (3.1%), which is consistent with rates published in other series. However, nearly all tube-related complications occurred following gastrectomy, for a complication rate of 12.8% (6 of 47), all of whom had undergone total gastrectomy. All tube-related complications were major, requiring invasive procedure or reoperation for indications such as bowel ischemia, bowel perforation, or acute obstruction. This tube complication rate might be considered higher than expected, but it is consistent with the study by Llaguna *et al*[18] in which 18 of 73 patients (24.7%) experienced a jejunostomy tube-related complication, with 10 patients (13.7%) experiencing a complication requiring reoperation or interventional radiology procedure. In addition, Patel *et al*[19] demonstrated that in a population of 132 patients who underwent total or subtotal gastrectomy, feeding jejunostomy placement was associated with a greater frequency of any grade complication (59% *vs* 41%, $P = 0.04$) and specifically any infectious complication (36% *vs* 17%, $P = 0.01$). Of note, the rate of major complications was not significantly different, and the authors did not separately identify tube-related complications. Only tube placement was associated with post-operative complications on multivariate analysis, whereas age, functional status, T stage, N stage, and extent of resection were not. The higher rate of tube-specific complications following total gastrectomy compared to subtotal gastrectomy or esophagectomy in the absence of technical error suggests an inherent difference in post-operative recovery. The combination of the lack of a gastric remnant with the performance of D2 lymphadenectomy and Roux-en-Y reconstruction may place the small bowel at greater risk of impaired recovery and therefore greater likelihood of tube-related complications.

Overall tube utilization rates at discharge were on the order of fifty percent for both esophageal and gastric resection. While the optimal time for placing a feeding jejunostomy tube is at the time of resection, this does not mean that it should be done solely for sake of ease or potential prophylaxis, as half of patients will recover to discharge without the need for prolonged

tube feeds. Specific resections were associated with need for tube feed supplementation, as patients who underwent transhiatal esophagectomy more frequently required nutritional supplementation at that time of discharge compared to Ivor-Lewis esophagectomy (59.8% *vs* 25.0%, respectively; $P < 0.0001$). A similar distinction was also seen when comparing total and subtotal gastrectomy patients (61.9% *vs* 25.4% respectively, $P = 0.0004$).

Parenteral nutrition has its own risks, such as central line sepsis, but has an advantage in that the decision to administer nutritional support may be postponed until the postoperative phase of recovery, when patients' early postoperative courses can better indicate a need for such support. An alternative method of enteral access that is receiving more attention is nasojejunal tube placement at operation[13,14]. This modality is less invasive than jejunostomy tubes or central lines with fewer associated complications, but is more aimed towards supplemental nutrition while the patient is in-house as opposed to long-term. Since the placement of a nasojejunal tube adds essentially no morbidity to the operation, our practice has shifted to routinely place these tubes at the time of total or subtotal gastrectomy in order to provide nutritional support.

Given suboptimal tube utilization rates, significant feeding tube-related complication rates, and the presence of alternative methods of nutritional supplementation, we would argue that feeding jejunostomy placement should not be considered an obligatory component of any upper gastrointestinal resection. Although this study is prospective in nature, it is limited in its generalizability to patients with upper gastrointestinal malignancy. Despite that, our data suggest that the majority of patients who undergo Ivor-Lewis esophagectomy or subtotal gastrectomy will recover adequate oral caloric intake in the short term. In addition, enteral supplementation *via* nasojejunal tube placement may be a preferable method of nutritional delivery following total gastrectomy. By reducing the frequency of feeding jejunostomy placement, tube-related complications would be minimized and tube utilization rates would be improved. How best to predict the need and optimal route for post-operative nutritional support would be optimally assessed in a randomized, prospective manner.

In conclusion, nutritional recovery following upper gastrointestinal resection for malignancy must be assessed according to the specific pathology being treated. Esophagectomy and gastrectomy have different risks based on operative approach and complication profiles. Feeding jejunostomy was associated with significant tube-related complications, particularly following total gastrectomy. This study suggests that jejunostomy tube placement is not obligatory following upper gastrointestinal resection for malignancy and that alternative methods of nutritional supplementation such as parenteral nutrition or nasojejunal tube placement are potentially better tolerated and allow enhanced patient selection for nutritional support.

COMMENTS

Background

Adequate nutrition has been demonstrated to be critical to the recovery process after major resection. Various methods of nutritional support may be employed, including but not limited to parenteral nutrition, nasojejunal tube feeds, or jejunostomy tube feeds. At many institutions, feeding jejunostomy tubes (FJT) are often placed as a matter of routine in conjunction with resection of upper gastrointestinal malignancy in order to gain enteral access for support during the immediate post-operative phase as well as in anticipation of adjuvant chemotherapy. This study evaluated the actual utilization rates of such feeding tubes upon discharge as well as to assess tube-related complication rates.

Research frontiers

Feeding jejunostomy has been widely studied in esophageal resection, but limited literature has evaluated them in major gastric resection. Although both esophageal and gastric malignancy are in the upper gastrointestinal tract, they are unique neoplasms and comparing utilization rates in each patient population has not been done to date.

Innovations and breakthroughs

In this study, tube utilization rates at discharge for both patient populations were on the order of 50%. However, utilization rates were higher in the subpopulations of total gastrectomy and transhiatal esophagectomy. Major tube-related complications were 3.1%; these were predominantly experienced by patients who underwent total gastrectomy. Meanwhile, Ivor-Lewis esophagectomy and subtotal gastrectomy patients were more likely to achieve adequate oral nutritional intake prior to discharge home.

Applications

This study suggests that nasojejunal feeding tube placement may be a preferred route of nutritional support over feeding jejunostomy following Ivor-Lewis esophagectomy and subtotal gastrectomy. This method of nutritional delivery has potential benefit as well for transhiatal esophagectomy and total gastrectomy patients, while avoiding the complications related to feeding jejunostomy placement, with consideration of parenteral nutrition as an alternative route if nasojejunal tube feeds are not able to be administered.

Peer-review

The authors of this paper evaluated feeding jejunostomy utilization for esophagectomy and gastrectomy for malignancy. Suboptimal utilization rates and significant tube-related major complications suggest that alternative methods of nutritional support to routine feeding jejunostomy placement allow enhanced patient selection.

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ORIGINAL ARTICLE

Retrospective Study

Clinicopathological features and surgical outcome of patients with fibrolamellar hepatocellular carcinoma (experience with 22 patients over a 15-year period)

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Author contributions: Wahab MA and El Hanafy E contributed to study concept; Wahab MA, El Hanafy E and El Nakeeb A contributed to data collection; El Hanafy E and El Nakeeb A contributed to data analysis; Wahab MA and Ali MA contributed to writing the draft; all authors have approved the manuscript in its final form and approving the manuscript in its final form.

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Abstract

AIM

To evaluate the clinicopathological features and the surgical outcomes of patients with fibrolamellar hepatocellular carcinoma (FL-HCC) over a 15-year period.

METHODS

This is a retrospective study including 22 patients with a pathologic diagnosis of FL-HCC who underwent hepatectomy over a 15-year period. Tumor characteristics, survival and recurrence were evaluated.

RESULTS

There were 11 male and 11 female with a median age of 29 years (range from 21 to 58 years). Two (9%) patients had hepatitis C viral infection and only 2 (9%) patients had alpha-fetoprotein level > 200 ng/mL. The median size of the tumors was 12 cm (range from 5-20 cm). Vascular invasion was detected in 5 (23%) patients. Four (18%) patients had lymph node metastases. The median follow up period was 42 mo and the 5-year survival was 65%. Five (23%) patients had a recurrent disease, 4 of them had a second surgery with 36 mo median time interval. Vascular invasion is the only significant negative prognostic factor

CONCLUSION

FL-HCC has a favorable prognosis than common HCC

and should be suspected in young patients with non cirrhotic liver. Aggressive surgical resection should be done for all patients. Repeated hepatectomy should be considered for these patients as it has a relatively indolent course.

Key words: Fibrolamellar hepatocellular carcinoma; Common hepatocellular carcinoma; Recurrence after resection fibrolamellar hepatocellular carcinoma; Pathology of fibrolamellar hepatocellular carcinoma; Survivalefter resection fibrolamellar hepatocellular carcinoma

Core tip: Fibrolamellar hepatocellular carcinoma (FL-HCC) has conventionally been considered to be a histologic variant of HCC, with distinct clinicopathologic features. Many series have mentioned that FL-HCC is less aggressive than conventional HCC. However, other studies have failed to confirm the observation of a better outcome in FL-HCC. Our study shows that FL-HCC has a favorable prognosis than common HCC and should be suspected in young patients with non cirrhotic liver. Aggressive surgical resection should be done for all patients. Repeated hepatectomy or excision of recurrent disease should be considered for these patients as it has a relatively indolent course.

Wahab MA, El Hanafy E, El Nakeeb A, Ali MA. Clinicopathological features and surgical outcome of patients with fibrolamellar hepatocellular carcinoma (experience with 22 patients over a 15-year period). *World J Gastrointest Surg* 2017; 9(2): 61-67 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i2/61.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i2.61

INTRODUCTION

Fibrolamellar hepatocellular carcinoma (FL-HCC) has conventionally been considered to be a histologic variant of hepatocellular carcinoma (HCC), with distinct clinicopathologic features. It is a rare primary hepatic malignancy that was first described as a pathological variant of HCC by Edmondson[1] in 1956.

FL-HCC is usually well circumscribed masses characterized by polygonal hepatic cells with deeply eosinophilic cytoplasm and abundant fibrous stroma arranged in thin parallel bands. On gross examination, there is a central scar which resulted from coalesced lamellar bands of fibrosis[2].

The etiology of FL-HCC remains unclear. It typically occurs in normal livers without underlying liver fibrosis or cirrhosis[3]. In contrast to HCC which usually found in the presence of cirrhosis or chronic hepatitis[4]. FL-HCC has been reported to occur in association with focal nodular hyperplasia a type of benign liver lesion[5,6]. Some suggest that FHN may be a benign precursor lesion to FL-HCC as both diseases share several features: They tend to present in younger patients, and in the setting of normal liver parenchyma. Pathologically both have as a stellate central scar on imaging studies and copper accumulation on histological examination[6,7].

Many series have mentioned that FL-HCC is less aggressive than conventional HCC[8-10]. However, other studies have failed to confirm the observation of a better outcome in FL-HCC[11-13]. Other studies reported that the survival was similar between common HCC and FL-HCC, and that may be related to the higher resectability rate which improve the survival of patients with FL-HCC[12,14].

The aim of this study was to evaluate the clinicopathological features and the surgical outcomes of patients with FL-HCC who were referred to our tertiary referral center over a 15-year period.

MATERIALS AND METHODS

This is a retrospective study of patients underwent hepatectomy for a pathologic diagnosis of FL-HCC over an 15-year period between February 1999 to February 2014, in gastroenterology surgical center, Mansoura University, Egypt. A total of 22 patients was diagnosed and underwent hepatectomy during this period. The diagnosis of FL-HCC was made depending on its histological and pathological characteristics by an independent pathologic team.

All patients were subjected to clinical assessment; laboratory investigation and imaging work up including: Ultrasonography, Enhanced computed tomography and MRI imaging study to evaluate the extent of the tumor, vascular involvement and lymph node affection. Clinicopathological parameters, including gender and age of patients; location, size and number of the tumor; safety margins; vascular invasion; lymph node metastasis status; operative details; morbidity and mortality; and survival and recurrence were collected. The parenchymal disease of the liver is defined as hepatitis C antibody and/or hepatitis B surface antigen was present. Safety margin is defined as complete tumor excision after surgical treatment proved by pathologic examination of the resected margins. Patients with synchronous malignancies were excluded from the study. Non of our patients underwent preoperative portal vein embolization or chemoembolization and they did not received adjuvant treatment.

Clinical staging of the tumor was performed using the American Joint Committee on Cancer staging criteria[15]. The extent of hepatic resection was defined according to the Brisbane 2000 Terminology of Liver Anatomy and Resections[16]: Right hepatectomy involves resection of segments V-VIII, whereas left hepatectomy involves resection of segments (II-IV). Extended right hepatectomy involves resection of segments IV-VIII, whereas extended left hepatectomy involves resection of segments (II-IV, V, VIII). All these resection may or may not involve segment I. Most of liver resections were performed with selective vascular inflow occlusion. However, intermittent clamping was used in selected

Table 1 Patient demographics

	FL-HCC (n = 22)
Median age, years (range)	29 yr (21 to 58)
Male/female	11/11 (50%:50%)
Hepatitis or cirrhosis	2 (9%)
Elevated AFP (> 200 ng/mL)	2 (9%)

FL-HCC: Fibrolamellar hepatocellular carcinoma; AFP: Alpha-fetaprotein.

Table 2 Tumor characteristics' and treatment features n (%)

	FL-HCC (n = 22)
Number	
Single	19 (86)
Multiple	3 (14)
Size (cm)	Median 12 cm (range, 5-20)
Location	9 right, 10 left, 3 bilateral
Hepatic resection	
Hepatectomy	16 (73)
Extended hepatectomy	4 (18)
Localized resection	2 (9)
Stage	
I	10 (45)
II	5 (23)
III	7 (32)
IV	0
Nodal metastases	4 (18)
Vascular invasion	5 (23)
Positive safety margin	2 (9)
Repeated hepatectomy	4 (18)

FL-HCC: Fibrolamellar hepatocellular carcinoma.

patients to avoid ischemia of the remnant liver. Liver transsection was performed using harmonic scalpel, ultrasonic dissector. Follow-up was obtained in the out-patient clinic by personal contact with the patients.

Survival analysis

Log-rank test and Kaplan-Meier curves were used for survival analysis. For continuous variables, descriptive statistics were calculated and were reported as median. Categorical variables were described using frequency distributions. Mortality was defined as death occurring in the hospital or within 30 d. Significance was defined as $P < 0.05$.

RESULTS

Twenty two patients with FL-HCC were diagnosed in our retrospective data base. All our patients underwent partial hepatectomy over a 15-year period. There were 11 male and 11 female with a median age of 29 years (range from 21 to 58 years). Two patients (9%) had liver cirrhosis due to hepatitis C viral infection while the remaining patients had a normal liver, and only 2(9%) patients had high AFP levels (> 200 ng/mL) (Table 1). In comparison to HCC, patients with common HCC were evaluated at our center[17], it was predominantly in male, the mean age was 54.8 ± 9.2 years, 100% had cirrhotic liver and AFP levels were elevated in all

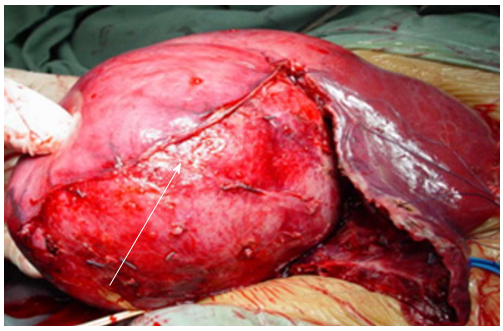

Figure 1 Large right lobe fibrolamellar hepatocellular carcinoma.

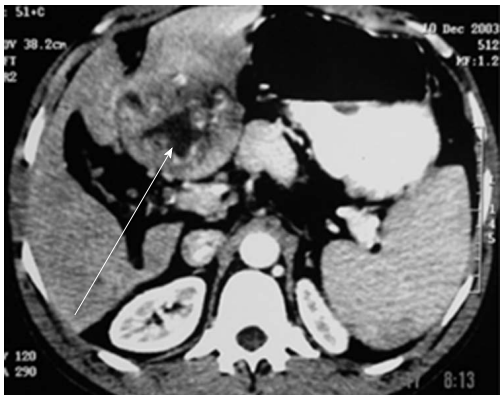

Figure 2 Fibrolamellar hepatocellular carcinoma left lobe.

patients. FL-HCC represents about 3% of patients with hepatic malignancies (1260 patients) during the study period.

Vague abdominal pain was the most common presentation, other were asymptomatic and discovered incidentally during physical examination or routine imaging work up. These tumors are well circumscribed, large and often have areas of hypervascularitywith a central scar Figure 1. Figure 2 shows FL-HCC at left liver lobe while Figure 3 demonstrates a different CT scans for FL-HCC in the right liver lobe.

Surgery and pathology

The type of hepatic resection for our 22 patients is shown in Table 2. Seventy three percent of cases required hepatectomy and 18% needed extended hepatectomy to excise their tumors. Multiple primary tumors were present in 3 patients. The median size of the tumors was 12 cm (range from 5-20 cm). Vascular invasion was detected in 5 (23%) patients. Four of those patients had microscopic vascular invasion, and one had microscopic invasion of the right hepatic vein. The safety margin was invaded in 2 (9%) patients who might be due to presence of the tumor closer tovascular structures which couldn't be resectable. Four (18%) patients had lymph node metastases.

In this study, 5 patients had a recurrent disease.Four patients had a second surgery with 36 mo median time interval. Three patients had a repeated liver resection (including both patients with microscopic invasion of

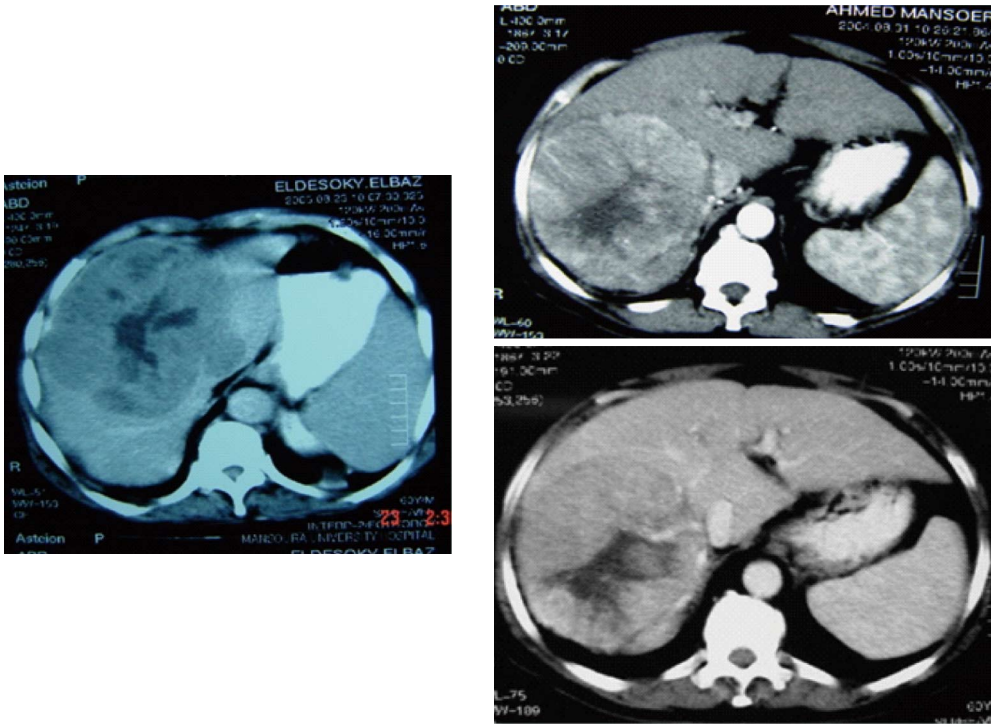

Figure 3 Fibrolamellar hepatocellular carcinoma right lobe.

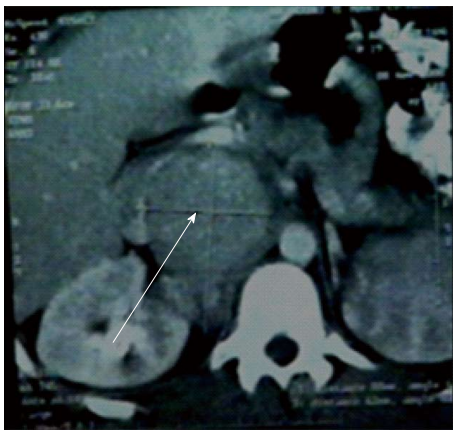

Figure 4 Large retro-caval lynph node 2-year after resection fibrolamellar hepatocellular carcinoma.

resection margins and 1 patient with vascular invasion) and one patient underwent resection of large retro-caval lymph node (Figure 4). The last patient had peritoneum dissemination and nothing was done for him. The median survival was 28 mo after the second operation in these patients. There was no hospital mortality.

Overall survival

The median overall survival in our 22 patients was 88 mo and the 5-year survival was 65%. The median follow up period was 42 mo. In our experience of hepatic resection for HCC in cirrhotic liver (n = 175), the median survival after surgical resection was 24 mo while 5-year survival was 10.7%[17].

The univariate analysis for overall survival was performed and includes the following variables: Age, gender, size and number of tumors, type of hepatic resection, vascular invasion, nodal metastases, and resection margins (Table 3). The two patients with positive microscopic margins developed a recurrent disease. Although radically resected patients have a

Table 3 Clinicopathologic features and survival in fibrolamellar carcinoma (figures in parenthesis reflect percentages)

Factor	*n* (%)	Overall survival (mo)	*P* value
Age (yr)			
< 40	16 (73)	86	
⩾ 40	6 (27)	72	0.4
Gender			
Female	11 (50)	84	
Male	11 (50)	79	0.6
Tumor size (cm)			
< 10	8 (36)	82	
⩾ 10	14 (64)	76	0.3
Number			
1	19 (86)	89	
> 1	3 (14)	77	0.2
Hepatic resection			
Hepatectomy	16 (73)	86	
Extended hepatectomy	4 (18)	77	
Localized resection	2 (9)	79	0.62
Nodal metastases			
Negative	18 (82)	88	
Positive	4 (18)	78	0.09
Vascular invasion			
Absent	17 (77)	92	
Present	5 (23)	58	0.03
Safety margin			
Negative	20 (91)	87	
Positive	2 (9)	72	0.08

Table 4 Published series on fibrolamellar hepatocellular carcinoma

Ref.	*n*	Age	Male: female	Cirrhosis/ hepatitis	AFP elevated	Median size (cm)	> 1 tumor	Positive node	Vascular invasion	Initial operation	Repeat operation	Median f/u	5 yr survival	Prognostic factor
Hemming *et al*[18], 1997	10	31	50:50	NR	10%	8	20%	20%	NR	Phx 100%	50%	101	70%	NR
El-Gazzaz *et al*[19], 2000	20	27	65:35	0% hep B	0%	14	20%	30%	55%	Phx 55% OLT 45%	NR	25	50%	NONE
Kakar *et al*[20], 2005	20	27	53:27	0%	3/13 (23%)	< 10 31% ⩾ 10 69%	10%	35%	NR	Phx 100%	NR	NR	62%	Metastasis at presentation
Stipa *et al*[21], 2006	28	28	43:57	0%	7%	9	11%	50%	36%	Phx 100%	61%	34	76%	Positive LN
Present study	22	29	50:50	9%/hepc	9%	12	13%	18%	23%	Phx 100%	18%	42	65%	Vascular invasiom

Hep: Hepatitis; AFP: Alpha-fetoprotein elevated (> 200 ng/mL); Phx: Partial hepatectomy; NR: Not reported; f/u: Follow up.

prolonged survival (87 mo *vs* 72 mo) it is not reach a statistical significance. Only vascular invasion was significant.

In our study, we have 8 patients with greater than 5-years follow up. Of these patients, 4 died of disease at 63, 67, 74 and 88 mo. Four patients were alive at 65-92 mo after surgery with no evidence of a recurrent disease.

DISCUSSION

FL-HCC has been considered to be a histologic variant of HCC, with distinctive morphological and clinical setting. This study confirms the distinctive clinicopathological finding of other studies that FL-HCC were larger in size than conventional HCC, affects young patients with no sex predilection and occurs in the healthy liver in absence of parenchymal disease or cirrhosis and without elevation of AFP level (Table 4)[18-21]. Elevations in AFP levels are uncommon with less than 10% of patients have AFP levels greater than 200 ng/mL[21]. In this study, only 2 patients (9%) had high AFP level (> 200 ng/mL).

FL-HCC occurs in normal livers without underlying liver fibrosis or cirrhosis[3]. Pinna 1997, reported that 6% of his patients were hepatitis C positive and 7% had cirrhotic liver[10]. In our study, 2 patients (9%) were hepatitis C antibody positive, this may be attributed to high prevalence of hepatitis C virus in our community.

Preoperatively, FL-HCC can be diagnosed by CT scan and MRI imagingcharacteristicas these tumors are usually heterogenous with areas of hypervascularity. Preoperative biopsy was avoided and our patients underwent surgery without biopsy which was reserved for patients who are unresectable. Ichikawa *et al*[22] 1999 reported that FL-HCC had 68% calcification, 65% abdominal lymphadenopathy and 71% central scar.

Surgical resection is the only hope for these patients which should be done whenever possible. Our patients had 73% hepatectomy, 18% extended hepatectomy, while only 9% needed localized resection. The 5-year survival was 65% after resection, which was comparable to the 50%-70% 5-year survival rates in other reported studies (Table 4)[18-21].

Several factors have been identified in the surgical studies of FL-HCC that can predict worse prognosis. More than one tumor, metastasis at presentation, vascular invasion and positive lymph nodes[10,12,20,21] have been identified to be a negative prognostic factors. In this study, vascular invasion is the only significant negative prognostic factor after resection.

Our patients have a low rate of lymph node metastasis (18%) compared to other series which range from 20%-50% (Table 4). This may be related to different tumor biology and the presence of liver cirrhosis in 9% of patients which may delay lymphatic metastases due to inhibition lymphatic outflow from the liver. On our published study on common HCC[17], lymph node metastases were found on only 8 from 175 patients (8%) this may confirm the previous data.

Despite the relatively indolent tumor biology of FL-HCC, it recurs after surgical resection. The site of recurrences includes the liver, regional lymph nodes, peritoneum, and lung[23]. Some authors recommend resection of a recurrent disease due to its indolent course and absence of alternative treatment option[2]. Four patients (18%) underwent a second surgery for a recurrent disease. Three patients underwent hepatic resection while one patient underwent resection of large retro-caval lymph node. This rate is lower than the reports 50%-61% in the other series[18,21]. However, the median survival was 28 mo after the second operation.

The aggressiveness and outcomes of FL-HCC vary significantly between previously published series. Some studies reported that FL-HCC is less aggressive than conventional HCC[8-10,24,25]. Other series reported that survival of FL-HCC was similar with common HCC[12,14] while other pathology and hepatology texts mention that it is associated with favorable prognosis[26-29]. Kakar *et al*[20], 2005 reported that FL-HCC is an aggressive tumor and nearly that half of patients develops lymph node or distant metastasis. In our study, the FL-HCC

has an indolent course than common HCC, better 5-year survival can be reached in absence of vascular invasion and positive safety margins.

In conclusion, FL-HCC has a favorable prognosis than common HCC and should be suspected in young patients with non cirrhotic liver. Aggressive surgical resection should be done for all patients. Repeated hepatectomy or excision of recurrent disease should be considered for these patients as it has a relatively indolent course.

ACKNOWLEDGMENTS

We thank all staff members of gastroenterology center.

COMMENTS

Background

Fibrolamellar hepatocellular carcinoma (FL-HCC) has conventionally been considered to be a histologic variant of hepatocellular carcinoma (HCC), with distinct clinicopathologic features. It is a rare primary hepatic malignancy. The etiology of FL-HCC remains unclear. It typically occurs in normal livers without underlying liver fibrosis or cirrhosis. In contrast to HCC which usually found in the presence of cirrhosis or chronic hepatitis. Some suggest that FHN may be a benign precursor lesion to FL-HCC as both diseases share several features: they tend to present in younger patients, and in the setting of normal liver parenchyma. The prognosis of FL-HCC is differ from common HCC.

Research frontiers

Many series have mentioned that FL-HCC is less aggressive than conventional HCC. However, other studies have failed to confirm the observation of a better outcome in FL-HCC. Other studies reported that the survival was similar between common HCC and FL-HCC, and that may be related to the higher resectability rate which improve the survival of patients with FL-HCC. The aim of this study was to evaluate the clinicopathological features and the surgical outcomes of patients with FL-HCC who were referred to their tertiary referral center over a 15-year period.

Innovations and breakthroughs

The epidemiology, surgical management and outcomes for patients with FL-HCC differs from one area of the world to another. The authors have a published data and experience from Western, Eastern and European countries. However, The authors have a little data from Middle East countries, and here they represent their work from a large gastroenterology and transplantation center in Egypt in dealing with patients with FL- HCC over a 15 years period.

Applications

The surgery of FL-HCC is differs from HCC as it occurs in non-cirrhotic liver, so aggressive surgery was adopted for more radical surgery even for a recurrent disease.

Terminology

Clinical staging of the tumor was performed using the American Joint Committee on Cancer (AJCC) staging criteria. The extent of hepatic resection was defined according to the Brisbane 2000 Terminology of Liver Anatomy and Resections: Right hepatectomy involves resection of segments V-VIII, whereas left hepatectomy involves resection of segments (II-IV). Extended right hepatectomy involves resection of segments IV-VIII, whereas extended left hepatectomy involves resection of segments (II-IV, V, VIII).

Peer-review

This manuscript seems worth to be reported, because clinicopathological features of FL-HCC are clearly written.

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CASE REPORT

Giant abdominal osteosarcoma causing intestinal obstruction treated with resection and adjuvant chemotherapy

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Abstract

Extraskeletal osteosarcoma (ESOS) is an uncommon tumor that accounts for 1% of all soft tissue sarcomas and 4% of all osteosarcomas. Its presentation may be atypical, while pain has been described as the most common symptom. Radiological findings include a large mass in the soft-tissues with massive calcifications, but no attachment to the adjacent bone or periosteum. We present the case of a 73-year-old gentle man who presented with a palpable, tender abdominal mass and symptoms of bowel obstruction. Computer tomography images revealed a large space-occupying heterogeneous, hyper dense soft tissue mass involving the small intestine. Explorative laparotomy revealed a large mass in the upper mesenteric root of the small intestine, measuring 22 cm × 12 cm × 10 cm in close proximity with the cecum, which was the cause of the bowel obstruction. Pathology confirmed the diagnosis of an ESOS. ESOS is an uncommon malignant soft tissue tumor with poor prognosis and a 5-year survival rate of less than 37%. Regional recurrence and distant metastasis to lungs, regional lymph nodes and liver can occur within the first three years of diagnosis in a high rate (45% and 65% respectively). Wide surgical resection of the mass followed by adjuvant chemotherapy or radiotherapy has been the treatment of choice.

Key words: Osteosarcoma; Sarcoma; Extraskeletal;

Intestinal obstruction; Abdominal mass; Soft tissue

Core tip: We present the case of an elderly man who presented with a palpable abdominal mass and signs of intestinal obstruction. Intra-operative findings revealed a mass in the right abdomen involving the small intestine, which was widely resected. A diagnosis of soft tissue osteosarcoma was confirmed by pathology; further treatment with chemotherapy followed. To our knowledge it has never been reported a case of abdominal obstruction due to soft tissue sarcoma in the literature. Due to its rarity, we strongly believe that the presentation of this case would contribute to further understanding of the biology and management of this tumor.

Diamantis A, Christodoulidis G, Vasdeki D, Karasavvidou F, Margonis E, Tepetes K. Giant abdominal osteosarcoma causing intestinal obstruction treated with resection and adjuvant chemotherapy. *World J Gastrointest Surg* 2017; 9(2): 68-72 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i2/68.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i2.68

INTRODUCTION

Extraskeletal osteosarcoma (ESOS) is a rare mesenchymal malignant soft tissue neoplasm. It constitutes 1%-2% of all soft-tissue sarcomas and 4%-5% of all osteosarcomas, while it is considered to be an aggressive tumor with an overall 5 year mortality rate up to 60%[1-3]. Patients are usually affected in the 6th decade of life and men are affected with a slightly higher frequency than women[4,5]. Their exact pathogenesis is not clear; even though there is some evidence that ESOS can be associated with trauma, radiation and radiotherapy[2,4]. The most common location includes the deep soft tissue of the thigh (47%), the upper extremity (20%) and the peritoneum (17%)[4].

We present a unique case of intestinal obstruction due to a giant abdominal osteosarcoma treated with resection and adjuvant chemotherapy.

CASE REPORT

A 73-year-old male patient presented to the emergency department with a two-week history of abdominal pain, progressive appetite loss, vomiting and constipation, with no reported weight loss. There was no history of pathological fractures. Physical examination revealed a palpable, tender mass in the central abdomen without any signs of acute abdomen or ascites.

Standard blood tests showed a mild increase in inflammatory markers (white blood cells, C-reactive protein), while tumor markers (CEA, CA19-9, AFP, PSA) were within normal limits.

Abdominal radiograph revealed air-fluid levels, as well as a rounded, densely calcified mass mainly occupying the right abdomen. Computed tomography (CT) revealed a large space occupying, heterogeneous soft tissue mass with cystic spaces involving the small intestine, surrounded by multiple massively enlarged lymph nodes (Figure 1).

The patient underwent an exploratory laparotomy. The intraoperative findings included a large mass in the upper mesenteric root of the small intestine, measuring 22 cm × 12 cm × 10 cm, occupying the right abdomen (Figure 2A). The tumor was in close proximity with the cecum, the right kidney and the urinary bladder and there were no signs of invasion to the surrounding organs or distant metastasis. There were also enlarged lymph nodes in proximity to the lesion. The tumor was excised en bloc with a 40 cm part of the ileum and lymph nodes of the mesenteric (Figure 2B).

Microscopic examination, with the use of Haematoxylin and Eosin stain, confirmed the diagnosis of soft tissue osteosarcoma (Figure 3).

In the multidisciplinary team meeting was decided that the oncologists should follow up the patient. The patient was furthermore treated with adjuvant chemotherapy (Adriamycin and Ifosfamide) and three years after surgery he remained disease free.

DISCUSSION

ESOS is an uncommon tumor that accounts for 1% of all soft tissue sarcomas and 4% of all osteosarcomas. It affects most commonly individuals older than 30 years. It has a mesenchymal origin that produces osseous components such as bone, osteoid and chondroid without being attached to the bone or the periosteum. History of trauma is related with soft tissue osteosarcoma as well as former radiotherapy especially in the breast region[1,6,7]. The most common sites where the soft-tissue osteosarcoma may arise are the deep tissue of the thigh, the upper and lower extremity and the retroperitoneum. However, few cases of ESOS have been reported arising in unusual sites, such as the larynx, kidney, esophagus, small intestine, liver, heart, urinary bladder, parotid, and breast[8].

The main symptoms include a slowly enlarging and painful mass while in some cases ulceration of the mass has been reported. To our knowledge a case report of intestinal obstruction due to a giant ESOS has never been reported in literature before.

These tumors are usually large at the time of diagnosis, with an average diameter of 9 cm. The size of the tumor constitutes a significant prognostic factor. Patients with a tumor size > 5 cm have usually a worse outcome despite the radical treatment. However, in some studies, the small size of the tumor did not result in a better prognosis or a long-term survival[7].

According to Allan *et al*[1], the diagnostic criteria of

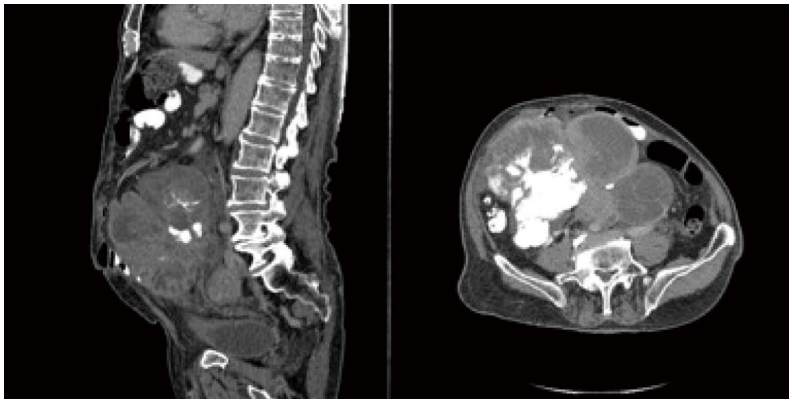

Figure 1 A giant heterogeneous, partially hyper dense soft tissue mass containing cystic spaces located in the right abdomen.

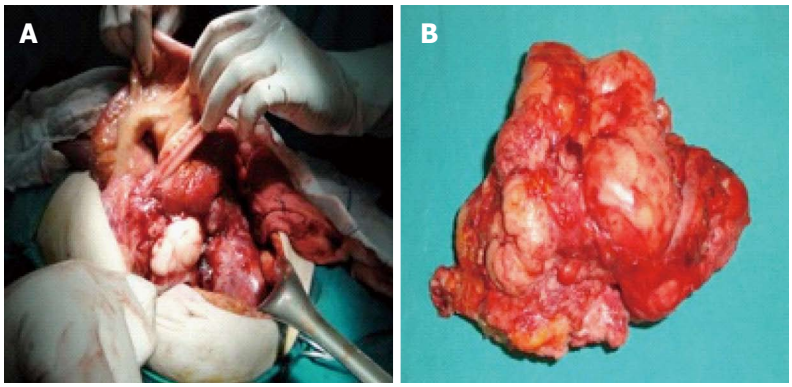

Figure 2 Intra-operative findings: A 22 cm × 12 cm × 10 cm mass occupying the right abdomen in close proximity with the cecum, the right kidney and the urinary bladder (A and B).

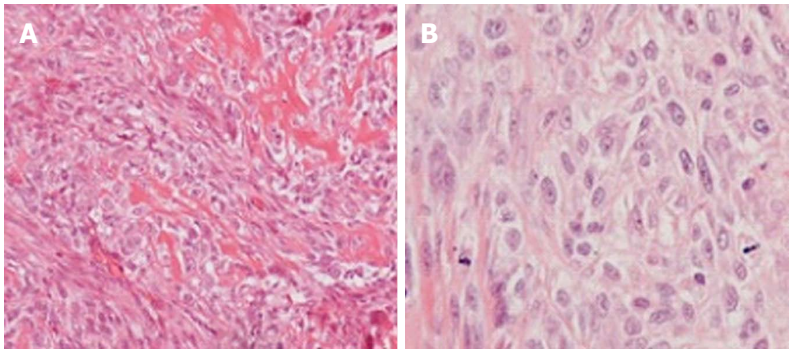

Figure 3 The tumor. A: The tumor consisted of atypical spindle or polyhedral cells that were intimately associated to neoplastic bone deposited in a lacy pattern (haematoxylin and eosin stain, original magnification × 20); B: The tumor cells were mitotically active and frequently demonstrated atypical mitotic figures (haematoxylin and eosin stain, original magnification × 40).

ESOS are the presence of a major morphological pattern of sarcomatous tissue and the production of malignant bone or osteoid, whose origin is not osseous. The microscopic examination reveals atypical spindled and epithelioid mesenchymal cells that produce a lace-like, abnormal osteoid. There is an increase of mitoses with pleomorphic cells, with or without deposition of hyaline cartilage. The tumor osteoid and bone is centrally located with a lucent edge, which is the reverse zonation from that seen in myositis ossificans[1]. Various types of soft-tissue osteosarcoma are reported, each of which follows a different histological pattern. The usual patterns include the chondroblastic, fibroblastic, telangiectatic, and small cell. Although a tumor can include more than 2 histological patterns, in case the major histological pattern represents 75% or more of the tumor, this specific type characterizes the lesion.

The immunohistochemical search usually shows that the neoplastic cells are positive for vimentin, alpha smooth muscle actin and osteonectin, CD99, S100 but are negative for c-kit, CD34, cytokeratin, epithelial membrane antigen, and desmin.

The radiological images of ESOS often present similarities with the images of parosteal osteosarcoma, however the parosteal osteosarcoma has a broad attachment to thickened cortical bone. The radiographs and the CT present ESOS as a large mass in the soft-tissues with massive calcifications, with no attachment to the adjacent bone or periosteum. The MRI images present a nonspecific intermediate signal on T1-weighted imaging and high signal intensity on T2-weighted imaging, which is enhanced by the administration of gadolinium. The presence of a pseudocapsule has also been reported. The tumor presents an increased radiotracer uptake in scintigraphy. Finally, the ESOS is presented as a multilobulated large mass with mineralized components and abnormal uptake on F-18-FDG PET/CT fusion images.

The diagnosis of ESOS should be made using the combination of the atypical clinical manifestations, the radiographical findings and the pathological verification. The differential diagnosis of the soft-tissue osteosarcoma includes various malignant and benign entities of soft-tissue origin[5], such as myositis ossificans, liposarcoma and histiocytoma.

ESOS has a high rate of regional recurrence (45%) and distant metastasis (65%). Common sites of involvement are the lungs (80%), the regional lymph nodes and the liver. Recurrence and/or metastasis usually occur within the first three years of the diagnosis[5].

Treatment of ESOS consists of wide surgical resection of the tumor or amputation combined with adjuvant chemotherapy or radiation. Even though ESOS is considered to be of low responsiveness to radiotherapy and/or to chemotherapy, with a response rate to chemotherapy up to 45%, the survival and recurrence rate may be reduced by postoperative adjuvant chemotherapy, while radiotherapy is still questioned for its results[9-11]. Goldstein-Jackson *et al*[12] recommend that all ESOS should be treated like conventional osteosarcoma with a combination of multiagent chemotherapy and surgery.

Finally, the prognosis is quite poor and a large percentage of the cases succumb to metastatic disease or recurrence within 2-3 years of the diagnosis with an overall 5-year mortality up to 60%.

In conclusion, ESOS is an unusual high-grade malignant soft tissue neoplasm with a poor prognosis and a 5-year survival rate less than 37%. Multiagent chemotherapy following radical surgery seems to be the best choice to treat these patients while radiation may also contribute in some cases. A careful follow-up of patients with soft-tissue osteosarcoma is required because of the high rates of local recurrence and distant metastasis despite the radical treatment.

COMMENTS

Case characteristics

A 73-year-old man presented to the emergency department with a two-week history of abdominal pain, progressive appetite loss, vomiting and constipation, with no reported weight loss.

Clinical diagnosis

Physical examination revealed a palpable, tender mass in the central abdomen without any signs of acute abdomen or ascites.

Differential diagnosis

The diagnosis of extraskeletal osteosarcoma (ESOS) should be made using the combination of the atypical clinical manifestations, the radiographical findings and the pathological verification.

Laboratory diagnosis

Standard blood tests showed a mild increase in inflammatory markers (white blood cells, C-reactive protein), while tumor markers (CEA, CA19-9, AFP, PSA) were within normal limits.

Imaging diagnosis

An abdominal radiograph and a computed tomography of the abdomen were performed with the findings discussed in the text.

Pathological diagnosis

Microscopic examination, with the use of haematoxylin and eosin stain, confirmed the diagnosis of soft tissue osteosarcoma.

Treatment

Wide surgical excision of the lesion and the involved intestine.

Term explanation

ESOS is an uncommon mesenchymal tumor that produces osseous components such as bone, osteoid and chondroid without being attached to the bone or the periosteum and accounts for 1% of all soft tissue sarcomas and 4% of all osteosarcomas.

Experiences and lessons

Multiagent chemotherapy following radical surgery seems to be the best choice to treat these patients while radiation also may contribute in some cases. A careful follow-up of patients with soft-tissue osteosarcoma is required because of the high rates of local recurrence.

Peer-review

This is a well written case report.

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AIM AND SCOPE

World Journal of Gastrointestinal Surgery (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

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ORIGINAL ARTICLE

Retrospective Study

Delayed gastric emptying following pancreaticoduodenectomy: Incidence, risk factors, and healthcare utilization

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Abstract

AIM

To characterize incidence and risk factors for delayed gastric emptying (DGE) following pancreaticoduodenectomy and examine its implications on healthcare utilization.

METHODS

A prospectively-maintained database was reviewed. DGE was classified using International Study Group of Pancreatic Surgery criteria. Patients who developed DGE and those who did not were compared.

RESULTS

Two hundred and seventy-six patients underwent pancreaticoduodenectomy (PD) (> 80% pylorus-preserving, antecolic-reconstruction). DGE developed in 49 patients (17.8%): 5.1% grade B, 3.6% grade C. Demographic, clinical, and operative variables were similar between patients with DGE and those without. DGE patients were more likely to present multiple

complications (32.6% *vs* 4.4%, ⩾ 3 complications, P < 0.001), including postoperative pancreatic fistula (POPF) (42.9% *vs* 18.9%, P = 0.001) and intra-abdominal abscess (IAA) (16.3% *vs* 4.0%, P = 0.012). Patients with DGE had longer hospital stay (median, 12 d *vs* 7 d, P < 0.001) and were more likely to require transitional care upon discharge (24.5% *vs* 6.6%, P < 0.001). On multivariate analysis, predictors for DGE included POPF [OR = 3.39 (1.35-8.52), P = 0.009] and IAA [OR = 1.51 (1.03-2.22), P = 0.035].

CONCLUSION

Although DGE occurred in < 20% of patients after PD, it was associated with increased healthcare utilization. Patients with POPF and IAA were at risk for DGE. Anticipating DGE can help individualize care and allocate resources to high-risk patients.

Key words: Delayed gastric emptying; Pancreaticoduodenectomy; Post-operative pancreatic fistula

Core tip: Delayed gastric emptying (DGE) frequently occurs following pancreaticoduodenectomy. Review of our institutional database revealed a DGE rate of less than 20% among patients who underwent PD. DGE was associated with increased healthcare utilization in terms of rates of various postoperative complications, length of hospital stay, and need for transitional care upon discharge. Patients with post-operative pancreatic fistula or intra-abdominal abscess formation were at risk for DGE. Anticipating DGE can help individualize care and allocate resources to high-risk patients.

Mohammed S, Van Buren II G, McElhany A, Silberfein EJ, Fisher WE. Delayed gastric emptying following pancreaticoduodenectomy: Incidence, risk factors, and healthcare utilization. *World J Gastrointest Surg* 2017; 9(3): 73-81 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i3/73.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i3.73

INTRODUCTION

Advances in surgery and critical care have decreased postoperative mortality following pancreaticoduodenectomy (PD) to less than 5% in high-volume centers, and, in addition, the management of post-operative morbidity has also improved[1-4]. However, delayed gastric emptying (DGE) remains one of the most frequent complications following PD, affecting 15%-30% of patients post-operatively[5-8]. DGE has been associated with increased hospital stay, higher readmission rates, and impaired quality of life[9,10]. Previous studies have suggested various factors that may influence DGE development, including technical approaches to PD (such as classic *vs* pylorus-preserving resection, antecolic *vs* retrocolic reconstruction) and presence of other intra-abdominal complications (such as pancreatic fistula or intra-abdominal abscess formation)[11-17].

The aims of this study were to examine a patient database and: (1) determine the incidence of DGE; (2) assess potentially associated risk factors for DGE; and (3) examine the impact of DGE on health care utilization. We hypothesized that the rate of DGE would be comparable to those reported in the literature; that other complications, such as postoperative pancreatic fistula (POPF) formation, may increase likelihood of DGE occurrence; and that DGE would be associated with increased use of health care resources.

MATERIALS AND METHODS

A prospectively-maintained database was queried to identify 276 consecutive patients who underwent PD at a single institution between 2005 and 2013. Data elements were extracted from this prospectively maintained database and charts were retrospectively reviewed to corroborate variables of interest. The 276 patients were classified into two groups: The group of patients who experienced postoperative DGE and the group of patients who did not.

Baseline demographics, clinical characteristics, and outcomes data were obtained from the medical charts and entered into a prospectively maintained database. Specific demographic data included age at time of diagnosis, gender, and race/ethnicity. The presence of co-morbid conditions, such as hypertension, diabetes mellitus, renal insufficiency, chronic pancreatitis, coronary artery disease, chronic obstructive pulmonary disease, and obesity were recorded, as were clinical characteristics such as presenting symptoms and specific laboratory values. The anesthesia reports were reviewed to record the American Society of Anesthesiologists classification score, operative time (defined as the time from incision to application of the final wound dressing), the estimated intraoperative blood loss, and intraoperative transfusion data. The operative reports were reviewed to record details of the procedure and intraoperative characteristics of the pancreas, such as texture and pancreatic duct size.

The primary outcome of interest was development of postoperative DGE, which was defined and graded using the International Study Group of Pancreatic Surgery (ISGPS) criteria[18]. With this definition, the severity of DGE was classified into grades based on the number of days nasogastric drainage was required and the number of days until solid oral intake was tolerated (Table 1). Grades B and C DGE were considered clinically significant.

Secondary outcomes of interest included rates of graded 90-d complications, length of hospital stay, reoperations and readmission rates, and need for transitional care upon hospital discharge. Operative mortality was defined as any death within 90 d of surgery. All complications were recorded using specific and standardized definitions.

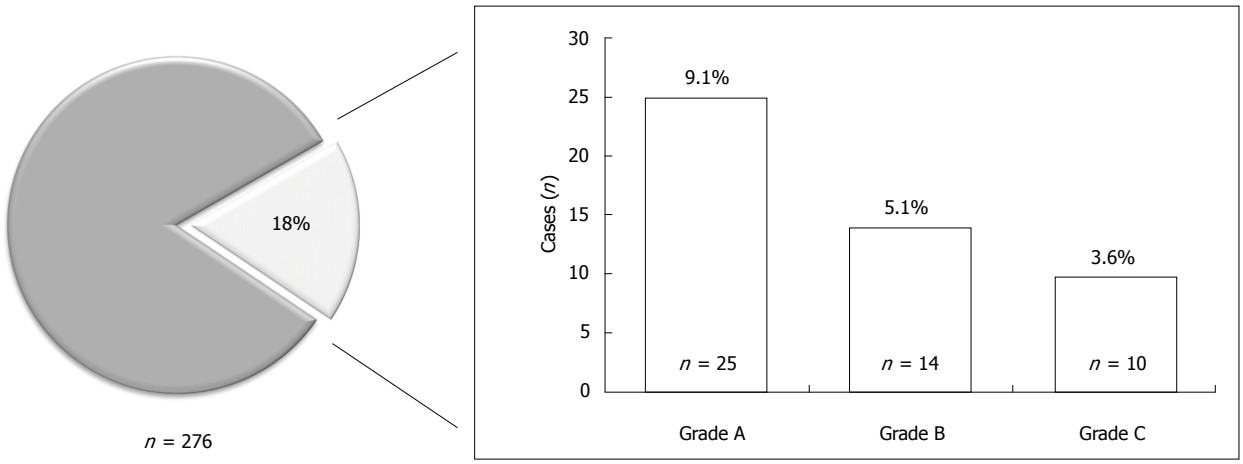

Figure 1 Incidence of post-operative delayed gastric emptying following pancreaticoduodenectomy. Among a cohort of 276 patients, 49 (17.8%) developed DGE. Among the 49 patients with DGE, 25 developed grade A DGE (representing 9.1% of the overall cohort of 276 patients), 14 developed grade B (5.1% of the overall cohort), and 10 developed grade C DGE (3.6% of the overall cohort). DGE: Delayed gastric emptying.

Table 1 Delayed gastric emptying classification based on International Study Group of Pancreatic Surgery definition

DGE grade	NGT required	Unable to tolerate solids orally by	Vomiting/distention	Use of prokinetics
A	4-7 d or reinsertion > POD 3	POD 7	±	±
B	8-14 d or reinsertion > POD 7	POD 14	+	+
C	14 d or reinsertion > POD 14	POD 21	+	+

Adapted from Wente *et al*[18]. NGT: Nasogastric tube; POD: Post-operative day; DGE: Delayed gastric emptying.

Complications were graded in severity using the Common Terminology Criteria for Adverse Events CTCAE (v4.03) (grade 1-5) unless otherwise specified[19]. Pancreatic fistula was graded using the International Study Group of Pancreatic Fistula (ISGPF) definition[20].

Statistical analysis

A descriptive analysis of the overall study cohort was performed. A univariate comparison of demographic, clinical, operative, and pathologic factors was performed between patients with and without DGE using Student *t* test for continuous variables and χ^2 test for categorical variables. In addition to the ISGPF definition for fistula, we also applied the fistula risk score (FRS) developed by Callery *et al*[21] to determine any potential association between the score and clinically significant DGE. The FRS is a ten-point scale that takes into consideration the weighted influence of four variables (soft pancreatic parenchyma, increased intraoperative blood loss, small duct size, and high-risk pathology) and may correlate with clinically relevant POPF development[21]. Multivariate logistic regression was then used to determine independent predictors of DGE in this cohort. Finally, data of the 49 DGE patients were further analyzed to determine duration of DGE, need for nutritional support, length of hospital stay, and discharge to transitional care facilities.

All results were reported with the appropriate summary statistic, measure of dispersion/variance, and measure of statistical significance. *P* values of < 0.05 were considered statistically significant. The statistical analysis was conducted using the Statistical Package or the Social Sciences, version 21 (SPSS Inc, Chicago, IL).

RESULTS

Of the 276 patients that underwent PD during the study period, 49 (17.8%) developed DGE. Of the 49 patients with DGE, 25 (9.1%) developed grade A, 14 (5.1%) developed grade B, and 10 (3.6%) developed grade C DGE (Figure 1). Characteristics of the overall study population and patients with and without DGE are shown in Table 2.

Patients with DGE had demographic features and clinical characteristics similar to those of patients without DGE. The majority of the patients (*n* = 221, 80.1%) underwent pylorus-preserving PD with antecolic hand-sewn enteric anastomosis (Table 3). None of the patients received a gastrostomy or jejunostomy tube and all nasogastric drainage tubes were removed in the operating room upon completion of the operation. Patients who developed DGE underwent procedures of comparable duration and had no significantly higher intraoperative blood losses. There was also no difference in the use of anastomotic pancreatic duct stents, the texture of the pancreas, or the distribution of pathological diagnoses in either group. The frequency and severity of complications were increased among patients who experienced DGE. Forty of the 49 patients (81.6%) with

Table 2 Demographic and clinical characteristics of overall study population and patients with or without delayed gastric emptying

	Overall (*n* = 276)	No DGE group (*n* = 227)	DGE Group (*n* = 49)	*P* values
Age	63.2 ± 11.92	62.9 ± 11.95	64.6 ± 11.77	0.348
Gender				0.339
Male	135 (48.9%)	108 (47.6%)	27 (55.1%)	
Female	141 (51.1%)	119 (52.4%)	22 (44.9%)	
Co-morbid conditions				
HTN	147 (53.3%)	119 (52.4%)	28 (57.1%)	0.568
COPD	13 (4.7%)	11 (4.8%)	2 (4.1%)	1
DM	67 (24.3%)	58 (25.6%)	9 (18.4%)	0.288
CRI	8 (2.9%)	6 (2.6%)	2 (4.1%)	0.635
History of pancreatitis	42 (15.2%)	36 (15.9%)	6 (12.2%)	0.557
History of ETOH use	122 (44.2%)	102 (44.9%)	20 (40.8%)	0.702
History of tobacco use	57 (20.7%)	49 (21.6%)	8 (16.3%)	0.390
BMI (mean ± SD)	26.7 ± 7.1	27.1 ± 7.28	25.6 ± 6.91	0.226
Presenting symptoms				
Weight loss	140 (50.7%)	115 (50.7%)	25 (51.0%)	0.921
Anorexia	29 (10.5%)	24 (10.6%)	5 (10.2%)	0.873
Early satiety	17 (6.2%)	16 (7.0%)	1 (2.0%)	0.323
Nausea	83 (30.1%)	74 (32.6%)	9 (18.4%)	0.058
Vomiting	43 (15.6%)	40 (17.6%)	3 (6.1%)	0.048
Jaundice	122 (44.2%)	103 (45.4%)	19 (38.8%)	0.419
Preop albumin	4.0 ± 0.60	4.0 ± 0.59	3.8 ± 0.62	0.038
Preop total bilirubin	2.5 ± 4.29	2.7 ± 4.49	1.8 ± 3.11	0.139
Preop hemoglobin	12.8 ± 1.85	12.8 ± 1.87	12.7 ± 1.76	0.734
Preop Cr > 1.2	40 (14.5%)	31 (13.7%)	9 (18.4%)	0.378

DGE: Delayed gastric emptying; HTN: Hypertension; COPD: Chronic obstructive pulmonary disease; DM: Diabetes mellitus; CRI: Chronic renal insufficiency; ETOH: Ethanol; BMI: Body mass index; Preop: Pre-operative; Cr: Creatinine.

Table 3 Operative and pathology details

	Overall (*n* = 276)	No DGE group (*n* = 227)	DGE Group (*n* = 49)	*P* values
ASA class				0.398
1	1 (0.4%)	1 (0.4%)	0 (0.0%)	
2	78 (28.3%)	59 (26.0%)	19 (38.8%)	
3	172 (62.3%)	144 (63.4%)	28 (57.1%)	
4	16 (5.8%)	14 (6.2%)	2 (4.1%)	
Operative time	452.1 ± 100.6	450.0 ± 100.87	461.6 ± 99.7	0.467
Procedure performed				0.169
Classic	55 (19.9%)	49 (21.6%)	6 (12.2%)	
Pylorus-preserving	221 (80.1%)	178 (78.4%)	43 (87.8%)	
EBL	515.7 ± 571.4	509.3 ± 533.59	544.0 ± 722.99	0.702
Transfusions	49 (17.8%)	37 (16.3%)	12 (24.5%)	0.178
Pancreas texture				0.264
Soft	144 (52.2%)	115 (50.7%)	29 (59.2%)	
Firm/hard	121 (64.8%)	103 (45.4%)	18 (36.7%)	
PD size	4.2 ± 2.29	4.3 ± 2.21	4.1 ± 2.65	0.612
PD anastomotic stent	117 (42.4%)	99 (43.6%)	18 (36.7%)	0.377
Vein resection	41 (14.9%)	34 (15.0%)	7 (14.3%)	0.902
Pathological diagnosis				
PDAC	118 (42.8%)	103 (45.4%)	15 (30.6%)	0.058
Neuroendocrine	12 (4.3%)	11 (4.8%)	1 (2.0%)	0.383
Ampullary	38 (13.8%)	30 (13.2%)	8 (16.3%)	0.567
Cystic	41 (14.9%)	32 (14.1%)	9 (18.4%)	0.446
Pancreatitis	33 (12.0%)	28 (12.3%)	5 (10.2%)	0.677
Cholangiocarcinoma	7 (2.5%)	5 (2.2%)	2 (4.1%)	0.807
Other	27 (9.8%)	18 (7.9%)	9 (18.4%)	0.026
Fistula risk score				
Negative (0 points)	34 (12.4%)	28 (12.4%)	6 (12.2%)	0.861
Low (1-2 points)	62 (22.6%)	58 (25.7%)	4 (8.2%)	0.008
Moderate (3-6 points)	138 (50.2%)	106 (46.9%)	32 (65.3%)	0.020
High (7-10 points)	30 (10.9%)	24 (10.6%)	6 (12.2%)	0.741

DGE: Delayed gastric emptying; ASA: American Society of Anesthesiologists; EBL: Estimated blood loss; PD: Pancreatic duct; PDAC: Pancreatic ductal adenocarcinoma.

Table 4 Rates of selected graded 90-d complication rates

	Overall (n = 276)	No DGE group (n = 227)	DGE Group (n = 49)	P values
Frequency of other complications (any grade)				
Patients with 0 complications	157 (56.9%)	157 (69.2%)	0 (0.0%)	< 0.001
Patients with 1 complication	51 (18.5%)	42 (18.5%)	9 (18.4%)	0.982
Patients with 2 complications	42 (15.2%)	18 (7.9%)	24 (49.0%)	< 0.001
Patients with 3 complications	11 (4.0%)	5 (2.2%)	6 (12.2%)	0.005
Patients with 4 complications	8 (2.9%)	5 (2.2%)	3 (6.1%)	0.153
Patients with ⩾ 5 complications	7 (2.5%)	0 (0.0%)	7 (14.3%)	< 0.001
Severity of complications				
Patients with any complication ⩾ Grade 3	60 (21.7%)	38 (16.7%)	22 (44.9%)	< 0.001
Patients with any complication ⩾ Grade 2	84 (30.4%)	47 (20.7%)	37 (75.5%)	< 0.001
Patients with any complication ⩾ Grade 1	119 (43.1%)	70 (30.8%)	49 (100.0%)	< 0.001
90-d mortality	6 (2.2%)	4 (1.8%)	2 (4.1%)	0.289
Re-operations	12 (4.3%)	10 (4.4%)	2 (4.1%)	1
Readmissions	40 (14.5%)	33 (14.5%)	7 (14.3%)	1
Pancreatic fistula	64 (23.2%)	43 (18.9%)	21 (42.9%)	0.001
Grade A	39 (14.1%)	29 (12.8%)	10 (20.4%)	
Grade B	19 (6.9%)	11 (4.8%)	8 (16.3%)	
Grade C	6 (2.2%)	3 (1.3%)	3 (6.1%)	
Bile leak	4 (1.4%)	1 (0.4%)	3 (6.1%)	0.019
Wound infection	20 (7.2%)	12 (5.3%)	8 (16.3%)	0.013
Wound dehiscence	3 (1.1%)	1 (0.4%)	2 (4.1%)	0.082
Intra-abdominal abscess	17 (6.2%)	9 (4.0%)	8 (16.3%)	0.012
Line infection	2 (0.7%)	2 (0.9%)	0 (0.0%)	0.033
Clostridium difficile	4 (1.4%)	1 (0.4%)	3 (6.1%)	0.019
Benign fluid collection	5 (1.8%)	2 (0.9%)	3 (6.1%)	0.041
Pneumonia	9 (3.3%)	5 (2.2%)	4 (8.2%)	0.056
Urinary tract infection	10 (3.6%)	5 (2.2%)	5 (10.2%)	0.018
Respiratory failure	9 (3.3%)	3 (1.3%)	6 (12.2%)	0.001
Encephalopathy	5 (1.8%)	1 (0.4%)	4 (8.2%)	0.004
Arrhythmia	16 (5.8%)	6 (2.6%)	10 (20.4%)	< 0.001
MI	4 (1.4%)	3 (1.3%)	1 (2.0%)	0.545
DVT	2 (0.7%)	2 (0.9%)	0 (0%)	1
PE	2 (0.7%)	2 (0.9%)	0 (0%)	1
Hemorrhage	4 (1.4%)	3 (1.3%)	1 (2.0%)	0.545
Renal failure	5 (1.8%)	3 (1.3%)	2 (4.1%)	0.216
Hepatic failure	1 (0.4%)	0 (0.0%)	1 (2.0%)	0.182
SMV/PV Thrombosis	8 (2.9%)	6 (2.6%)	2 (4.1%)	0.635

DGE: Delayed gastric emptying; MI: Myocardial infarction; DVT: Deep venous thrombosis; PE: Pulmonary embolism; SMV/PV: Superior mesenteric vein, portal vein.

DGE presented at least 1 other complication, whereas in the group of patients without DGE, 70% of patients presented no complications at all. Of the 49 patients with DGE, 37 (75.5%) had at least 1 complication greater than grade 2 severity in comparison to only 20.7% of patients in the group without DGE. Post-operatively, pancreatic fistula developed in 64 (23.2%) patients. Patients with DGE were more likely to experience clinically significant POPF than those without DGE (22.4% *vs* 6.2% grade B-C POPF, P < 0.001). Patients with DGE were also more likely to have intra-abdominal abscess (16.3% *vs* 4.0%, P = 0.012) (Table 4).

DGE lasted 8.7 d on average. However, many of the patients in the cohort had grade 1 DGE and, when excluded, the average duration of clinically significant grade B-C DGE was 14.5 d. A nasogastric tube was inserted in 14 of 24 patients (58.3%) with grade B-C DGE and managed with TPN in 69.8% of patients. Patients with DGE had a longer hospital stay (median, 12 d *vs* 7 d, P < 0.001) and were more likely to be discharged to transitional care facilities (24.5% *vs* 6.6%, P < 0.001) (Figure 2). They were equally likely to require reoperations or readmissions. Analysis of the FRS showed that 77.5% of patients with DGE had moderate or high scores (*vs* 57.5% of patients without DGE who had moderate or high scores). On multivariate analysis, patients with clinically significant post-operative pancreatic fistula formation and intra-abdominal abscess formation had a higher likelihood of having delayed gastric emptying (Table 5).

DISCUSSION

Delayed gastric emptying is one of the most common complications following PD, but it remains difficult to predict. Previous studies have suggested various factors associated with DGE development, such as technical approaches to pancreatectomy (classic *vs* pylorus-preserving resection or antecolic *vs* retrocolic reconstruction), and presence of other intra-abdominal

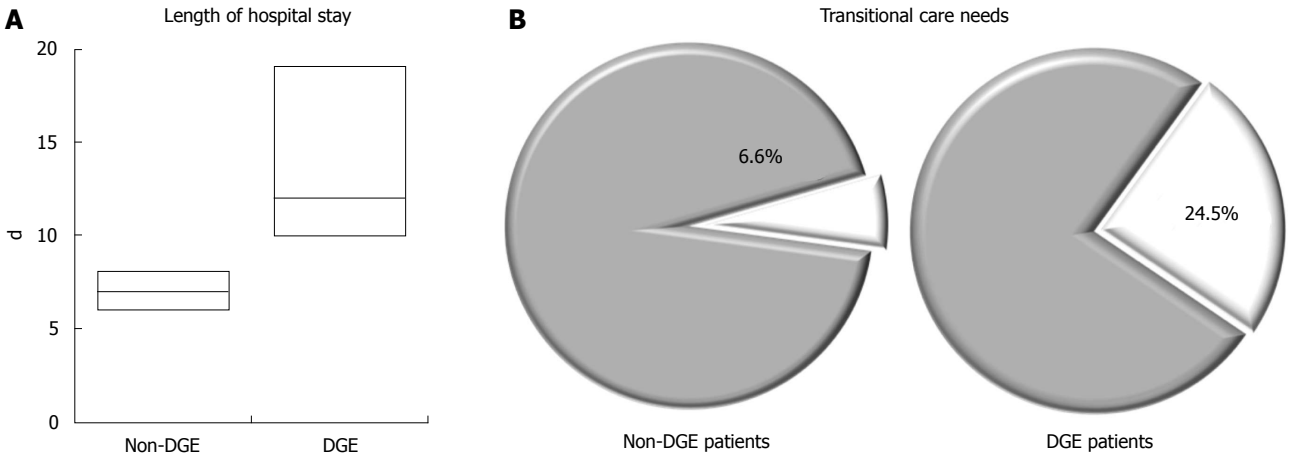

Figure 2 Health care utilization associated with delayed gastric emptying. Patients with DGE had a longer hospital stay (median 12 d *vs* 7 d, $P < 0.001$) and were more likely to be discharged to transitional care facilities (24.5% *vs* 6.6%, $P < 0.001$). DGE: Delayed gastric emptying.

Table 5 Multivariate analysis of the characteristics of patients with Pancreaticoduodenectomy

	Odds ratio (95%CI)	*P* value
Pancreatic fistula	3.39 (1.35-8.52)	0.009
Intra-abdominal abscess	1.51 (1.03-2.22)	0.035
PDAC diagnosis	1.01 (0.524-1.94)	0.982
Moderate/high FRS	0.99 (0.98-1.01)	0.463

PDAC: Pancreatic ductal adenocarcinoma; FRS: Fistula risk score.

complications such as pancreatic fistula or intraabdominal abscess formation[11-17]. In this series, we found a DGE rate of less than 20%; an association of DGE with a higher rate of post-operative complications, particularly post-operative pancreatic fistula formation; and significantly increased healthcare utilization, including longer length of hospital stay and greater need for transitional care upon discharge.

Most of our patients (n = 221, 80.1%) underwent pylorus-preserving PD without intraoperative placement of nasojejunal, gastrostomy, or jejunostomy tubes. All nasogastric tubes were removed in the operating room upon completion of the operation. Reinsertion of a nasogastric tube for gastric decompression, or inability to tolerate oral intake, or abdominal distention, emesis, or need for prokinetic agents thus constituted DGE based on ISGPS criteria (Table 1). Although our DGE rate was relatively low and consistent with the rates of other reported series, it was associated with other complications and lengthier hospital stay, and this raised the question of whether specific interventions, such as prophylactic placement of enteric tubes, may be worthwhile to mitigate potential consequences of DGE.

Mack *et al*[22] conducted a randomized study between 1999 and 2002 to assess the feasibility and safety of prophylactically placing double-lumen gastrojejunostomy tubes in patients undergoing PD. They found that insertion of a gastrojejunostomy tube was safe and decreased the incidence of DGE, length of hospital stay, and hospital costs[22]. They viewed the insertion of the gastrojejunostomy tube as an adjunctive measure for providing gastric decompression without the need for a nasogastric tube or its associated risk for respiratory discomforts, and also as a means of providing enteral nutrition, should it be needed. No larger trials have been conducted to confirm Mack *et al*'s[22] findings or to determine the effect of similar interventions on long-term quality of life, nutritional outcomes, or receipt of oncologic care, such as time to initiation of adjuvant therapy. Widespread adoption of this approach in the perioperative setting would, however, expose the majority of patients to tubes they may not need postoperatively, as well as to associated complications, such as tube dislodgments, leaks, infections, aspiration, and peritonitis[23].

In our study, a nasogastric tube was inserted postoperatively for gastric decompression in 14 of 24 patients (58.3%) with grade B or C DGE. We did not observe any complications with placement of a nasogastric tube in the early postoperative period. If grade B or C DGE persisted, patients were either supported with TPN and/or a nasojejunal feeding tube for enteral feeding was placed by an interventional radiologist. We did not use endoscopically placed gastrostomy or combined gastrostomy-jejunal tubes. Although we did not perform any cost estimate analysis of parenteral *vs* enteral feeding in this cohort, it is well established that enteral nutrition is less costly than TPN[24,25]. Data from Mack *et al*[22], as well as cost-analysis modeling[26], demonstrated that costs for patients treated with a gastrojejunostomy tube were less than those for patients treated without a gastrojejunostomy, even though 100% of patients in the gastrojejunostomy group received nutritional supplementation compared with only 20% to 40% of the patients in the group treated by more standard methods[22,26].

In an era focused on increasing patient throughput and standardizing postoperative care plans, identifying

patients who may deviate from the expected postoperative course and implementing strategies to curtail downstream effects is important. Placing enteral tubes in all patients undergoing PD would certainly result in significant over-treatment and risk complications associated with the tube. However, placement in patients at higher risk for developing DGE could potentially facilitate an earlier discharge, improve patient comfort, and decrease health care costs.

Our multivariate analysis showed that patients with pancreatic fistula or intra-abdominal abscess formation had a significantly higher likelihood of developing DGE. This correlation is consistent with those found in other published series[27,28]. In a large multi-institutional study of the American College of Surgeons National Surgical Quality Improvement Program Pancreatectomy Demonstration Project, only pancreatic fistula, postoperative sepsis, and reoperation were independently associated with DGE in 711 patients undergoing PD or total pancreatectomy[27].

Although the majority of patients with DGE in this study also had other postoperative complications, we did identify 9 patients with isolated DGE. These patients were no different than patients without DGE with regards to clinical features or operative factors. Five of these 9 cases of DGE were clinically insignificant and lasted between 4 to 6 d. Although our DGE rate in this series is around 20%, which is consistent with those reported in the literature, this rate captures patients with even clinically-insignificant episodes of DGE as well as those patients who required insertion of nasogastric tube for reasons that may not have been related to DGE, such as prolonged intubation secondary to pneumonia. These patients, however, represent a very small subset of patients with DGE.

The DGE rate in this series is lower than most other institutional experiences reported in the literature, such as the series by Welsch *et al*[29] in which a DGE rate of 44.5% was recorded. While most operative features, such as rate of vascular reconstruction, operative time, estimated blood loss, and patient co-morbidities appear similar to our series, we believe the low rate in this series is due largely to the uniformity of surgical approach within our cohort. All cases were performed by a single surgeon in a consistent manner utilizing a pylorus preserving pancreaticoduodenectomy with hand-sewn antecolic enteric anastomoses. While we cannot conclude that any one particular technique leads to lower rates of DGE, this series does demonstrate that consistency and experience over time with a specific method can allow it to be safely performed with acceptable outcomes.

Because of the association between pancreatic fistula and intra-abdominal abscess formation with DGE in this series as well as others, efforts to reduce morbidity of these common post-operative complications should continue. If patients identified as higher risk for POPF or abscess formation are the same ones identified as higher risk for DGE development, perhaps these patients may benefit from specific treatment approaches, such as prophylactic intraoperative placement of nasojejunal tubes or gastrojejunostomy tubes. Anticipating DGE in patients may also allow providers to plan for potential delays in recovery, individualize patient care, and improve allocation of resources (such as transitional care) to high-risk patients. We applied the FRS to our study population in order to determine whether a higher score correlated with increased risk of DGE. While on univariate analysis, a moderate to high FRS correlated with development of DGE, on multivariate analysis, a moderate-high FRS did not predict greater likelihood of DGE development postoperatively. However, the authors believe that further evaluation of the FRS in larger studies or in a prospective manner is warranted to truly determine if this score can aid in identifying patients with DGE.

Limitations of the current study include its retrospective nature and a relatively small cohort of patients with DGE. Strengths of this study include the homogeneity of the study population and the perioperative care. The patients were all operated on in a largely uniform manner (pylorus-preserving resection, antecolic reconstruction) and treated similarly post-operatively (no nasogastric decompression tubes, standardized postoperative care plans, *etc.*). Furthermore, no patients were excluded from this study and detailed post-operative data up to at least 90 d post-operatively is available for each of our patients. In this homogenous population, we identified the presence of postoperative fistula as the only predictor for DGE. Furthermore, w were able to demonstrate an association between moderate/high FRS and clinically significant DGE, suggesting a potential role of this score in predicting clinically significant DGE as well as POPF formation.

In summary, although DGE occurred in less than 20% of patients undergoing PD, it was associated with significantly higher complication rates, longer hospital stay, and increased healthcare utilization postoperatively. Patients with a high risk for pancreatic fistula or intra-abdominal abscess formation are at higher risk for developing DGE. Anticipating DGE in patients following PD is important and may allow providers to plan for potential delays in recovery, individualize patient care, and improve allocation of resources to high-risk patients.

COMMENTS

Background

Delayed gastric emptying (DGE) remains one of the most frequent complications following pancreaticoduodenectomy (PD), affecting 15%-30% of patients post-operatively. DGE has been associated with increased hospital stay, higher readmission rates, and impaired quality of life.

Research frontiers

The aims of this study were to examine a patient database and: (1) determine the incidence of DGE; (2) assess potentially associated risk factors for DGE; and (3) examine the impact of DGE on health care utilization.

Innovations and breakthroughs

DGE occurred in less than 20% of patients undergoing PD. It was associated with significantly higher complication rates, longer hospital stay, and increased

healthcare utilization postoperatively. Patients with a high risk for pancreatic fistula or intra-abdominal abscess formation were at higher risk for developing DGE.

Applications

Anticipating DGE in patients following PD is important and may allow providers to plan for potential delays in recovery, individualize patient care, and improve allocation of resources to high-risk patients.

Peer-review

It is a well written manuscript analyzing the DGE in PF. All the analyses are well explained and supported with facts.

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ORIGINAL ARTICLE

Observational Study

Resection of complex pancreatic injuries: Benchmarking postoperative complications using the Accordion classification

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Author contributions: Krige JE designed and conducted the study; Krige JE, Jonas E and Kotze UK collected and analysed and interpreted the data; Setshedi M performed the statistical analysis; Krige JE, Jonas E, Thomson SR drafted the manuscript; Navsaria PH and Nicol AJ conducted critical revisions; all authors read and approved the final version of the manuscript.

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Abstract

AIM

To benchmark severity of complications using the Accordion Severity Grading System (ASGS) in patients undergoing operation for severe pancreatic injuries.

METHODS

A prospective institutional database of 461 patients with pancreatic injuries treated from 1990 to 2015 was reviewed. One hundred and thirty patients with AAST grade 3, 4 or 5 pancreatic injuries underwent resection (pancreatoduodenectomy, *n* = 20, distal pancreatectomy, *n* = 110), including 30 who had an initial damage control

laparotomy (DCL) and later definitive surgery. AAST injury grades, type of pancreatic resection, need for DCL and incidence and ASGS severity of complications were assessed. Uni- and multivariate logistic regression analysis was applied.

RESULTS

Overall 238 complications occurred in 95 (73%) patients of which 73% were ASGS grades 3-6. Nineteen patients (14.6%) died. Patients more likely to have complications after pancreatic resection were older, had a revised trauma score (RTS) < 7.8, were shocked on admission, had grade 5 injuries of the head and neck of the pancreas with associated vascular and duodenal injuries, required a DCL, received a larger blood transfusion, had a pancreato-duodenectomy (PD) and repeat laparotomies. Applying univariate logistic regression analysis, mechanism of injury, RTS < 7.8, shock on admission, DCL, increasing AAST grade and type of pancreatic resection were significant variables for complications. Multivariate logistic regression analysis however showed that only age and type of pancreatic resection (PD) were significant.

CONCLUSION

This ASGS-based study benchmarked postoperative morbidity after pancreatic resection for trauma. The detailed outcome analysis provided may serve as a reference for future institutional comparisons.

Key words: Pancreas; Injury; Complications; Accordion classification

Core tip: Pancreatic injuries result in considerable morbidity and mortality rates if the injury is inadequately treated. This analysis benchmarked the severity of complications after pancreatic resection for trauma using the Accordion Severity Grading System. By applying univariate logistic regression analysis, the mechanism of injury, a revised trauma score < 7.8, shock on admission to hospital, the need for an initial damage control laparotomy, an increasing pancreatic injury grade and the type of pancreatic resection were found to be significant variables for complications. However, multivariate logistic regression analysis showed that only age and the type of pancreatic resection were significant. Post-operative morbidity after pancreatic resection for trauma in this study was substantial and an increasing complication severity grade, as measured by the Accordion severity scale, required escalation of intervention and prolonged hospitalisation.

Krige JE, Jonas E, Thomson SR, Kotze UK, Setshedi M, Navsaria PH, Nicol AJ. Resection of complex pancreatic injuries: Benchmarking postoperative complications using the Accordion classification. *World J Gastrointest Surg* 2017; 9(3): 82-91 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i3/82.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i3.82

INTRODUCTION

Major pancreatic resections are technically complex procedures, especially so when performed as an emergency in severely injured patients who also have multiple other injuries[1,2]. There are wide-ranging disparities in the reported overall postoperative morbidity rates after pancreatic injuries due to non-standardised analyses and a lack of comprehensive datasets which specifically document outcome after resection of complex pancreatic injuries[3-5]. The absence of an appropriate and defined methodology to measure and register peri-operative outcome, precludes the generation of validated outcome data, fundamental to accurate benchmarking of surgical performance and internal quality control[6]. Both the number and severity of postoperative complications are recognised key short-term surrogate markers of the quality of operative intervention and surgical outcome[7].

The development and application of internationally accepted and validated International Study Group of Pancreatic Surgery (ISGPS) definitions of complications in elective pancreatic surgery has provided accurate, robust and consistent data which has allowed reliable comparisons of, for example, the incidence of post-operative pancreatic fistulas[8], bleeding[9] and delayed gastric emptying (DGE)[10]. Similarly, the 6-scale Accordion Severity Grading System (ASGS) which discriminates post-operative complication severity following elective surgery on the basis of escalating interventional criteria, is now widely accepted as a credible, scoring system which is easy to apply and is reproducible with minimal inter-observer variability[11].

Earlier studies assessing outcome after pancreatic resections for major pancreatic injuries have applied unqualified primary endpoints with differing descriptions and definitions which consequently have resulted in flawed conclusions. Our group has previously evaluated other aspects of pancreatic trauma and, as one of the world's busiest high volume academic trauma centers, has sufficient prospective granular data available to investigate organ-specific research questions[12-15]. The aim of this research project was to provide a detailed analysis to benchmark the severity of complications after pancreatic resection for severe trauma in a civilian patient population using the ASGS.

MATERIALS AND METHODS

Study design

Groote Schuur Hospital is a high-volume, integrated academic referral centre serving a population of 3 million people with an annual operative trauma volume averaging 13000 patients. All HPB trauma is managed in the Level 1 Trauma Centre in conjunction with the Hepatopancreatobiliary and Surgical Gastroenterology units. A retrospective analysis of prospectively collected data derived from a comprehensive and dedicated institutional pancreatic trauma database which includes clinical, operative and postoperative information on all

Table 1 Expanded Accordion Classification

	Expanded Accordion Classification (levels of severity)
Mild	Requires only minor invasive procedures that can be done at the bedside physiotherapy and the following drugs are allowed: Antiemetics, antipyretics, analgesics and electrolytes
Moderate	Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics Blood transfusions and total parenteral nutrition are also included
Severe	Invasive procedure/no GA, requires management by an endoscopic, interventional procedure or re-operation without general anesthesia
Severe	Invasive procedure under GA or single organ system failure requires management by an operation under general anesthesia or results in single organ system failure
Severe	Organ system failure and invasive procedure under GA or multisystem organ failure, such complications would normally be managed in an increased acuity setting but in some cases patients with complications of lower severity might also be admitted to an ICU
Deaths	Postoperative death

GA: General anaesthetic; ICU: Intensive care unit.

patients treated for pancreatic trauma was performed of all adult patients who had a resection for a pancreatic injury between January 1990 and April 2015. Current guidelines of good clinical practice were followed and data collection and analysis were approved by the departmental, institutional and university research and ethics review boards. A statistical review of the study was performed by a biomedical statistician.

Data collection

The medical records including operative, intensive care, radiology and endoscopy reports were reviewed and data abstracted were entered by a specially trained nurse reviewer and recorded using a standardised data form after affirmation by a senior study surgeon. Details of the methodology used to record the variables for each patient have previously been published[12-17]. A comprehensive data set of complications and related key variables were recorded.

Classification of surgical complications

Postoperative complications were scored using the expanded ASGS[11] (Table 1). In this study grade 1 and 2 complications were regarded as minor, grade 3 as moderate, 4 as serious and grade 5 complications as life-threatening. Grade 6 complications resulted in the death of the patient and included death from any cause within 30 d of surgery. The overall complication rate was reported as the number of patients with at least one complication. In patients with several complications, the highest graded complication was used for analysis of the complication severity.

Definitions

Shock was defined as a systolic blood pressure less < 90 mm Hg pre- or intra-operatively. Pancreatic injury grade[18], pancreatic fistula[8], organ dysfunction[19], infectious complications and septic shock[20] were defined and graded according to internationally consensus guidelines.

Initial management

Initial resuscitation was implemented using Advanced Trauma Life Support (ATLS) guidelines. Emergency surgery was undertaken in patients who had an acute abdomen with clinical signs of peritonitis or evidence of major intra-abdominal bleeding. From 1995 onwards hemodynamically unstable patients who had major associated organ and visceral vascular injuries had an initial damage control laparotomy (DCL) before later definitive intervention[21]. Patients in whom imaging revealed the need for intervention or had a high clinical suspicion of a major pancreatic injury underwent urgent exploration.

Operative management of pancreatic injury

Operative management of the pancreatic injury was based on our institutional trauma protocol, based on the hemodynamic stability of the patient, the magnitude and extent of associated injuries and the location and severity of the pancreatic injury[12,22]. In brief, major lacerations of the body or tail of the pancreas with likely duct injury were treated by distal pancreatectomy. Pancreatoduodenectomy (PD) was restricted to patients with non-salvageable injuries who had disruption of the ampulla of Vater or major devitalising injuries of the pancreatic head and duodenum and was done as a primary procedure during the initial operation if the patient was stable or as a secondary staged procedure after the DCL. A pylorus-preserving PD was the preferred pancreatic head resection[16]. All pancreatic resections were drained intra-operatively.

DCL

DCL was applied in critically injured patients with severe metabolic acidosis as indicated by a pH < 7.2, hypothermia with a core temperature < 35 ℃ or coagulopathy[21]. This involved an abbreviated laparotomy for rapid control of intra-abdominal bleeding, closure of visceral perforations and temporary abdominal wall closure. Patients were transferred to an intensive care unit for invasive monitoring, cardiopulmonary support and urgent volume replacement to correct acidosis, coagulopathy and hypothermia and restore normal physiology[23].

Management of postoperative intra-abdominal, pancreatic and duodenal complications

Postoperative intra-abdominal collections were drained

Table 2 Demographic and clinical data for patients with and without complications

	Total (n = 130)	Those with complications (n = 95)	Those without complications (n = 35)	P-value
Age (yr), median (range)	26 (13-73)	28 (13-73)	24 (15-59)	0.0064[a]
Mechanism of injury				
GSW	88 (67.7%)	63 (66.3%)	25 (71.43%)	0.6490[c]
Stab	7 (5.4%)	6 (6.3%)	1 (2.86%)	
Blunt	35 (26.9%)	26 (27.3%)	9 (25.71%)	
Hospital stay, median (range)	8 (1-255)	23 (1-255)	9 (5-58)	0.0000[a]
ICU stay	77 (59.23%)	68 (71.58%)	9 (25.71%)	0.0000[b]
Number ICU days, median (range)	3 (0-153)	4 (0-153)	3 (0-7)	0.0000[a]
RTS				
< 7.8	49 (37.69%)	44 (46.32%)	5 (14.29%)	0.001[b]
7.8	81 (62.3%)	51 (53.68%)	30 (85.71%)	
Patients shocked on admission (n, %)	46 (35.4%)	42 (44.21%)	4 (11.43%)	0.001[b]
Patients who received a blood transfusion (n, %)	103 (79.2%)	79 (83.16%)	24 (68.57%)	0.069[b]
Units of blood transfused, median units (range)	84.5 (0-124[a])	8 (0-124)	2 (0-28)	0.0000[a]
Damage control surgery	30 (23.1%)	27 (28.42%)	3 (8.57%)	0.0176[b]
Pancreatic injury site				
Head and neck of pancreas	24 (18.5%)	20 (21.05%)	4 (11.43%)	0.0443[c]
Body of pancreas	57 (43.8%)	44 (46.32%)	13 (37.14%)	
Tail of pancreas	49 (37.7%)	31(32.63%)	18 (51.43%)	
AAST				
Grade 3	107 (82.3%)	74 (77.89%)	33 (94.28%)	0.0297[c]
Grade 4	4 (3.1%)	3 (3.16%)	1 (2.86%)	
Grade 5	19 (14.6%)	18 (18.95%)	1 (2.86%)	
Associated abdominal injuries				
Nil (isolated injury)	14 (10.8%)	10 (10.53%)	4 (11.43%)	0.8833[c]
1 or 2 organs injured	51 (39.2%)	37 (38.95%)	14 (40%)	
3 or more injured	65 (50%)	48 (50.53%)	17 (48.57%)	
Associated injured organs				
Liver	53 (40.7%)	40 (42.11%)	13 (37.14%)	0.6109
Kidney	53 (40.7%)	34 (35.79%)	19 (54.29%)	0.0579
Spleen	52 (40%)	39 (41.05%)	13 (37.14%)	0.6876
Stomach	49 (37.7%)	32 (33.68%)	17 (48.57%)	0.1217
Diaphragm	38 (29.2%)	28 (29.47%)	10 (28.57%)	0.9204
Colon	32 (24.6%)	27 (28.42%)	5 (14.29%)	0.0983
Duodenum	22 (16.9%)	20 (21.05%)	2 (5.71%)	0.0393[a]
Pancreatic resection type				
Pancreaticoduodenectomy	20 (15.4%)	19 (20%)	1 (2.86%)	0.0004[c]
Distal pancreatectomy and splenectomy	95 (73%)	70 (73.68%)	25 (71.4%)	
Distal pancreatectomy with spleen preservation	15 (11.5%)	6 (6.32%)	9 (25.7%)	
Associated vascular injuries	24 (18.5%)	24 (25.26%)	0 (0%)	0.001[b]
Patients who had a repeat laparotomy (n, %)	58 (44.6%)	55 (57.89%)	3 (8.57%)	0.0000[b]
No. of repeat laparotomies done, median (range)	0 (1-10)	1 (0-10)	0 (0-1)	0.0000[a]
Death	19 (14.62%)	19 (20%)	0 (0%)	0.004[b]

[a]WRS: Wilcoxon rank sum; [b]CS: χ^2; [c]KW: Kruskal-wallis. RTS: Revised trauma score; GSW: Gunshot wound.

percutaneously using ultrasound- or CT-guided catheter placement. Endoscopic therapy techniques were used to treat persistent pancreatic and duodenal fistulas and pancreatic fluid collections[24,25].

Statistical analysis

The data were analysed using Stata version 11 (Stata Corp. 2009. Stata: Release 11. Statistical Software. College Station, TX: StataCorp LP). For bivariate analysis the Pearson chi-square or Kruskal-Wallis tests were used for categorical variables, and the non-parametric Wilcoxon rank-sum test for numerical variables. Univariate and multivariate logistic regression models were used to evaluate the odds ratios (OR) and 95% confidence intervals of clinical variables (while excluding collinearity). All statistical tests were two-tailed and a P-value < 0.05 was considered statistically significant.

RESULTS

Patient demographics

Between January 1990 and April 2015 a total of 461 patients were treated for pancreatic injuries of whom 130 had a pancreatic resection for either grade 3, 4 or 5 injuries. Most patients were men and 74% had sustained penetrating injuries, predominantly gunshot wounds (GSW) (Table 2). One third of patients were shocked on admission and 30 patients (23.1%) had an emergency operation.

Anatomic site and severity of injury

One-fifth of patients had pancreatic head or neck injuries and four-fifths had injuries involving either the pancreatic body or tail. More than 80% sustained AAST grade 3 injuries and 18% had grade 4 or grade 5

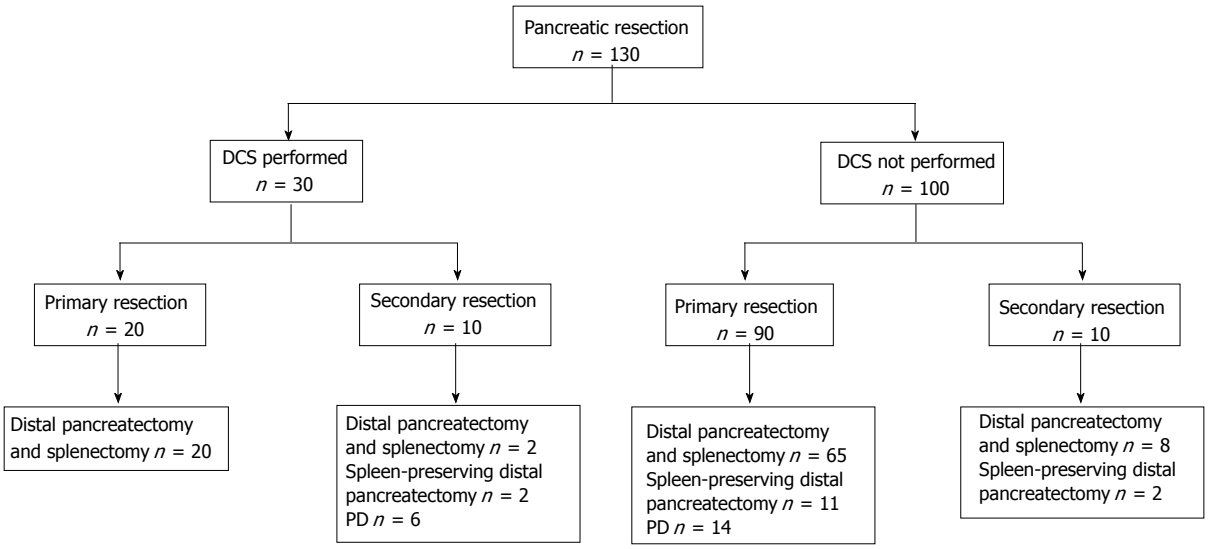

Figure 1 Pancreatic resection for trauma in 130 patients. PD: Pancreatoduodenectomy; DCS: Damage control of surgery.

injuries (Table 2).

Associated injuries

Fifty-two patients (40%) had 77 extra-abdominal injuries of whom 65 (50%) had three or more associated adjacent organ injuries, predominantly involving the liver and spleen. Fourteen patients had an isolated pancreatic injury. Twenty-four patients (18%) had associated vascular injuries, of whom 15 had an IVC injury. The presence of an associated vascular injury correlated significantly (P = 0.007) with shock at presentation.

Surgery

The 130 patients underwent a total of 287 laparotomies. Their surgical therapy is detailed in Figure 1. Thirty of the 130 patients (23%) had an initial DCL. Twenty patients had a PD, 14 of which were completed during the index laparotomy and 6 at a second laparotomy. Thirteen patients underwent a pylorus-preserving PD, and 7 had a conventional PD. Fifty-eight patients (44.6%) had a repeat laparotomy (range 1-10), 25 following an initial DCL, 16 for intra-abdominal infection unresolved by percutaneous catheter drainage, 10 for control of intra-abdominal bleeding and 7 for small bowel obstruction. Ninety five patients (73.1%) had a distal pancreatectomy and splenectomy, and 15 (11.5%) had a spleen-preserving distal pancreatectomy.

Complications

Of the 130 patients who had a pancreatic resection, 35 made an uneventful recovery without any postoperative complications. A total of 238 complications occurred in the remaining 95 patients. The severity of postoperative complications as classified using the ASGS is summarized in Table 3. Twenty-nine events were related to bleeding (intra-abdominal bleeding: n = 11, DIC: n = 18), 52 patients had respiratory related complications (21.8% of all events) and 20 had renal complications (8.4% of all events). Systemic sepsis occurred in 19 patients, intra-abdominal infections in 42 and wound infection in nine. Overall complications occurred in 95% of patients who had a PD compared to 69% who had a distal pancreatectomy (P = 0.0004).

Thirty-three patients had a total of 36 pancreatic complications following pancreatic resection (Table 4). Twenty-four patients developed a pancreatic fistula, 15 of which resolved on conservative management alone. Nine patients with persistent fistulae had ERCP with sphincterotomy and pancreatic duct stenting (n = 7) or pancreatic duct sphincterotomy only (n = 2). Two patients developed symptomatic pseudocysts which were treated with endoscopic ultrasound-guided transgastric stent drainage. Eight patients had peri-pancreatic fluid collections of which seven were successfully drained percutaneously. One patient with a complex pancreato-colo-cutaneous fistula underwent a left hemicolectomy. Three of 20 patients (15%) developed a pancreatic fistula after PD compared to 21 of 110 (19%) after a distal pancreatectomy (Table 4).

Duration of hospital stay was analysed for the different ASGS grades. In patients with more than one complication the highest grade was used. Those with no post-operative complications (grade 0, n = 35) had a median 9 (range: 5-58) day post-resection hospital stay. Grade 1 patients (n = 3) spent 14, 23 and 34 d in hospital, grade 2 (n = 14, median 22, range 6-94 d), grade 3 (n = 17, median 24, range: 9-58 d), grade 4 (n = 40, median 33, range: 7-255 d), grade 5 (n = 2, 9 and 19 d) and grade 6 (n = 19, median 14, range: 1-52).

Mortality

Nineteen patients (14.6%) died post-operatively (GSW 15, blunt 3, stab 1) of whom 13 were shocked on admission, 10 had major vascular injuries, 11 had 3 or more associated abdominal organ injuries required a median of 25 units of blood (range 4-89). Five

Table 3 Accordion Severity Grade in 130 patients

Accordion Severity Grade	Mild	Moderate	Severe: Invasive/no GA	Severe: Invasive/GA	Severe: Organ failure	Death	Total
	1	2	3	4	5	6	*n* = 130
Surgical complications							
Pancreatic							
Fistula	1	11	6	6[a]	--	--	24 (18.5%)
Peri-pancreatic collection	--	3	4	1	--	--	8 (6.6%)
Pseudocyst	--	--	1	1	--	--	2 (1.5%)
Pancreatic necrosis				2			2 (1.5%)
Intra-abdominal							
Postoperative ileus	2	--	--	--	--	--	2 (1.5%)
Intra-abdominal infection	--	9	17	16	--	--	42 (32.3%)
Biliary fistula	--	1	--	1	--	--	2 (1.5%)
Small bowel obstruction	--	1	--	7	--	--	8 (6.6%)
Enterocutaneous fistula	--	9	--	--	--	--	9 (6.9%)
Anastomotic leak	--	--	--	3	--	--	3 (2.3%)
Abdominal compartment syndrome	--	--	--	3	--	--	3 (2.3%)
Wound							
Wound infection	--	7	--	2[b]	--	--	9 (6.9%)
Wound dehiscence	--	1	--	1	--	--	2 (1.5%)
Bleeding							
Intra-abdominal	--	4	--	6	--	1	11 (8.5%)
DIC	--	7	--	--	6	5	18 (13.8%)
Non-surgical complications							
Respiratory							
Pleural effusion	9	2	--	--	--	--	11 (8.5%)
Atelectasis	2		--	--	--	--	2 (1.5%)
Pneumonia	--	14	--	--	--	--	14 (10.7%)
Respiratory failure	--	--	--	10	6	9	25 (19.2%)
Renal							
Renal failure	--	--	--	8	10	1	19 (14.6%)
Intra-abdominal urine leak	--	--	--	1	--	--	1 (0.8%)
Systemic sepsis	--	12	--	--	4	3	19 (14.6%)
Other	1[c]	1[d]	--	--	--	--	2 (1.5%)
Total	15 (6.3%)	82 (34.5%)	28 (11.8%)	68 (28.6%)	26 (10.9%)	19 (8.0%)	238

[a]Pancreatic-colo-cutaneous fistula (one patient), [b]Abdominal wall sepsis, [c]Jaundice, [d]Bedsore, GA: General anaesthetic; DIC: Disseminated intravascular coagulation.

deaths occurred within the first 24 h as a result of complications related to bleeding, DIC and shock due to a combination of complex peri-pancreatic visceral vascular injuries. Fourteen patients died after 24 h (median 17 d, range 2-52 d) of multi-organ failure (MOF), respiratory failure (*n* = 9), DIC (*n* = =5), septic shock (*n* = 3), renal failure (*n* = 1) and abdominal bleeding (*n* = 1). Four patients (20%) died after PD, including two of the six patients who underwent a delayed PD and reconstruction after DCL (Table 4).

Patients who were older, those who had a RTS $\geqslant$ 7.8, were shocked on admission, had grade 5 injuries with associated vascular or duodenal injuries, required a DCL, received a larger blood transfusion, had a PD or repeat laparotomies were more likely to have complications after pancreatic resection (Table 2). Applying univariate logistic regression analysis mechanism of injury, RTS $\geqslant$ 7.8, shock on admission, DCL, greater AAST grade and type of pancreatic resection (PD) were significant variables for complications (Table 5). Multivariate logistic regression analysis, however showed only age and type of pancreatic resection (PD) to be significant (Table 5).

DISCUSSION

The present study is the largest series to date of consecutive patients undergoing a major pancreatic resection for trauma and represents a select cohort of severe pancreatic injuries with the common denominator a main pancreatic duct injury. To our knowledge, this is the first study to examine ASGS metrics to assess the usefulness of the scoring system to benchmark the spectrum and severity of complications after pancreatic resection for trauma. Unlike the planning and precision of elective pancreatic resections performed under controlled conditions with prior knowledge of co-morbidities, extent of pathology and anatomical considerations, the complexities and unpredictable operative demands surgeons are faced with during a pancreatic resection for trauma frequently require flexible or innovative strategies[22]. There seldom is the opportunity to evaluate and study the details of the injury pre-operatively and resection is often undertaken under unfavourable circumstances when other competing life-threatening injuries are present and take precedence[16].

Table 4 Outcome according to type of pancreatic resection performed

	Pancreaticoduodenectomy (n = 20)	Distal pancreatectomy and splenectomy (n = 95)	Distal pancreatectomy with spleen preservation (n = 15)	P-value[1]
No. of patients with any complication	19 (95%)	70 (73.7%)	6 (40%)	0.0014
Complications non-surgical	15 (75%)	58 (61.1%)	2 (13.3%)	0.0006
Complications surgical (Other)	12 (60%)	37 (38.9%)	4 (26.7%)	0.1111
Complications pancreatic	3 (15%)	25 (26.3%)	5 (33.3%)	0.4339
Days in hospital, median (range)	22 (3-94)	17 (1-255)	15 (5-58)	0.1797
ICU admissions	19 (95%)	55 (57.9%)	3 (20%)	0.0001
Days in ICU, median (range)	4 (1-20)	7 (1-153)	7, 9, 16 respectively	0.0099
Outcome died	4 (20%)	14 (14.7%)	1 (6.7%)	0.5445

[1]Kruskal Wallis. ICU: Intensive care unit.

Table 5 Logistic regression analysis of risk factors for developing complications

Risk factor	Univariate logistic regression			Multivariate logistic regression		
	Odds ratio	95%CI	P-value	Odds ratio	95%CI	P-value
Age median, range	0.9	0.58-1.43	0.699	0.9	0.82-0.99	0.031
Mechanism of injury	0.9	0.89-0.98	0.017	0.4	0.12-1.39	0.155
RTS (< 7.8)	5.1	1.85-14.5	0.002	10.8	0.15-788	0.277
No. of patients shocked on admission	6.1	2.0-18.8	0.001	0.5	0.00-30.2	0.728
No. of patients who received a blood transfusion	2.3	0.93-5.53	0.073	0.5	0.00-3.64	0.486
Damage control surgery	1.6	1.18-2.2	0.030	1.36	0.68-2.69	0.373
Pancreatic injury site	1.8	0.99-3.15	0.050	2.4	0.57-100	0.231
AAST	0.5	0.23-0.92	0.028	3.8	0.67-21.9	0.131
Pancreatic resection type	4.8	1.91-12.0	0.001	65.7	3.13-1381	0.007
Associated abdominal injuries	1.1	0.32-3.7	0.883	12.9	0.39-423	0.152

The accurate intra-operative assessment of major pancreatic injuries may be complex and the surgeon may be faced with a range of uncertainties, some of which only become apparent during the procedure[16,17,22]. When major blood loss and shock occur, strategies including rapid haemostasis and damage control intervention become imperative, necessitating deferred resection and/or reconstruction at a more opportune time when abnormal physiological parameters have been restored[17,26]. After resection, technical difficulties may arise in the reconstruction of the pancreatic and biliary anastomoses due to a mismatch in size with non-dilated biliary and pancreatic ducts, often aggravated by gross edema of the jejunum and small bowel mesentery and soft pancreatic parenchyma[12,16]. Although 20 patients in our study had a PD for grade 5 injuries, a procedure of this magnitude is seldom necessary and should only be undertaken in stable patients when lesser operations are not feasible[16]. Although pancreas-specific complications were surprisingly low after PD, the overall complication rate in this category of resection was high. This emphasizes the need for combined and integrated involvement of both trauma and HPB surgeons familiar with the full spectrum and exigencies of pancreatic trauma[17].

The salient features of this study are the high proportion of patients who required a pancreatic resection for major injuries and the substantial morbidity and mortality associated with it. Major injuries to the pancreas remain a significant source of morbidity even when treated in well-resourced high-volume specialist trauma referral centers[21,22,27]. Outcome is influenced by the mechanism, anatomical location, grade and complexity of the pancreatic injury, the amount of blood lost, duration of hypovolemic shock, the quality of resuscitation, number of associated injuries and the appropriateness and quality of surgical intervention[3,15,27,28]. Overall reported morbidity rates following pancreatic injury range from 30% to 70% with the higher reported percentages generally being the result of severe trauma with higher AAST grades, associated injuries, diagnostic delay and inadequate or inappropriate initial treatment[15,27,28]. In the current study the number and severity of post-operative complications reflect the consequences of surgery in severe multiply injured patients. Associated injuries were common, in keeping with collateral damage seen with abdominal gunshot injuries. One half of patients had three or more associated injuries and the complexities of management were further compounded by associated vascular injuries present in one of every five patients. The dominant complications were infective, both intra-abdominal and systemic, respiratory, renal and related to bleeding. A substantial number of patients required a repeat laparotomy either for definitive management following an initial DCL (*i.e.*, delayed resection) or for intra-abdominal infection unresolved after percutaneous catheter drainage, control of intra-abdominal bleeding, or for small bowel obstruction.

A variety of factors specifically contribute to the development of pancreas-related complications following trauma, including the mechanism and grade of the injury, especially GSWs and associated vascular, hollow viscus and solid organ injuries[29] and neglect of a main pancreatic duct injury may lead to local complications including pseudocysts, fistulas, sepsis and secondary hemorrhage[29]. Pancreatic fistulas occur in up to 38% of patients and intra-abdominal abscesses in 34%[29]. In a study from Los Angeles County Hospital pancreas-related complications developed in 27.9%, including pseudocysts in 14.9% and fistulas 1.9%[29].

Our data concur with the findings of others in that early deaths after major pancreatic trauma are related to the number and severity of associated injuries[30]. Overall mortality in this study was 14.6% with the presence of shock, due to associated vascular injuries being significantly related to early mortality. Late deaths were due to sepsis and MOF. Deaths specifically related to the pancreas were uncommon. A substantial number of patients required a repeat laparotomy either for definitive management following an initial DCL or for postoperative complications that could not be managed by percutaneous or endoscopic intervention. The DCL patients had a mortality of 31%. In a two-centre study from Philadelphia and Columbus, Ohio which sought to determine the optimal initial operative management in damage control operations, 42 patients with pancreatic injuries underwent either packing, drainage or resection. Mortality in their study population was substantial (packing only, 70%; packing with drainage, 25%, distal pancreatectomy, 55%)[30].

Although this study represents the largest detailed analysis of major pancreatic resections for trauma to date, there are several specific limitations that should be taken into account when interpreting the data and outcome. The most substantial concern is that this is a single centre study in a high-volume tertiary referral centre and although these results may be similar to other major academic institutions, the data are not valid for community-based hospitals with lesser resources. The study design sought to avoid possible non-measurable biases that may result from patient selection, referral patterns and local differences in treatment policies by using complications and death as the main outcomes to provide consistent and objective end-points. A further concern is that the ASGS scores only the highest grade complication, without considering the burden of multiple but lesser complications in the same patient[31]. Specific strengths of the current study and of our analysis are the size of the cohort and the use of validated ISGPS definitions to score postoperative complications which have provided dependable and robust data and allowed reliable comparisons[8-11].

In conclusion, postoperative morbidity after pancreatic resection for trauma in this study was substantial and an increasing complication severity grade, as measured by the ASGS, required escalation of intervention and prolonged hospitalisation. The injured pancreas is an unforgiving organ, especially if severely damaged. Accurate intraoperative decision-making is crucial for a favourable outcome. A wide spectrum of options need to be considered, including initial damage control with delayed resection and/or reconstruction which is applicable as the default option in a select group of unstable patients. In applying the ASGS, we have established a benchmark for pancreatic resections for trauma by using current standardized definitions for grading severity of pancreatic complication. This will facilitate future comparative assessments and serve as a reference for improving outcome. Benchmarking is not restricted to comparative analyses of outcome, but should serve as a mechanism for transforming surgical practice and enhancing quality of care. To further develop this, future studies should include the calculation of the total burden of multiple complications in individual patients by utilising the comprehensive complication index, a factor which is relevant in trauma patients with several injured organs[32].

COMMENTS

Background

The pancreas is the least injured of the intra-abdominal solid organs but results in considerable morbidity and mortality rates if the injury is incorrectly assessed or inadequately treated. Outcome is influence by the complexity of the pancreatic injury, the number and severity of associated vascular and visceral injuries, the duration of shock and the quality and nature of surgical intervention. Two-thirds of patients who survive more than 48 h have major complications as a result of the pancreatic and associated injuries, and the one third of patients who die later do so because of intra-abdominal or systemic septic complications or multi-organ failure. Despite the substantial morbidity no studies have previously performed a detailed analysis of complications after pancreatic resection for trauma using standardized methodology.

Research frontiers

There is consensus that the modern management of complex pancreatic trauma is best achieved by collaborative team work between trauma and pancreatic surgeons. However, the optimal management of complex pancreatic injuries remains undefined due to the lack of high quality evidence. Despite a plethora of papers on pancreatic trauma, none have specifically addressed the spectrum of complications as patterns of injury and methods of intervention have progressed. Earlier studies assessing outcome after pancreatic resections for major pancreatic injuries have applied unqualified primary endpoints with differing descriptions and definitions which consequently have resulted in flawed conclusions. This analysis evaluated post-resection complications by applying robust and reliable methodology and objective and reproducible end-points in a large cohort of consecutive patients treated at a tertiary referral center. Internationally accepted and validated definitions of complications and grading scores including the 6-scale Accordion Severity Grading System (ASGS) were used to benchmark the severity of complications.

Innovations and breakthroughs

The present study represents the largest single center series of patients undergoing pancreatic resection for trauma. The number and severity of post-operative complications reflect the consequences of surgery in severe multiply injured patients. Associated injuries were common, in keeping with collateral damage seen with abdominal gunshot injuries. One half of patients had three or more associated injuries and the complexities of management were further compounded by associated vascular injuries present in one of every five patients. The dominant complications were infective, both intra-abdominal and systemic, respiratory, renal and related to bleeding. A substantial number of patients required a repeat laparotomy either for definitive management following an initial damage control laparotomy (*i.e.*, delayed resection) or for intra-abdominal infection unresolved after percutaneous catheter drainage,

control of intra-abdominal bleeding, or for small bowel obstruction. Overall 73% of patients had complications of which three quarters were Accordion grades 3-6. Patients more likely to have complications after pancreatic resection were older, had a revised trauma score < 7.8, were shocked on admission, had grade 5 injuries of the head and neck of the pancreas with associated vascular and duodenal injuries, required a damage control laparotomy, received a larger blood transfusion, had a pancreatoduodenectomy and repeat laparotomies. Applying univariate logistic regression analysis, mechanism of injury, revised trauma score < 7.8, shock on admission, damage control laparotomy, increasing AAST grade and type of pancreatic resection were significant variables for complications. Multivariate logistic regression analysis however showed that only age and type of pancreatic resection were significant.

Applications

Postoperative morbidity after pancreatic resection for trauma in this study was considerable and an increasing complication severity grade, as measured by the ASGS, required escalation of intervention and prolonged hospitalisation. Accurate intraoperative decision-making is crucial for a favourable outcome. A wide spectrum of options need to be considered, including initial damage control with delayed resection and/or reconstruction which is applicable as the default option in a select group of unstable patients. In applying the Accordion scale, the authors have established a benchmark for pancreatic resections for trauma by using current standardized definitions for grading severity of pancreatic complication. This will facilitate future comparative assessments and serve as a reference for improving outcome. Benchmarking is not restricted to comparative analyses of outcome, but should serve as a mechanism for transforming surgical practice and enhancing quality of care. To further develop this, future studies should include the calculation of the total burden of multiple complications in individual patients by utilising the comprehensive complication index, a factor which is relevant in trauma patients with several injured organs.

Terminology

The validated International Study Group of Pancreatic Surgery definitions of complications after pancreatic surgery provided an accurate, robust and consistent method to allow reliable comparisons of the incidence of post-operative pancreatic fistulas, bleeding and delayed gastric emptying. Similarly, the 6-scale Accordion Severity Grading System which discriminates post-operative complication severity following elective surgery on the basis of escalating interventional criteria, is now widely accepted as a credible, scoring system which is easy to apply and is reproducible with minimal inter-observer variability.

Peer-review

This is an interesting article based on the management of complex pancreatic injuries in 461 patients over a twenty five-year period containing a lot of important data. It is a well-written paper, documented and with acceptable outcome in such severe injuries.

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CASE REPORT

Laparoscopic retrosternal gastric pull-up for fistulized mediastinal mass

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Author contributions: Molena D designed the study, surgically retrieved tumor, and followed up finding; Barbetta A, Lidor AO and Stem M researched literature and reviewed manuscript; Mungo B conducted literature review, collected data and drafted manuscript.

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Abstract

We describe the case of a patient successfully reconstructed with laparoscopic retrosternal gastric pull-up after esophagectomy for unresectable posterior mediastinal inflammatory myofibroblastic tumor, eroding into the esophagus and compressing the airways. A partial esophagectomy with esophagostomy was performed for treatment of esophageal pleural fistula and empyema, while the airways were managed with the placement of an endobronchial stent. Gastrointestinal reconstruction was performed using a laparoscopic approach to create a retrosternal tunnel for gastric conduit pull-up and cervical anastomosis. The patient was discharged uneventfully after 6 d, and has done very well at home with normal diet.

Key words: Esophageal surgery; Minimally invasive surgery; Esophageal fistula; Laparoscopic retrosternal bypass; Gastric conduit

Core tip: Retrosternal gastric tube has been used in various clinical scenarios, for both malignant and benign esophageal disease. The laparoscopic approach allowed for a simple, fast, and controlled dissection of the retrosternal plain and reconstruction of the alimentary tract. This approach should be considered as a valid

alternative for reconstruction of the alimentary tract in patients where the prevertebral route is not available.

Mungo B, Barbetta A, Lidor AO, Stem M, Molena D. Laparoscopic retrosternal gastric pull-up for fistulized mediastinal mass. *World J Gastrointest Surg* 2017; 9(3): 92-96 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i3/92.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i3.92

INTRODUCTION

The safety and feasibility of laparoscopic retrosternal esophageal bypass using a gastric conduit has recently been described for the management of esophageal corrosive strictures[1]. Retrosternal gastric pull-up can be used for reconstruction after esophagectomy when a prevertebral route is not available, or as an option to create an esophageal bypass for unresectable esophageal tumors[2]. We report herein a successful case of totally laparoscopic retrosternal gastric pull-up for a fistulized unresectable mediastinal inflammatory myofibroblastic tumor.

CASE REPORT

A 52-year-old man was referred to our division for evaluation of a mediastinal mass, initially detected two years earlier on a computed tomography performed for back pain. The patient was treated with steroids for presumptive fibrosing mediastinitis, however his symptoms progressively increased, with worsening shortness of breath, stridor and severe dysphagia. Multiple biopsies performed through esophagogastroduodenoscopy (EGD), bronchoscopy and mediastinoscopy failed to provide a diagnosis. The bronchoscopy showed extrinsic compression of the right main stem bronchus as well as the right upper lobe bronchus and the bronchus intermedius. The latter was almost completely obstructed and required placement of an endobronchial stent. EGD revealed a large mass eroding into the esophageal wall. A follow up computed tomography (CT) scan confirmed the presence of an enlarging subcarinal mass, measuring approximately 9.7 cm × 6 cm × 8.6 cm, completely surrounding the carina, the bronchi bilaterally, the esophagus and compressing the left atrium (Figure 1). A PET scan showed the mediastinal mass to be intensely hypermetabolic. After VATS biopsy of the mass, the patient developed empyema due to creation of esophageal-mass-pleural communication. Partial esophagectomy and infraclavicular esophagostomy was performed to treat the fistula and facilitate resolution of the empyema, although complete resection of the mass was not achievable. The final pathology of the resected specimen was consistent with inflammatory myofibroblastic tumor. The patient subsequently underwent treatment with high-dose steroids and definitive radiation. After appropriate recovery, he was admitted for

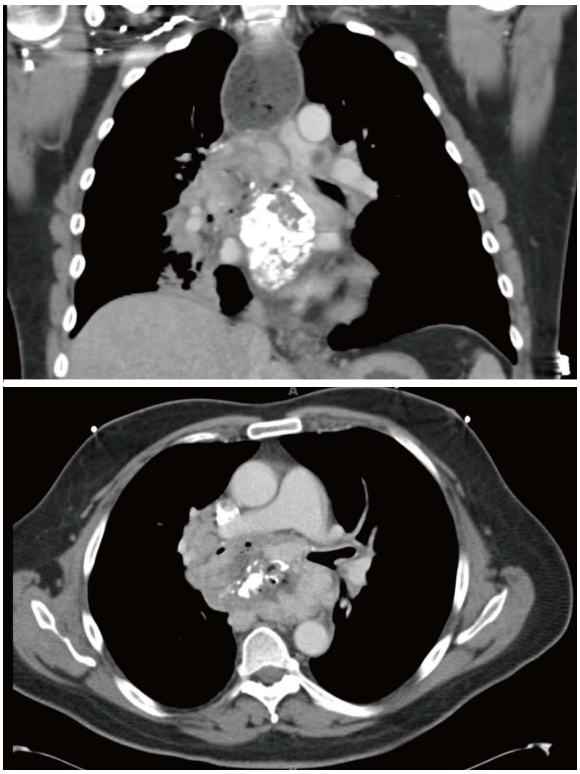


Figure 1 Coronal and axial computed tomography view of the partially calcified subcarinal mass surrounding the carina, the bronchi, and eroding into the esophagus (note the mediastinal air).

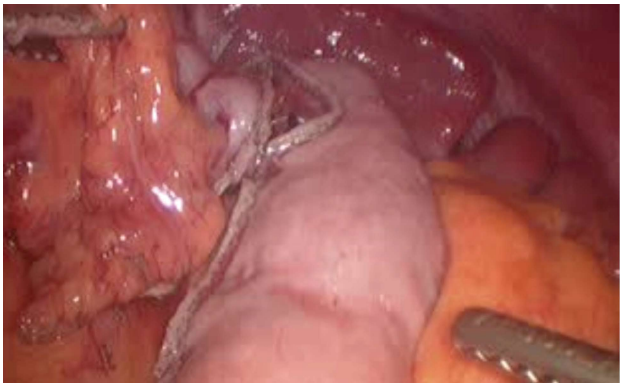


Figure 2 Intraoperative view of the gastric conduit after complete tubularization.

gastrointestinal reconstruction. Due to unavailability of the prevertebral route, which was occupied by the unresectable mass, a retrosternal route was chosen.

The patient was placed in supine position on the operating table and a standard laparoscopic approach was used. After complete mobilization of the stomach, a 10-cm wide gastric conduit was created by dividing the right and left gastric arteries and the proximal portion of the stomach (Figure 2). The distal esophageal stump was dissected free from the mediastinal attachments, removed *en-bloc* with the proximal stomach and sent to pathology with no residual tumor identified (Figure 3). Pyloric drainage was achieved *via* injection 200 units

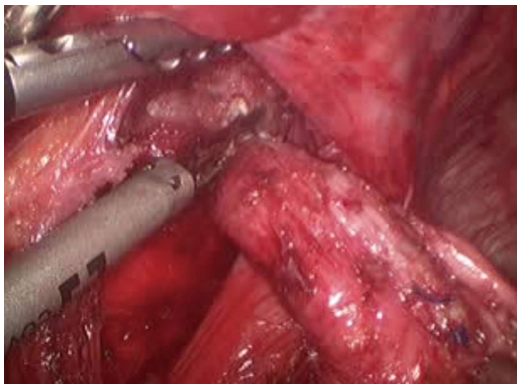
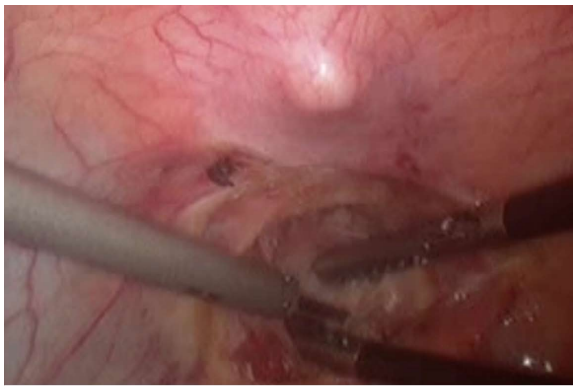


Figure 3 Dissection of the esophageal stump into the mediastinum.



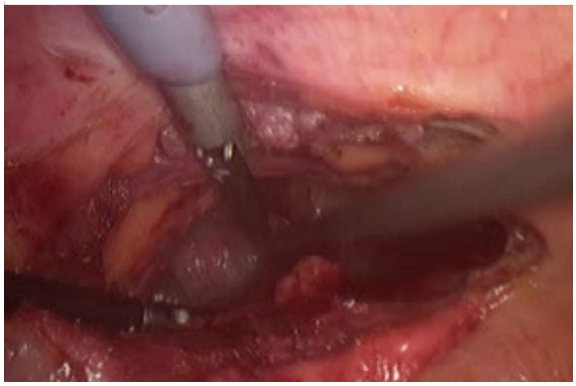


Figure 4 A wide substernal tunnel is created under direct visualization immediately posterior to the xyphoid process.

of botulin toxin into the pyloric muscle. The substernal dissection was then started immediately posterior to the xyphoid process (Figure 4). The avascular plane between the pericardium, the sternum and bilateral mediastinal pleura was developed with ultrasonic dissection and a tunnel about 15-cm wide was created from the abdomen all the way up to the thoracic inlet (Figure 4). The esophagostomy was then taken down and the proximal esophagus was exposed through a left cervical incision. The dissection from the neck was carried down to the substernal tunnel previously created. The gastric conduit was then pulled-up to the neck and the proximal portion of the stomach was externalized through the cervical incision. The conduit was very well perfused and the length was excellent. A stapled anastomosis using a

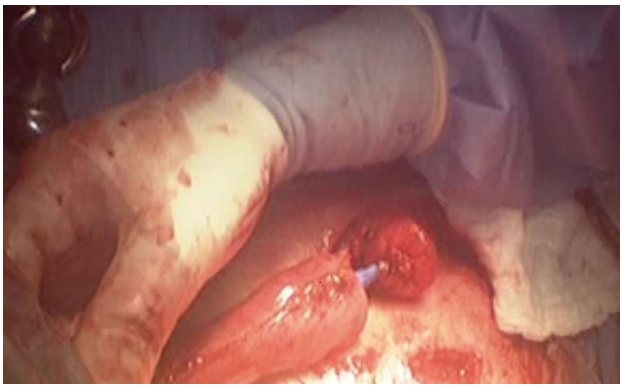


Figure 5 Circular mechanical stapled anastomosis at the neck.

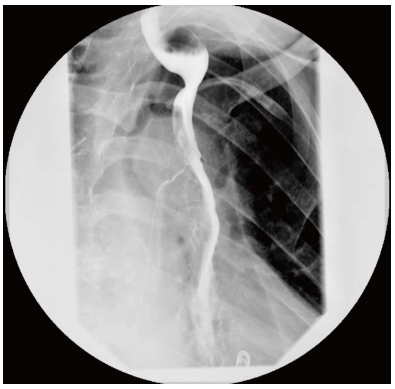


Figure 6 Esophagram demonstrating normal transit of contrast trough the anastomosis and prompt gastric emptying.

28-French circular mechanical stapler was performed (Figure 5) and the tip of the conduit was resected with a linear stapler. The anastomosis was pulled down below the sternal notch. The gastric conduit was secured to the diaphragm in order to avoid herniation of intra-abdominal organs into the mediastinum and a feeding jejunostomy was placed.

The patient had an uneventful recovery. A swallow study showed good gastric emptying and no anastomotic leak (Figure 6) and the patient was started on liquid diet and discharged on post-operative day 6. At home, he was gradually advanced to regular diet and weaned off tube feeding. At 8 mo after the procedure, he is eating a regular diet and has no symptoms.

DISCUSSION

Retrosternal gastric tube reconstruction has been used in various clinical scenarios, for both malignant and benign esophageal disease. Esophageal bypass surgery can be an option to treat patients with a fistula between the esophagus and the airways, providing relief from aspiration symptoms through separation of the respiratory and alimentary tracts[3]. Moreover, retrosternal gastric pull-up has been reported to be particularly beneficial for patients at high risk of developing locoregional recurrence after esophagectomy to prevent conduit

obstruction and inability to eat[4]. In a randomized study by van Lanschot *et al*[4], retrosternal gastric tube reconstruction was described as a simple and safe technique with similar technical, functional results and postoperative recovery to a prevertebral reconstruction[5]. Retrosternal bypass can also be useful for unexpected unresectable cancers or perforated ones[5]. Javed *et al*[1,6] have recently described a laparoscopic technique for esophageal bypass in patients with corrosive esophageal strictures, using either a gastric or a colonic conduit. The authors reported on safety, feasibility and effectiveness of the minimally invasive technique, along with the well-known advantages, such as faster recovery and minimal postoperative pain. Moreover, the use of laparoscopy allowed direct visualization of the substernal dissection, avoiding injury to the pleura or lung and negligible blood loss[1,6].

An alternative route that can be used is the placement of the conduit in the subcutaneous space. This approach has several disadvantages: It is the longest route available, often needing either the colon or the jejunum as conduits, it is associated with higher risk of conduit trauma and twisting and has a potential negative esthetical impact. For these reasons the subcutaneous route is reserved as the last option for patients with previous mediastinal surgery and pleural infection or mediastinal fibrosis[7,8].

Esophageal reconstruction most commonly involves the stomach (< 90%)[9], followed by colon, jejunum, and pedicle skin-muscle flaps. Colon interposition is the first choice for selected patients with esophageal cancer when the stomach is unavailable or for benign esophageal diseases especially in young patients, with the intent of preserving the stomach[10]. Although long-term results for coloplasty are similar to gastroplasty, the reconstruction with the stomach generally involves a simpler operation with only one anastomosis[11]. The gastric conduit is usually better perfused than the colon leading to a lower incidence of conduit necrosis[12,13].

We found retrosternal pull-up a particularly well suited technique for the case we described, due to non-availability of prevertebral route, unresectability of the mediastinal mass and history of empyema. The laparoscopic approach allowed for a simple, fast, and controlled dissection of the retrosternal plain and reconstruction of the alimentary tract. This approach should be considered as a valid alternative for reconstruction of the alimentary tract in patients where the prevertebral route is not available.

COMMENTS

Case characteristics

A 52-year-old man presented with a 2-year history of mediastinal mass causing back pain, and increase of shortness of breath, stridor and severe dysphagia.

Clinical diagnosis

Mediastinal mass compressing the right main stem bronchus, right upper lobe and intermedius bronchus and eroding the esophageal wall.

Differential diagnosis

Lung cancer, sarcoma, esophageal cancer.

Imaging diagnosis

Computed tomography scan showed an enlarging subcarinal mass, completely surrounding the carina, bronchi bilaterally the esophagus and compressing the left atrium. Positron emission computed tomography scan showed a hypermetabolic mass. Esophagogastroduodenoscopy and video-assisted thoracic surgery biopsy.

Pathological diagnosis

The resected specimen was consistent with inflammatory myofibroblastic tumor.

Treatment

Partial esophagectomy and infraclavicular esophagostomy, high-dose of steroids and definitive radiation and a finally gastrointestinal reconstruction with a retrosternal route.

Related reports

To treat esophageal-mass-pleural fistula and facilitate resolution of the empyema a partial esophagectomy with esophagostomy were performed, with no complete resection of mass achievable. The gastric tube was chosen for alimentary tract reconstruction. The retrosternal route was used as the prevertebral route was unavailable due to the unresectability of the mediastinal mass and history of empyema.

Term explanation

VATS: Video-assisted thoracic surgery. Inflammatory myofibroblastic tumor is a rare benign or locally aggressive tumor. It is characterized by dense inflammatory infiltrated cells in a myxoid or collagenous stroma.

Experiences and lessons

The retrosternal gastric tube is a valid approach for reconstruction of alimentary tract when a prevertebral route is unsuitable. Furthermore this esophageal bypass represents an option to treat patients with airways-esophagus fistula. Minimally invasive approach provides different advantages such as a direct visualization during substernal dissection, as well as a fast recovery and minimal postoperative pain.

Peer-review

It's a well described case of a laparoscopic retrosternal gastric bypass.

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ORIGINAL ARTICLE

Retrospective Study

Trends with neoadjuvant radiotherapy and clinical staging for those with rectal malignancies

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Author contributions: Reddy SS designed, performed the research, and wrote the paper; Handorf B performed the statistical analysis; Farma JM and Sigurdson ER edited and supervised the project.

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Abstract

AIM

To see how patterns of care changed over time, and how institution type effected these decisions.

METHODS

A retrospective analysis was performed using the National Cancer Database, looking at all patients that were diagnosed with rectal cancer from 1998 to 2011. We tested differences in rates of treatment and stage migration using χ^2 tests and logistic regression models.

RESULTS

A review of ninety thousand five hundred and ninety four subjects underwent multimodality therapy for cancer of the rectum. Staging and response to treatment varied greatly between centers. Forty-six percent of the time staging was missing in academic practices, *vs* fifty-four percent of the time in community centers (P < 0.001). As a result, twenty-percent were down-staged and eight percent up-staged in academia, whereas only fifteen percent were down-staged and 8% up-staged in community practices (P < 0.001). Forty-two percent of individuals underwent radiation before surgery in 1998.

Within two years this increased to fifty-three percent. This increased to eighty-six percent by 2011 ($P < 0.001$). Institution specific treatment varied greatly. Fifty-one percent received therapy before surgery in academic centers in 1998. Thirty-nine percent followed this pattern in the same year in the community ($P < 0.001$). By 2011, ninety-one percent received radiation before their procedure in academic centers, *vs* eighty-four percent in the community ($P < 0.001$). Rates of adoption were better in academia, although an increase was seen in both center types.

CONCLUSION

From the study dates of 1998 to 2011, preoperative treatment with radiation has been on the rise. There is certainly an increased rate of use of radiation in academia, however, this trend is also seen in the community. Practice patterns have evolved over time, although rates of assigning clinical stage are grossly underreported prior to initiation of preoperative therapy.

Key words: Neoadjuvant therapy; Community; Rectal cancer; Academic

Core tip: This paper serves to show how changes in practice patterns evolve over time. The adoption of these practice patterns differ across institution type, and the role of appropriate clinical staging is often not included. In order for proper treatments to be initiated, we not only need data substantiated by level one evidence, but we also need proper clinical staging so we can ensure appropriate therapies are delivered to these patients.

Reddy SS, Handorf B, Farma JM, Sigurdson ER. Trends with neoadjuvant radiotherapy and clinical staging for those with rectal malignancies. *World J Gastrointest Surg* 2017; 9(4): 97-102 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i4/97.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i4.97

INTRODUCTION

The implementation of radiotherapy for rectal cancer has seen many adaptations over time, particularly when comparing adoption in community *vs* academic centers in the United States. Surgical resection with sound oncologic technique is a critical component. Various series report local regional recurrence rates anywhere between 50%-60% in patients undergoing surgery for rectal adenocarcinoma[1-3]. Histological grade, primary tumor invasion, and length of the lesion, have all been found to influence rates of local recurrence[1,2,4]. Another important correlate for local recurrence are those subset of patient found to have positive nodal disease[4]. Local recurrence rates, in addition to overall survival, were both adversely affected when any of these criteria were met.

The use of radiotherapy was initially met with skepticism, as many believed that surgery, which included a total mesorectal excision (TME), offered superior results. Heald *et al*[5] surmised that patients with low tumors did no worse than those with high tumors when treated by anterior resection, provided that the mesorectum is excised intact with the cancer. Karanjia *et al*[6] and Heald *et al*[7] went as far as to suggest that less margins may not increase recurrence or effect survival, as long as a good TME was performed. As surgical techniques for rectal cancer improved, innovations regarding the selective use of radiotherapy were also being explored. Despite this, many continue to argue that a technically sound TME may eliminate radiation[8,9].

The addition of radiotherapy to surgical resection has been an evolving process, and several randomized controlled trials have compared various regimens to surgery alone. Many of these trials were done in an academic institution, and although validated by randomized trials, adoption into the community initially lagged. The Colorectal Cancer Collaborative Group reviewed twenty eight randomized trials, and found a decreased risk of recurrence when preoperative therapy was given[10]. The Dutch group implemented short course radiation and TME, and found lower recurrence rates then when TME was done by itself[11]. Implementation of chemoradiotherapy (CRT) was widely adopted in the 1990's, when two trials were completed. These compared pre and postoperative therapy.

Despite prospective data showing the success of radiation, its adoption within the community seems limited, and could partially be a result of inaccurate initial staging. Using the National Cancer Database (NCDB) we looked to see how patterns of care changed over time, and how institution type effected these decisions. We also looked to see if clinical staging was lacking, and if so, how this effected the adoption of neoadjuvant therapies.

MATERIALS AND METHODS

A retrospective review was performed using the NCDB. All patients diagnosed with rectal cancer from 1998 to 2011 were included. Patients were stratified by those who underwent surgery as initial treatment, *vs* those who underwent neoadjuvant radiotherapy. Of these patients, clinical staging was reviewed, and compared between academic and community centers. Clinical stage was further divided into node positive and node negative disease, and tumor response by induction therapy was determined by final pathological stage. Differences in rates of treatment and stage migration were tested using χ^2 tests and Cochran-Armitage tests for trend.

RESULTS

A review of ninety-thousand five hundred and ninety four subjects underwent multimodality therapy for cancer of the rectum. The total cohort included 62%

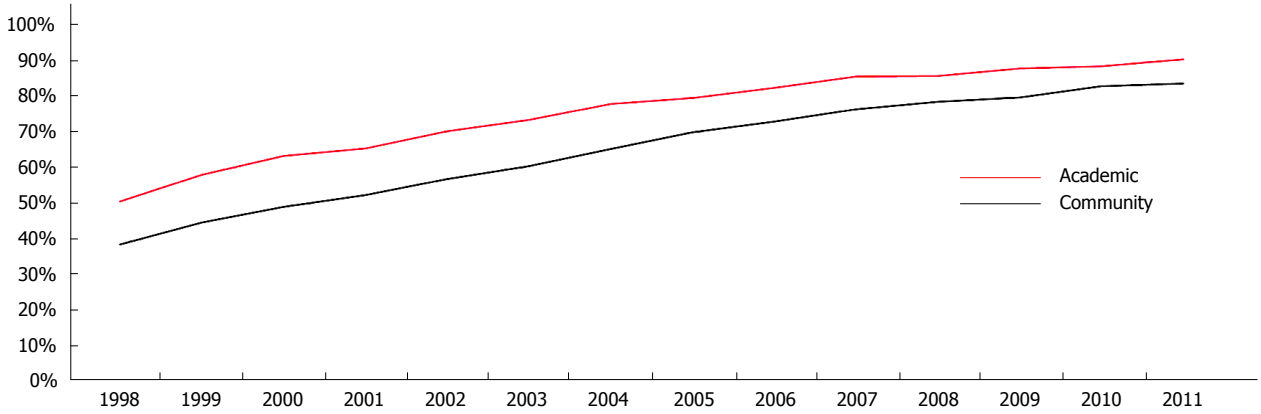

Figure 1 Trends in the adoption of neoadjuvant therapy. Graphical interpretation of the adoption of neoadjuvant therapy over time when comparing academic and community institutions.

Table 1 Patient demographics

Demographics (%)	
Gender	
Male	62
Female	38
Age	
< 50	18
51-70	54
> 70	28
Race	
Caucasian	88
African American	8
Other	4
Insurance	50
Private	43
Medicare/Medicaid	
None	4
Other	3

males and 38% female. Fifty-four percent of patients were between the ages of 51-70. The overwhelming majority of patients were Caucasian, at 88%. Patient's insurance status was 50% privately insured, and 43% with Medicare/Medicaid (Table 1).

Forty-two percent of individuals underwent radiation before surgery in 1998. Within five years, this proportion had increased to 64%, and over the course of the study period we saw a 33% increase in adoption of radiotherapy. By 2011, 86% received induction radiotherapy prior to surgery ($P < 0.001$). In 1998, 51% of patients underwent induction radiotherapy when seen in an academic center *vs* 39% when seen in the community. Within five years there was a rise in the routine application of radiotherapy at 74% and 61%, respectively. By 2011, 91% of academic centers, and 84% of community centers routinely used induction radiotherapy in the treatment of rectal cancers ($P < 0.001$). Adoption was better in academia overall, but an increase was seen in both center types (Figure 1).

Across the cohort of patients who received neoadjuvant radiotherapy, 21% did not have a clinical stage recorded, 25% had no pathological stage, and 6% had neither recorded. When assessing staging differences between academic and community centers, clinical stage was unknown in 17% *vs* 23%, respectively ($P < 0.001$). Pathological staging was not recorded 24% of the time in academic centers, and 26% of the time in the community ($P < 0.001$). Neither stage was recorded in 5% and 6% of the time in academic *vs* community centers, respectively ($P < 0.001$). Overall, staging was incomplete 46% of the time in academic centers, and 55% of the time within the community ($P < 0.001$) (Table 2).

Overall response to treatment showed that seventeen percent were down-staged, eight percent up-staged, and twenty-four percent had no change. Within academic centers, twenty percent were down-staged, eight percent up-staged, and twenty-six percent had no changes. Down-staging in the community occurred fifteen percent of the time, up-staging eight percent, and no changes in twenty-three percent. Patients at academic centers were down-staged more often after neoadjuvant therapy than when in the community ($P < 0.001$) (Table 3). Patients were also stratified by T-stage and nodal status. Fifty-four percent with clinically negative nodes had node negative disease on final pathology. Twenty-two percent of patients without palpable nodes were found to be node positive. Thirty-seven percent were down-staged to node negative status.

DISSCUSION

The use of neoadjuvant radiation has increased over time. Unfortunately evidence-based medicine remains difficult to enforce[12]. In our review, adoption of these practices seems to be initially lower within the community compared to academics; however, trends suggest a steady increase in its implementation. One explanation for this is the non-uniform anatomic definition of rectal cancer, and as a result, the lack of appropriate clinical staging done. In a systematic review searching for national and international guidelines, no consensus concerning a definition was found[13]. Four guidelines used fifteen centimeters from the anus as the anatomic rectum, and

Table 2 Institutional staging

Unknown staging	%
Overall unknown	
Path stage	25
Clinical stage	21
Both stages	5
Academic unknown	
Path stage	24
Clinical stage	17
Both stages	5
Community unknown	
Path stage	26
Clinical stage	23
Both stages	6

Table 3 Trends in staging

Unknown staging	%
Overall	
Up-stage	8
Down-stage	17
No change	24
Academic	
Up-stage	8
Down-stage	20
No change	26
Community	
Up-stage	8
Down-stage	15
No change	23

two used twelve centimeters[13]. In addition to this, how measurements were made varied between consensus guidelines; some used proctoscopy, others flexible endoscopy, and some MRI. The lack of a universal definition could be attributing to the lack of compliance in undergoing appropriate staging studies and thus assigning clinical stage, and subsequent delivery of care.

Staging modalities

Standardized treatment would not be possible without appropriate staging modalities. Proper disease staging will determine whether or not induction therapy would be of value. Imaging options include endorectal ultrasound, computerized tomography, and magnetic resonance imaging[14]. We found that 21% of patients that underwent neoadjuvant therapy had no clinical stage recorded. Although clinical staging seems to occur less within the community, it is difficult to tell if this is a result of improper data collection, or reflective of the institution itself. Similarly, pathological staging was unavailable more often within community centers than in academic places. Charlton *et al*[15] demonstrated that fellowship trained surgeons more often ordered endorectal ultrasounds and MRI's. They were also more likely to refer for neoadjuvant treatments[15]. Although not certain, this could be suggestive that this trend would hold in academic centers, as opposed to the community based practices. In our review, in patients with data available for staging, it seemed as though academic institutions had improved rates of down staging tumors, when compared to the community. This could be correlated to the difference in clinical stage recorded amongst these centers. However, a flaw in our work is that we do not know whether clinical staging was done or simply not recorded.

TME

The use of TME challenged implementation of radiotherapy in the treatment algorithm. Since its inception, reductions in local recurrence, improved survival, and sphincter preservation have been noted. The main issue with this surgical approach is that it is operator dependent. Whether or not the surgeon has been properly instructed in the technique ultimately plays a role in recurrence patterns. Unfortunately, whether or not a TME was implemented at the time of surgical resection in our study is not known. One could argue that surgeons practicing in academic centers have had extra training in TME's, and this again supports the lack of adoption of evidence-based practices within the community. When properly performed, a TME provides excellent local control. Heald *et al*[5] found a recurrence rate of 7.2%. Several years later this was 3.5%[16]. Macfarlane *et al*[17] confirmed recurrence rates of 5% with TME, 25% with conventional surgery and radiotherapy, and 13.5% with conventional surgery and CRT. Enker *et al*[9] reports recurrence in 7.3%. Nodal involvement and perineural invasion were statistically significant risk factors.

Use of radiotherapy

In terms of neoadjuvant radiotherapy, the German group looked to challenge the recommended standard therapy of postoperative CRT. After randomization, 6% recurred locally in the preoperative group, *vs* 13% in the postoperative arm[18]. Despite strong evidence, there remains a subset of clinicians that challenge this, and advocate a selective approach to induction therapy. In a single center, retrospective cohort study, Williamson and colleagues supported an individual approach to when CRT was used. The mention a 5-year recurrence rate of 6.5% in the treatment group, *vs* 0% when surgery was done by itself[19]. Patients receiving treatment were selected on the basis of an involved circumferential margin. This explains the variation in recurrence between these arms. However, this represents a prime example of how treatments patterns differ across institutions. To elaborate on this further, the PROSPECT trial initially evaluated patients who were candidates for a low anterior resection with TME, and were given six cycles of FOLFOX[20]. If disease was stable or progressed, then they would proceed to preoperative CRT, if they were responders, then they would go straight to surgery. The pilot study by Schrag *et al*[20] demonstrated that those who had chemotherapy had complete pathologic response rates of 25%, and a 0% four-year local recurrence rate.

SEER data by Fitzgerald *et al*[12], the use of radio-

therapy was 17% in 1998, which increased to 51% in 2007. In our review, 42% of patients received induction radiotherapy, which increased to 64% in five years. By 2011, 85% of patients seen received neoadjuvant radiotherapy for rectal cancer ($P < 0.001$). Similar trends were noted by Jobsen *et al*[21], finding a steady increase in the utilization of neoadjuvant radiotherapy from 1997-2008. It remains evident that a trend for the routine use of neoadjuvant radiotherapy is there. However, factors such as volume and facility type certainly play a role[22,23]. Stewart *et al*[22] surmised that hospitals where teaching was a priority, increased the likelihood of receiving neoadjuvant treatments ($P < 0.0001$). In our review, fifty-one percent of those treated in academia underwent preoperative therapy *vs* 39% when seen in the community. By 2011, 91% of academic centers, and 84% of community centers, routinely used radiotherapy ($P < 0.001$).

Caring for those with of locally advanced rectal cancer has evolved over the decades. Advances in surgical technique with TME revolutionized the field of rectal surgery, and offered patients superior local control than when compared to conventional surgery alone. Several studies have suggested this benefit, attributing higher local recurrence rates to inadequate TME's[24-26]. As clinical trial accrual escalated, the implementation of radiotherapy to the treatment algorithm was the next logical step. The Dutch group found that preoperative therapy was safe in patients, even if they were to undergo surgery[27]. Despite this, adoption of the routine use of neoadjuvant radiotherapy was a difficult undertaking. The data shows a trend favoring the influence of evidence-based medicine, which in turn affects the way in which we practice medicine. In order for this to continue, we must work on improving recording of clinical stage, so that patients are not only eligible for potential clinical trials, but receive the current standard of care. Although smaller discrepancies continue to exist between academic and community centers in terms of its usage of neoadjuvant therapy, the overall trends are on the rise.

COMMENTS

Background

The implementation of radiotherapy for rectal cancer has seen many adaptations over time, particularly when comparing adoption in community *vs* academic centers in the United State. Surgical resection with total mesorectal excision is a critical component. Various series report local regional recurrence rates anywhere between 50%-60% in patients undergoing surgery for rectal adenocarcinoma. The addition of radiotherapy to surgical resection has been an evolving process, and several randomized controlled trials have compared various regimens to surgery alone. Many of these trials were done in an academic institution, and although validated by randomized trials, adoption into the community initially lagged.

Research frontiers

The adoption of radiotherapy for this disease has altered the way in which we treat this disease. As with any new therapy, there are always experiments being conducted to see if the authors again can change their practicing treatment plan.

Innovations and breakthroughs

In this study the authors looked to see how patterns of treatment changed over time. Differences between the types of facility administering care were reviewed, and whether appropriate clinical staging was assigned was critiqued.

Applications

This study suggests that radiotherapy had slow adoption into mainstream practice, but over time, practice patterns changed.

Terminology

Radiation: This is the emission or transmission of energy in the form of waves or particles. The use of radiation in clinical practice has greatly changed the way the authors treat disease in the modern era.

Peer-review

The paper is interesting.

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ORIGINAL ARTICLE

Observational Study

Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer

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Abstract

AIM

To review surgical outcomes for patients undergoing pancreatectomy after proton therapy with concomitant capecitabine for initially unresectable pancreatic adenocarcinoma.

METHODS

From April 2010 to September 2013, 15 patients with initially unresectable pancreatic cancer were treated with

proton therapy with concomitant capecitabine at 1000 mg orally twice daily. All patients received 59.40 Gy (RBE) to the gross disease and 1 patient received 50.40 Gy (RBE) to high-risk nodal targets. There were no treatment interruptions and no chemotherapy dose reductions. Six patients achieved a radiographic response sufficient to justify surgical exploration, of whom 1 was identified as having intraperitoneal dissemination at the time of surgery and the planned pancreatectomy was aborted. Five patients underwent resection. Procedures included: Laparoscopic standard pancreaticoduodenectomy (n = 3), open pyloris-sparing pancreaticoduodenectomy (n = 1), and open distal pancreatectomy with irreversible electroporation (IRE) of a pancreatic head mass (n = 1).

RESULTS

The median patient age was 60 years (range, 51-67). The median duration of surgery was 419 min (range, 290-484), with a median estimated blood loss of 850 cm^3 (range, 300-2000), median ICU stay of 1 d (range, 0-2), and median hospital stay of 10 d (range, 5-14). Three patients were re-admitted to a hospital within 30 d after discharge for wound infection (n = 1), delayed gastric emptying (n = 1), and ischemic gastritis (n = 1). Two patients underwent R0 resections and demonstrated minimal residual disease in the final pathology specimen. One patient, after negative pancreatic head biopsies, underwent IRE followed by distal pancreatectomy with no tumor seen in the specimen. Two patients underwent R2 resections. Only 1 patient demonstrated ultimate local progression at the primary site. Median survival for the 5 resected patients was 24 mo (range, 10-30).

CONCLUSION

Pancreatic resection for patients with initially unresectable cancers is feasible after high-dose [59.4 Gy (RBE)] proton radiotherapy with a high rate of local control, acceptable surgical morbidity, and a median survival of 24 mo.

Key words: Pancreatic cancer; Pancreatectomy; Pancreas; Proton therapy; Radiotherapy

Core tip: Patients undergoing pancreatectomy for resectable pancreas cancers have a significant risk of local and regional recurrence. That risk could be reduced if patients received moderate-dose preoperative radiotherapy. Many surgeons, however, are concerned that conventional X-ray-based radiotherapy could complicate what is already a complicated operation. The current series documents the surgical outcomes for 15 patients with initially unresectable pancreatic cancers who underwent pancreatectomy after high-dose [59.40 Gy (RBE)] proton-based radiotherapy. The lack of increased surgical toxicity suggests that proton radiotherapy may represent an optimal vehicle for the delivery of moderate dose neoadjuvant radiotherapy in the setting of resectable disease.

Hitchcock KE, Nichols RC, Morris CG, Bose D, Hughes SJ, Stauffer JA, Celinski SA, Johnson EA, Zaiden RA, Mendenhall NP, Rutenberg MS. Feasibility of pancreatectomy following high-dose proton therapy for unresectable pancreatic cancer. *World J Gastrointest Surg* 2017; 9(4): 103-108 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i4/103.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i4.103

INTRODUCTION

Patients undergoing pancreatectomy for tumors which are believed to be resectable by preoperative imaging experience high rates of lymph node positivity, margin positivity and local/regional recurrence[1-6]. In spite of this, many surgeons are reluctant to recommend neoadjuvant radiotherapy which might have the potential to sterilize microscopic disease in the operative bed and reduce the incidence of these events. This reluctance is presumably due to concerns that even moderate dose radiotherapy in the range of 50.40 Gy might complicate what is already a lengthy and complicated operation.

The current series reviews the surgical outcomes for a group of patients with initially unresectable disease who, after high-dose proton radiotherapy [59.40 Gy (RBE)] and chemotherapy (oral capecitabine, 1000 mg, twice a day), achieved enough of a radiographic response to justify surgical exploration. The favorable physical characteristics of proton radiotherapy are demonstrated in Figures 1 and 2. Specific attention is paid to the surgical metrics of: Duration of surgery; estimated blood loss; and hospital length of stay which are compared to benchmark studies in the surgical literature.

MATERIALS AND METHODS

This is a retrospective single-institution study of patients enrolled on either the University of Florida Health Proton Therapy Institute PC-01 trial for patients with unresectable disease or the University of Florida Health Proton Therapy Institute outcomes-tracking study. The statistical methods of this study were reviewed by Christopher G Morris from the Department of Radiation Oncology, University of Florida College of Medicine.

From April 20, 2010 to September 30, 2013, 15 patients with initially unresectable pancreatic cancer were treated with full-dose proton therapy with concomitant capecitabine at 1000 mg taken orally twice a day. All patients received 59.40 Gy (RBE) to the gross disease, and 1 patient also received 50.40 Gy (RBE) to the high-risk nodal targets. There were no treatment interruptions or chemotherapy dose reductions. Patient details can be found in Table 1.

The technical details for the delivery of proton radiation therapy have been described previously[7,8]. In summary, optimized 2- or 3-field 3-dimensional conformal passive-scatter proton plans were created in which 95% of the

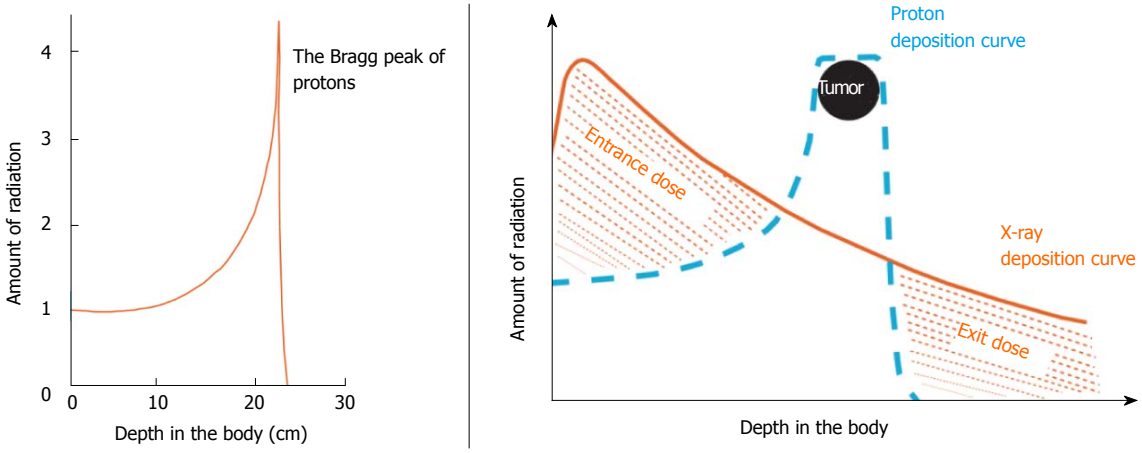

Figure 1 Favorable physical characteristics of proton radiotherapy are demonstrated. A: Charged particles such as protons travel a finite distance into tissue, as determined by their energy, and then release that energy within a tightly defined region called the "Bragg peak"; B: By delivering a range of energies toward the tumor target, several Bragg peaks can be formed to create a "spread-out Bragg peak" that conforms to the depth and position of the tumor target.

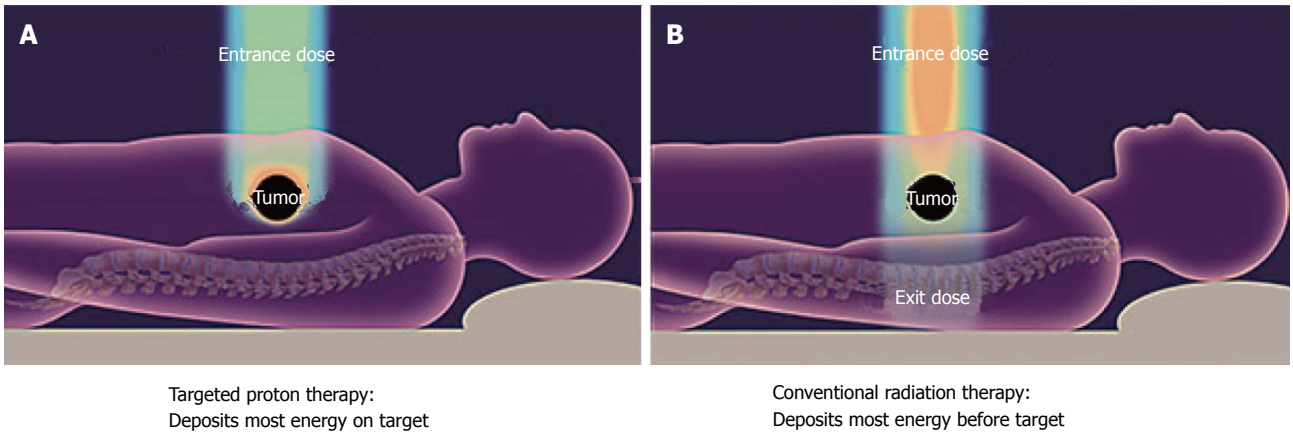

Figure 2 Conventional radiotherapy. With conventional radiotherapy (A) using X-rays (photons), the highest dose is deposited where the beam enters the patient. The dose at the tumor target is significantly less than the entry dose. Also, an exit dose is delivered beyond the tumor target. With protons (B), the entry dose is low. The highest dose is deposited at the depth of the tumor target, and there is no exit dose beyond the target.

planning target volumes received 100% of the prescribed dose, and 100% of the planning target volumes received at least 95% of the prescribed dose. Normal-tissue constraints included the following: Spinal cord, < 46 Gy; right kidney, V18 < 70%; left kidney, V18 < 30%; liver, V30 < 60%; and small bowel (including duodenum) and stomach, V20 < 50%, V45 < 15%, V50 < 10%, and V54 < 5%. These target coverage goals and normal-tissue limits were met for all patients with minor patient-specific adjustments. A typical proton therapy plan is shown in Figure 3.

To document surgical outcomes, we used treatment records to verify the type and extent of resection, procedure duration, blood volume lost during the procedure, length of hospital stay, number of days spent in intensive care, readmission for surgical complications, pathologic assessment of the surgical specimens, local disease control, distant disease control, and overall survival.

RESULTS

Six patients achieved a radiographic response sufficient to justify surgical exploration. Of these, 1 patient was identified as having intraperitoneal dissemination at the time of surgery and the planned pancreatectomy was aborted. Five patients underwent resection. Procedures included laparoscopic standard pancreaticoduodenectomy (n = 3), open pyloris-sparing pancreaticoduodenectomy (n = 1), and open distal pancreatectomy with irreversible electroporation of a pancreatic head mass (n = 1). Median age was 60 years (range, 51-67). These patients had been initially designated as having unresectable disease based on superior mesenteric artery and celiac artery encasement (n = 2), inferior vena cava encasement with invasion of the posterior abdominal wall (n = 1), biopsy-positive regional nodal metastasis (n = 1), or mesenteric root involvement with abutment of the celiac and hepatic arteries (n = 1).

Two patients underwent gross total (R0) resections and subsequent pathology showed minimal residual disease. Two patients had gross subtotal (R2) resections. One patient, who after negative pancreatic head biopsies underwent distal pancreatectomy and irreversible

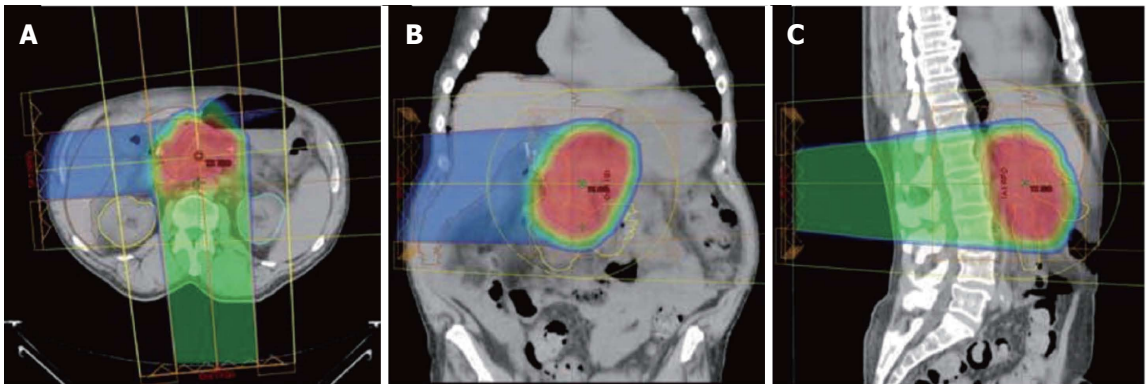

Figure 3 Typical proton dose distributions used to treat pancreatic cancers. Shown in the axial (A), coronal (B), and sagittal (C) projections. A heavily weighted (75% of the target dose) posterior or posterior oblique field is combined with a more lightly weighted (25% of the target dose) right lateral oblique field. Because protons are associated with a low entry dose and no exit dose compared with X-rays, there is significant sparing of small bowel and stomach tissue, which are highly sensitive to radiation damage. This normal-tissue sparing explains the low incidence of gastrointestinal toxicity when protons are used to deliver upper abdominal radiotherapy.

Table 1 Patient details

Patient	1	2	3	4	5
Age	55	60	51	68	67
Stage	T3 N1	T4 N0	T4 N0	T4 N0	T4 N0
Comorbidities	None	Colon cancer	Unintentional weight loss	None	Unintentional weight loss
Resection type	Laparoscopic	Laparoscopic	Laparoscopic	Open	Open
Surgery duration (min)	339	465	419	290	484
Estimated blood loss (mL)	300	800	850	2000	1000
Intensive care stay (d)	1	1	0	2	0
Total hospital stay (d)	5	11	6	10	14
Complications	Wound infection	Delayed gastric emptying	None	None	Delayed gastric emptying and gastritis
Readmission within 30 d	4 d for wound infection	2 d for nausea and vomiting	None	None	2 d for gastritis

electroporation of the pancreatic head mass, had no identifiable malignancy in the surgical specimen. In none of the 5 cases did the surgeon document any complaint regarding the texture of tissue around the resection, exceptional bleeding, difficulty with closure, postoperative wound complications, or any other issue that could be attributed to the irradiated state of the tumor and surrounding tissues.

The median duration of the surgical procedures was 419 min (range, 290-484 min). Estimated blood loss (EBL) ranged from 300 to 2000 cm^3 with a median of 850 cm^3. The median intensive-care stay for these patients was one day (range, 0-2) and median hospital stay (LOS) was 10 d (range, 5-14). Three patients were readmitted to a hospital within 30 d after discharge: The first was a patient discharged on postoperative day 5 who was then readmitted for wound infection on day 9. The second was discharged on postoperative day 11 who was then readmitted the next day with the primary complaint of delayed gastric emptying. The third was a readmission on postoperative day 19 for ischemic gastritis following discharge on postoperative day 10.

Only 1 patient demonstrated ultimate local progression at the primary site, which occurred 7 mo after surgery in 1 of the patients who underwent an R0 resection. The median survival for the 5 resected patients was 24 mo (range, 10-30); the 4 patients with locally controlled disease ultimately developed distant metastases.

DISCUSSION

The above surgical metrics for patients with initially unresectable disease who received dose escalated radiotherapy to 59.4 Gy (RBE) compare favorably to those observed in four published studies that, for the most part, involved surgery for resectable patients who had not received neoadjuvant radiotherapy (Table 2): (1) Tseng *et al*[9] published a series analyzing 650 procedures performed by experienced surgeons at the MD Anderson Cancer Center (Houston, TX). The mean operative time was 513 min. The mean EBL was 725 cc and the average LOS was 13 d. The authors acknowledge that some patients underwent preoperative radiation therapy or chemotherapy but these numbers were not reported; (2) Speicher *et al*[10] reported an average procedure length of 431 min in a series of 140 pancreaticoduodenectomies performed by experienced surgeons in which 40% were performed laparoscopically. Patients experienced a mean

Table 2 Surgical metrics for pancreatectomy - A comparison of the published studies

Published study	Operating room time (min)	Estimated blood loss (cc)	Length of hospital stay (d)
Tseng[9]	513	725	13
Speicher[10] open	NA	500	NA
Speicher[10] laparoscopic	NA	200	NA
Speicher[10] total	431	NA	10
Asbun[11] open	401	1032	12.4
Asbun[11] laparoscopic	541	195	8
Florida Agency for Healthcare Administration	NA	NA	11
Current series	419	850	10

NA: Not applicable.

EBL of 200 mL when a laparoscopic approach was used, and 500 mL with hybrid or open procedures. The mean LOS was 10 d with a 37% readmission rate. There is no mention of neoadjuvant therapy in these cases; (3) Asbun and Stauffer[11] at the Mayo Clinic reported similar metrics. For 215 open and 53 laparoscopic pancreaticoduodenectomies, the EBL averaged 1032 cm^3 and 195 cm^3, mean LOS was 12.4 d and 8 d, and average operating room time was 401 and 541 min, respectively. The authors did not record whether these patients had been irradiated before surgery; and (4) The Florida Agency for Healthcare Administration database[12] reported the statewide median length of stay following pancreatectomy in the years from 2010 to 2012 to be 11 d (mean ± SD, 14 ± 11.5).

It is an accepted precept of oncology that patients with solid tumors cannot be cured if local and regional tumor control cannot be achieved. For patients with nonmetastatic pancreatic cancer, it is also generally accepted that local control cannot be achieved without extirpative surgery. As such, surgery represents a necessary condition for cure. Nevertheless, because surgery alone is associated with a high local and regional failure rate, it is rarely a sufficient condition for cure. Patients undergoing pancreaticoduodenectomy with negative lymph nodes and negative surgical margins will experience a 50%-80% chance of local-regional tumor recurrence if adjuvant therapies are not offered[1,2]. Even when postoperative chemotherapy and radiotherapy are delivered, the local-regional failure rates range from 28% in the Radiation Therapy Oncology Group 97-04 trial[3] to 36% in the Massachusetts General Hospital (Boston, MA) experience[4]. Although its methodological and statistical flaws have been well-described[13], the results of the European Study Group for Pancreatic Cancer-1 trial suggest that postoperative X-ray-based radiation therapy not only fails to improve patient survival but may be associated with a nominal survival decrement, presumably due to radiation therapy toxicity[14,15].

The failure of postoperative radiation therapy to even reliably sterilize microscopic disease in the postoperative setting might be explained in two ways: First, to allow for postoperative recovery after pancreaticoduodenectomy, upper abdominal radiation therapy cannot be delivered until 10 or 12 wk have elapsed. This time interval potentially allows for the progression of malignant cells in a hypoxic tumor bed. Second, because a large volume of small bowel is transposed into the postoperative radiation therapy field, it is generally not possible to deliver X-ray doses over 50 Gy, which may be inadequate to eradicate even microscopic disease growing in such a hypoxic environment.

While it is recognized that patients undergoing pancreatic resection have a high local-regional failure rate-even in the setting of negative surgical margins and negative lymph nodes-contemporary data from two high-volume institutions suggest that margin-negative, lymph node-negative pancreatectomies are relatively uncommon. The series published by investigators at Johns Hopkins University (Baltimore, MD) on 905 patients undergoing pancreaticoduodenectomy between 1995 and 2005 indicated a 41% margin-positivity rate and a 79% node-positivity rate[5]. The series from investigators at Memorial Sloan-Kettering Cancer Center (New York, NY) on 625 resections conducted between 2000 and 2009 indicated a 16% margin-positivity rate and a 70% node-positivity rate[6]. Based on these data, as well as the low likelihood of reliably sterilizing microscopic disease in the postoperative tumor bed with radiotherapy, it is likely that even "resectable" patients could benefit from preoperative radiation therapy, perhaps with fields that could cover regional lymph nodes. With the current series showing no increase in surgical morbidity after high dose proton radiotherapy, it is arguable that protons allow for the safe delivery of this oncologically rational intervention.

The surgical duration, EBL, and LOS for pancreatectomy following high-dose [59.40 Gy (RBE)] proton radiotherapy for patients with initially unresectable disease in this series are comparable to those observed in studies that, for the most part, involved surgery for resectable patients who had not received neoadjuvant radiotherapy. These data strongly suggest that standard dose [50.40 Gy (RBE)] neoadjuvant proton radiotherapy should not increase the difficulty of pancreatectomy in patients with resectable disease.

COMMENTS

Background

Nearly every patient cured of adenocarcinoma of the pancreas has had complete surgical resection of the tumor. Because this malignancy is initially

asymptomatic, tumors are often very locally advanced at diagnosis and may not be resectable without removing vital tissues such as the major abdominal arteries. For many years chemotherapy and photon radiotherapy have been used to shrink advanced tumors in an attempt to make them resectable. Proton therapy has not previously been used for this purpose but is promising because it can be carefully shaped to spare the normal tissues of the abdomen such as the stomach, duodenum, spinal cord, and kidneys from radiation. This new treatment option will only be acceptable if it does not increase the rate of complications at the time of resection of the tumor.

Research frontiers

Proton radiotherapy has been used in the treatment of cancer for many decades but has only recently become widely available. Much meticulous research must be done to show whether proton treatment offers advantages over standard treatments for each type of cancer. The first step in each line of inquiry is to demonstrate that proton radiotherapy is safe, and then efficacy can be addressed.

Innovations and breakthroughs

In the current work the authors have shown for the first time that proton radiotherapy given prior to attempted resection of initially unresectable pancreas cancers does not result in increased rates of surgical complications.

Applications

In the large fraction of patients with pancreatic cancer who have an unresectable tumor at the time of diagnosis, proton radiotherapy offers one safe option for neoadjuvant treatment intended to downstage the tumor and make surgical resection possible.

Terminology

One patient in this study was treated with irreversible electroporation. This is an emerging technology in which the surgeon disrupts the integrity of tumor cell membranes using a high voltage, high frequency electrical field, leading to eventual cell death.

Peer-review

This paper is very interesting and suitable for publication in this journal.

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ORIGINAL ARTICLE

Prospective Study

Five-year outcomes of laparoscopic sleeve gastrectomy as a primary procedure for morbid obesity: A prospective study

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Abstract

AIM

To prospectively evaluate the postoperative morbi-mortality and weight loss evolution of patients who underwent a laparoscopic sleeve gastrectomy (LSG) as a primary bariatric procedure during 5 years of follow-up.

METHODS

Since 2006, data from patients undergoing a highly restrictive primary LSG have been prospectively registered in a database and analysed. Preoperative co-morbid conditions, operating time, hospital stay, early and late complications rate and evolution of weight loss after 5 years of follow-up were analysed.

RESULTS

A total of 156 patients were included, 74.3% of whom were women. The mean age was 43.2 ± 13.1 years and the mean body mass index (BMI) was 41.5 ± 7.9 kg/m^2. Seventy patients (44.8%) presented a BMI under 40 kg/m^2. The mortality rate was 0%. The leakage rate was 1.2%, and the total 30-d morbidity rate was 5.1% (8/156). With a mean follow-up of 32.7 ± 28.5 (range 6-112) mo, the mean percent of excess of weight loss (%EWL) was 82.0 ± 18.8 at 1 year, 76.7 ± 21.3 at 3 years and 60.3 ± 28.9 at 5 years. The mean percent of excess of BMI loss (%EBMIL) was 94.9 ± 22.4 at 1 year, 89.4 ± 27.4 at 3 years and 74.8 ± 29.4 at 5 years. Patients with preoperative BMI less than 40 kg/m^2 achieved greater

weight loss than did the overall study population. Diabetes remitted in 75% of the patients and HTA improved in 71.7%. CPAP masks were withdrawn in all patients with obstructive sleep apnoea.

CONCLUSION

LSG built with a narrow 34 F bougie and starting 3 cm from the pylorus proved to be safe and highly effective in terms of weight loss as a stand-alone procedure, particularly in patients with a preoperative BMI lower than 40 kg/m^2.

Key words: Sleeve gastrectomy; Morbid obesity; Bariatric surgery; Obesity surgery; Laparoscopy; Long-term results; 5-year results

Core tip: The number of laparoscopic sleeve gastrectomies (LSGs) performed worldwide as a primary bariatric procedure has grown exponentially in recent years, given the simplicity of the technique, the low complication rate and the good short- and mid-term results regarding weight loss and the resolution of co-morbidities. However, there are a limited data from long-term studies. In this study, a standardized LSG proved to be safe (no mortality and a leakage rate of 1.2%) and highly effective in terms of weight loss after 5-year of follow-up, particularly in patients with a low preoperative body mass index. This manuscript provides additional evidence supporting the role of laparoscopic sleeve gastrectomy as a stand-alone procedure for selected morbidly obese patients.

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INTRODUCTION

The laparoscopic bariatric procedure commonly referred to as "sleeve gastrectomy" (LSG) is a left partial gastrectomy of the fundus and body to create a long tubular gastric conduit constructed along the lesser curve of the stomach[1].

LSG was initially proposed as a first-stage procedure to reduce the mortality and postoperative morbidity of more complex bariatric procedures in higher-risk patients[2], such as the duodenal switch, to complete the biliopancreatic diversion or the Roux-en-Y gastric bypass (RYGB) in a second stage. Soon, it was noted that many patients frequently lost sufficient weight such that a second-stage operation became unnecessary[3]. LSG is not merely a restrictive procedure. LSG provokes a rapid gastric emptying of solid food, accelerates intestinal transit and induces a favourable change in the gut hormones, thereby facilitating weight loss through restriction and appetite suppression, given the reduction in the ghrelin levels after resection of the gastric fundus[3-7]. Since then, LSG has been performed as a primary and definitive bariatric procedure in patients whose weight and medical condition are not sufficiently severe to require a complex bariatric operation, moving to a second stage only in those selected patients in which weight loss was inadequate[8]. Eventually, LSG was performed in some patients with special conditions in which the usual bariatric operations might be too aggressive[9].

The number of LSGs performed worldwide has grown exponentially over the last decade, because it appears to be an easier and safer technique[10-13]. Many surgeons now perform LSG as their standard bariatric operation[3]. The advantages of the LSG include its technical simplicity, shorter operative time, maintenance of bowel integrity and preservation of the pylorus[3,10]. The long-term problems associated with other complex bariatric procedures, including internal hernias and small bowel obstruction are avoided with LSG. In addition, patients who underwent LSG had fewer nutritional deficiencies than that did patients who underwent RYGB or biliopancreatic diversion[14]. The LSG can later be modified by a laparoscopic approach if required, to a more complex procedure (such as RYGB or duodenal switch) in patients who develop severe gastroesophageal reflux symptoms or those who regain weight.

LSG has proven highly effective at achieving durable weight loss and co-morbidity reduction over the short and intermediate terms and is comparable in some aspects to RYGB, the current gold standard in bariatric surgery[7,15-18]. However, some questions must be answered regarding the long-term results of LSG because there are a limited data from long-term studies and because of the variability in both the reported follow-up among series and the rate of patients lost to follow-up.

The aim of this study was to assess the safety and outcomes of patients who underwent a LSG as a primary bariatric procedure in analysing mortality, postoperative morbidity rate, late complications and evolution of weight loss after 5 years of follow-up.

MATERIALS AND METHODS

Patients selection and study design

From 2006 to January 2016, data from patients who underwent a LSG as a single procedure treating morbid obesity were collected in an electronic database (Microsoft Access 2003 Microsoft Corporation, Redmond, QA, United States) for analysis. All study participants, or their legal guardian, provided informed written consent prior to study enrolment. The study was officially registered under the identification number researchregistry 1580 on researchregistry.com.

The indications for LSG included patients with body mass index (BMI) less than 45 kg/m^2, primary

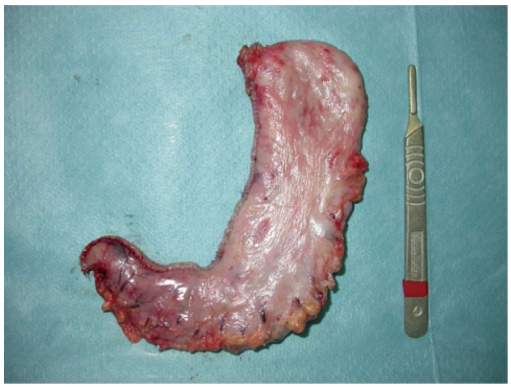

Figure 1 Specimen after sleeve gastrectomy. The whole fundus had to be removed. Stapler firings must be properly aligned to avoid excessive narrowing of the sleeve and functional obstruction due to rotation.

procedure in super-obese patients as the initial stage of a two-staged approach for weight loss (RYGB or BPD in 2 stages), adolescents (under 18 years old of age) with morbid obesity and obese patients with impaired medical conditions or other important co-morbidities such as liver cirrhosis.

The first endpoint of this study was to assess the safety of the procedure by analysing the 30-d mortality and early postoperative complications: Suture leak rate, haemorrhages, wound infection rate, deep venous thrombosis, pulmonary embolism and cardiac and pulmonary complications.

The second endpoint was to evaluate the outcome of LSG in terms of weight loss 5 years after the procedure. Weight loss was measured using BMI evolution and the percentage of excess weight loss (%EWL). Given the variability of %EWL depending on the definition of ideal body weight, we also used the percentage of excess body mass index loss (%EBMIL)[19]. Excessive BMI itself was defined as initial BMI minus 25. Values are reported as the mean ± standard deviation.

The following variables were also evaluated: Resolution of preoperative co-morbid conditions [diabetes, hypertension, obstructive sleep apnoea syndrome (OSA)], length of hospital stay and late complications (stricture, functional obstruction, gastroesophageal reflux, trocar-site hernia rate).

Surgical technique

Under general anaesthesia the patients were placed in the reverse Trendelenburg position with the surgeon standing between the legs. All patients received intravenous antibiotic prophylaxis with 2 g of cefazoline. Compression stockings were used during the operation to prevent deep vein thrombosis and thromboembolism.

The procedure was performed using 4 or 5 ports (two or three 12-mm trocars and two 5-mm trocars). The greater curvature of the stomach was completely freed starting from the antrum (3 cm proximal to pylorus) until the left pillar of the diaphragm and the gastroesophageal junction were completely exposed. If a hiatal hernia is identified, dissection should be carried posteriorly to achieve appropriate closure of the crus. If a hernia is found, it should be repaired[10]. A harmonic scalpel (Ultracision®, Ethicon Endo-Surgery Inc., Johnson and Johnson, Cincinnati, OH, United States) was used to divide the gastroepiploic and the short gastric vessels. Then, the adhesions of the posterior side of the stomach were dissected to achieve an appropriate sleeved stomach. The LSG was performed by sequentially firing an articulating linear stapler (Echelon Flex™ Endopath, Ethicon Endo-Surgery Inc., Johnson and Johnson, Cincinnati, OH, United States). The gastric division started at 3 cm proximal to the pylorus. Two 60-mm green staple cartridges (open height = 4.1 mm) were usually used to transect the antrum, and gold (3.8 mm) and blue loads (3.6 mm) were later applied at the gastric corpus and fundus. The whole fundus had to be removed. Special attention was required at that point to avoid rotation and functional obstruction of the sleeve by ensuring equal (and not excessive) traction on both walls of the stomach. It is of utmost importance to align the stapler firings properly to avoid excessive narrowing, especially at the level of the *incisura angularis* (Figure 1).

The calibration of the LSG was obtained using a 34 F oral gastric tube (1.13 cm). The gastric stapled line was always oversewn with a 2/0 absorbable running suture (Monoplus®, B. Braun, Melsungen, Germany) in the 125 initial cases. A bovine pericardial strip (BPS-Peristrip) was used in 5 patients. Since 2014, bioabsorbable membranes (Gore Seamguard® from WL Gore and Associates, Newark, DE, United States) were used instead of the reinforcement suture to achieve better hemostasis and reduce the suture leakage rate[15]. Intraoperative leak testing using methylene blue dye was routinely performed. A suction Blake or Jackson-Pratt drain was placed along the suture line. Finally, the gastric specimen was withdrawn through the right 12-mm port. All 12-mm wounds were closed with Monoplus® or Monomax® 2/0 sutures (B. Braun, Melsungen, Germany) using an Endoclose™ trocar-site closure device (Covidien Products, Medtronic, Minneapolis, MN, United States).

Patients started to walk 8 to 12 h after the procedure. A liquid diet was initiated on the first postoperative day and was implemented for two weeks. The patients were usually discharged on the second or third postoperative day. The treatment included oral analgesia, proton-pump inhibitors (PPI) and low molecular weight heparin against deep vein thrombosis for 30 d.

Postoperative follow-up

The first follow-up control was scheduled at the medical office eight days after the procedure. Follow-up data were obtained at the medical office after 15 d, 1, 3, 6 mo, 1 year and semi-annually thereafter by the surgeon who performed the procedure and by a nutritionist. All data were prospectively collected.

RESULTS

Data from 156 patients who underwent LSG until January 2016 were analysed. Of the patients, 116 (74.4%) were

Table 1 Patients' characteristics and general data of the series

Number of patients	156
Age[1] (yr)	43.2 ± 13.2 (16-71)
Gender (Female/male)	116 / 40
BMI[1] (kg/m^2)	41.5 ± 7.9
BMI < 40 kg/m^2	70 (44.9)
BMI 40-50 kg/m^2	71 (45.5)
BMI > 50 kg/m^2	15 (9.6)
Comorbidity	
HTA	39 (25)
Diabetes	12 (7.6)
Obstructive sleep apnea (with CPAP)	21 (13.4)
Other	67 (42.9)
Operating time[1] (min)	95 ± 14.1 (65-155)
Hospital stay[1] (d)	3.5 ± 0.7 (1-18)
Follow-up[1] (mo)	32.7 ± 28.5 (6-112)

[1]Data are frequency counts (percentage of total) or the mean ± SD plus range in parentheses. BMI: Body mass index; HTA: Arterial hypertension; CPAP: Continuous positive airway pressure.

Table 2 Mortality, early and late complications after laparoscopic sleeve gastrectomy *n* (%)

Mortality	0
Total 30-d complications	8 (5.1)
Staple line leakage	2 (1.2)
Staple line haemorrhage	1 (0.6)
Wound infection	2 (1.2)
Pneumonia	1 (0.6)
Cutaneous rash	1 (0.6)
Urethral bleeding	1 (0.6)
Late complications	
Symptomatic gastroesophageal reflux	24 (15.3)
Hiatal hernia needing laparoscopic repair	1 (0.6)
Gastric stricture – conversion to gastric by-pass	1 (0.6)
Symptomatic cholelithiasis	7 (4.4)

Data are frequency counts (percentage of total).

women, and 40 (25.6%) were men; overall, the mean age was 43.2 ± 13.1 (range 16-71) years, and the mean BMI was 41.5 ± 7.9 (range 34-76) kg/m^2. Seventy patients (44.9%) presented BMI under 40 kg/m^2, and only 15 patients (9.6%) were super-obese (BMI greater than 50 kg/m^2). All the procedures were performed laparoscopically by the same surgeon. The mean hospital stay was 3.5 ± 0.7 d (range: 1-18). All patients completed the 6-mo outpatient follow-up at the medical office. The mean follow-up was 32.7 ± 28.5 mo (Table 1).

The mean operating time was 95 ± 14.1 min. Conversion to laparotomy was necessary in 2 patients (1.2%) due to intraoperative haemorrhage. One patient was a woman suffering from a cavernous transformation of the portal vein and the other required a lateral segmentectomy to remove a bleeding 8-cm liver haemangioma.

Morbidity and mortality

No mortality was observed in this series. The total 30-d postoperative complication rate was 5.1% (8/156 patients). The type and severity of complications are listed in Table 2. A leakage in the staple-line was detected in 2 women (1.2%). The first woman (after oversewing the staple line) healed successfully with medical management 14 d after. The second (Peristrips® reinforcement) required a laparoscopic reoperation to drain a subphrenic abscess secondary to a leak at the angle of His. No endoprosthesis or self-expanded wall-stent was needed. There was no relationship between leakage and patients' BMI, age or technical difficulties during the sleeve gastrectomy procedure. Intraoperative leak testing was not predictive of the later development of staple line leaks. No patients presented with deep vein thrombosis or pulmonary embolism.

Regarding late complications, one patient (without symptoms of previous staple-line leak) developed a gastric stricture 10 mo after the LSG and submitted to a laparoscopic gastric bypass (0.6%). Twenty-four patients (15.3%) referred to new-onset symptoms suggesting gastroesophageal reflux requiring daily low-dose of PPI. One of these patients developed a hiatal hernia and underwent laparoscopic hiatoplasty and a Hill gastropexy with good outcomes. To date, three patients (1.9%) have developed a trocar-site hernia. Cholecystectomy due to symptomatic gallstones was performed during the follow-up in 7 patients (4.4%); 2 of them presented with acute pancreatitis. There were no data on the cholelithiasis rate in asymptomatic patients.

Weight loss

The mean follow-up was 32.7 ± 28.5 mo (range 6-112). There were 140 patients with at least 1 year of follow-up. Fifty-one patients reached more than 5 years of follow-up.

The mean initial BMI was 41.5 ± 7.9 kg/m^2 (range 34.2-76.0), and the mean initial percentage of excess of weight (%EW) was 83.1 ± 18.1%. The preoperative BMI of 72 patients (44.9%) was less than 40 kg/m^2. Marked weight loss was observed during the first year in all patients, achieving a mean BMI of 26.4 kg/m^2, with a mean %EWL of 82.0 ± 18.8 and a mean %EBMIL of 94.9 ± 22.4 after the 1-year follow-up. However, weight loss dropped progressively during the follow-up with remarkable differences among the patients (Figure 2). The mean %EBMIL was 89.4 ± 27.4 at 3 years and 74.8 ± 29.4 (range: 27.2-119.0) at 5 years. The evolution of mean BMI, %EWL and %EBMIL at different follow-up points is shown in Figure 2 and Table 3.

The overall success rate, defined when %EWL is > 50%, was 96.1% of the patients after 1 year, 95.1% after 2 years, 89.5% after 3 years, 82.1% after 4 years and 73.0% after 5 years. It must be highlighted that the patients with a lower initial BMI, especially those with initial BMI under 40 kg/m^2, achieve excellent results in terms of %EWL and %EBMIL (Figure 3).

Revisional surgery

During postoperative follow-up, re-operation because of weight regain from %EWL > 50% to %EWL < 30% was necessary in 4 patients (2.5%), all of them beyond

Table 3 Weight loss results of laparoscopic sleeve gastrectomy over time

Follow-up	Preoperative	1 yr	2 yr	3 yr	4 yr	5 yr
n	156	140	99	66	56	51
BMI[1]	41.5 ± 7.9	26.6 ± 4.4	26.3 ± 3.7	27.2 ± 5.8	28.7 ± 5.5	30.1 ± 6.1
%EWL[1]		82.0 ± 18.8	86.1 ± 28.9	76.7 ± 21.3	72.8 ± 22.6	60.3 ± 28.9
%EBMIL[1]		94.9 ± 22.4	93.7 ± 23.5	89.4 ± 27.4	81.1 ± 28.3	74.8 ± 29.4

[1]Data are frequency counts (total) or the mean ± SD. BMI: Body mass index; %EWL: Percentage of excess weight loss; %EBMIL: Percentage of excess body mass index loss.

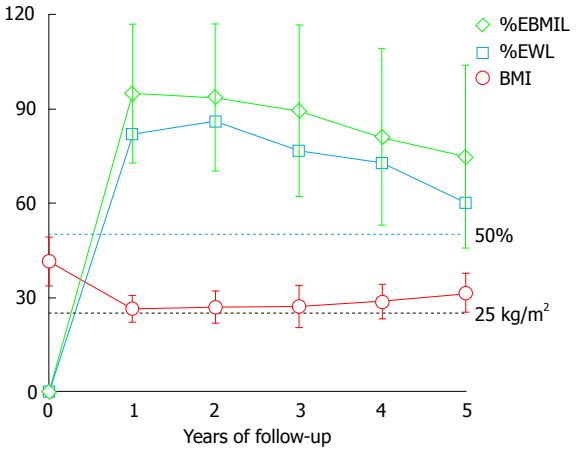

Figure 2 Evolution of body mass index, excess weight loss and excess body mass index loss during the follow-up. BMI: Body mass index; %EWL: Percent of excess weight loss; %EBMIL: Percent of excess body mass index loss.

the fourth year of follow-up. A 70-year-old woman received a laparoscopic re-sleeve, one patient underwent a SADI's and two received a laparoscopic RYGB.

Resolution of co-morbidities

After the first postoperative year, the rate of remission or improvement of hypertension was 71.7% (total remission in 25 patients and improvement in 3). CPAP was withdrawn in all patients with obstructive sleep apnoea (OSA). Complete remission of type 2 diabetes (T2DM) was observed in 75% (9/12) of preoperative diabetic patients (remission was considered when anti-diabetic medication was discontinued and blood glucose level was under 120 mg/mL). One patient receiving preoperative insulin improved and now receives per-oral anti-diabetic medication.

DISCUSSION

The first endpoint of this study was to assess the safety of LSG as a primary bariatric procedure. LSG has gained popularity in recent years given its theoretical technical simplicity and low rate of complications[10,11,15]. However, LSG can be a very difficult procedure even for laparoscopic surgeons with advanced skills. The surgeon's experience and some technical aspects, such as the bougie size (less than 40 F) and the distance to the pylorus being less than 4 cm from the first stapling, have been previously reported as risk factors for the development of complications after a LSG[13].

The mortality rate in this series was nil and the rate of 30-d severe complications related to the procedure was 1.9% (Table 1). The rate of staple-line leak and fistula, which is the most feared postoperative complication after LSG, was low in this series (1.2%), even when using a thin bougie to calibrate the stomach and sectioning the stomach at a short distance from the pylorus. According to the International Sleeve Gastrectomy Expert Panel[10], the average leak rate is 1.06% ± 1.13%. There is currently no consensus on the most effective measures to prevent the leakage and fistula, but we share the concept that reinforcing the staple line (with sutures or buttressing material) during LSG can significantly reduce the leakage rate[7,15,20]. The method for doing so is still a matter of debate[21]. Some reports showed no differences between oversewing of the staple line and the use of buttresses[22-24]. However, a systematic review of 88 included studies representing 8920 patients[15] found that the leak rate in LSG was significantly lower using absorbable membrane (Seamguard®) staple-line reinforcement (1.1%) than was oversewing (2.0%), bovine pericardial strip (BPS-Peristrips®) reinforcement (3.3%), or no reinforcement (2.6%). We observed one leak after oversewing of the staple line and another after the use of Peristrips®. No leaks were observed in the Seamguard® subgroup but the small number of patients in this series does not allow further analysis. It must be noted that the significantly highest incidence of leaks was reported when using both sutures and buttressing material (3.6%); consequently, this approach should always be avoided[24].

The second endpoint was to evaluate the evolution of weight loss after LSG as a primary bariatric procedure. The overall results of this study reinforce the evidence that LSG was effective at achieving a significant weight loss over short- and mid-term follow-up. Comparable outcomes in terms of weight loss over a 5-year period were reported at the 3rd International Summit of Sleeve Gastrectomy[3], with a mean percentage of excess weight loss of 62.7%, 64.7%, 64.0%, 57.3%, and 60.0% after 1, 2, 3, 4, and 5 years, respectively. These data are all consistent with other studies published to date[16,25-38] (Table 4). LSG outcomes are comparable to the gold standard procedure in bariatric surgery, the RYGB[6], thus

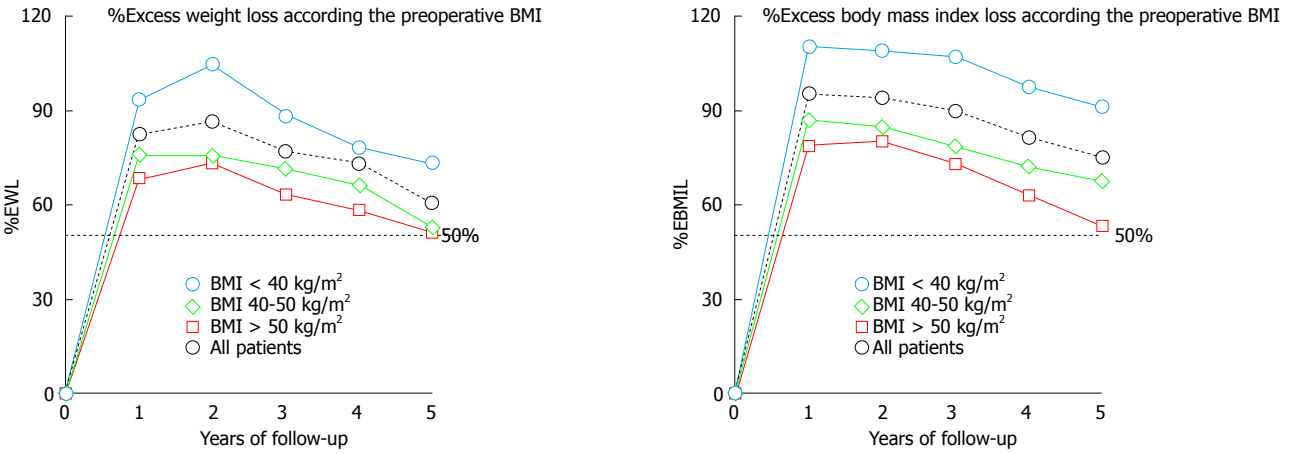

Figure 3 Excess weight loss evolution and excess body mass index loss evolution according to preoperative body mass index. Patients with a preoperative BMI under 40 kg/m^2 achieve better results after 5-year of follow-up. BMI: Body mass index; %EWL: Percent of excess weight loss; %EBMIL: Percent of excess body mass index loss.

Table 4 Long-term weight loss outcome of laparoscopic sleeve gastrectomy for morbid obesity

Author	Year	Patients with 5-yr follow-up	Mean initial BMI (kg/m^2)	%EWL 1 yr	%EWL 5 yr	%EBMIL 1 yr	%EBMIL 5 yr
Bohdjalian[26]	2010	26	48.2 ± 1.3	57.5 ± 4.5	55.0 ± 6.8		
Himpens[27]	2010	30	39		53.3		
D'Hondt[28]	2011	83	39.3	78.5	54.4		
Braghetto[29]	2012	60	38.4 ± 5.1	57.3	57.3		
Sarela[30]	2012	13	45.9	76	69 (8 yr)		
Rawlins[31]	2013	49	65	56	85.8		91
Sieber[32]	2014	62	43.0 ± 8.0			61.5 ± 23.4	57.4 ± 24.7
Boza[33]	2014	112	34.9	88	62.9		
Liu[34]	2015	44	41.0 ± 7.0	70.5	57.2		
Lemanu[35]	2015	55	50.7	56	40		
Pok[36]	2015	61	37.3 ± 8.1	76.5	72.6		
Alexandrou[37]	2015	30	55.5 ± 1.7	65.2 ± 6.1	56.4 ± 5.8		
Perrone[38]	2016	162	47.4 ± 4.2			75.1 ± 18.9	78.8 ± 23.5
Hoyuela	2016	51	41.5 ± 7.9	82.0 ± 18.8	60.3 ± 28.9	94.9 ± 22.4	74.8 ± 29.4

BMI: Body mass index; %EWL: Percentage of excess weight loss; %EBMIL: Percentage of excess body mass index loss.

supporting the role of LSG as a stand-alone bariatric operation for morbid obesity.

However, a significant amount of patients may regain weight over time after LSG. Long-term results of LSG still are an ongoing concern, and 10-year follow-up data are actually scarce. Furthermore, a high rate of patients lost to long-term follow-up is not uncommon in previously reported series. Although weight regain was evident with time, data from our series and some long-term observational studies indicate that a significant number of patients maintained good weight loss beyond 5 years of follow-up (Table 4). A recent systematic review of 16 long-term studies including 492 patients revealed the %EWL to be 62.3%, 53.8%, 43% and 54.8% at 5, 6, 7 and 8 or more years of follow-up, respectively[25]. Arman *et al*[39] reported a mean %EBMIL of 62.5% in patients who kept the simple sleeve construction (74.6% overall-study series) after a mean follow-up of 11.7 years.

It is still unclear why LSG ceases to be effective over time in terms of weight loss in some patients, but several reasons could be involved, including dilation of the gastric tube, insufficient gastric fundus resection (where ghrelin is produced) or hyperactivity of previously silent ghrelin-producing cells and other hormonal changes[6,26,39,40]. Inadequate adherence to aftercare changes in eating behaviour and lack of physical activity could play a role of paramount importance in patients with poorer maintenance of weight loss. A recent systematic review by Karmali *et al*[41] concluded that the underlying causes leading to weight regain are multi-factorial and related to patient- and procedure-specific factors.

Our data showed better results regarding weight loss when the initial BMI was lower. Patients with an initial BMI less than 40 kg/m^2 registered excellent results (73% of EWL and 90.8% of EBMIL at 5 years) compared with the overall study population (Figure 3). Age > 60 years, pre-existing co-morbidities and BMI superior to 50 kg/m^2 were identified as prognostic factors of poorer outcome after LSG. Super-obese patients also had poorer weight loss results in this series. These results allow us to suggest that LSG could be routinely used as a sole bariatric technique for patients whose BMI was less than

40 kg/m^2.

However, we observed high variability among patients regarding weight loss maintenance over time, even in patients with similar characteristics. No other significant differences were found between subgroups of patients probably due to the small sample of patients with 5 years of follow-up. Identifying preoperative predictive factors of success might be useful for developing strategies to improve bariatric surgery outcomes and patient selection. Further long-term follow-up randomized studies that include a larger number of patients are needed to identify which patients would benefit the most from LSG.

The last endpoint was to analyse the resolution of preoperative co-morbidities in the patients who underwent a LSG. LSG allowed CPAP to be withdrawn in all patients in the series with preoperative OSA and achieved the resolution of hypertension and T2DM in more than 70%. The improvement of T2DM occurred soon after surgery, even without significant weight loss yet being achieved, and this fact could be attributed to hormonal changes, such as increased GLP-1 secretion or decreased ghrelin[6]. The long-term effects of LSG on T2DM evolution are under continuous evaluation, and Aminian *et al*[42] recently reported a 44% of long-term relapse of T2DM after initial remission and continuous complete remission for $\geqslant$ 5 years ("cure") was achieved in only 3% of the patients. LSG and RYGB showed comparable remission rates of T2DM in a long-term observational study[18], but a meta-analysis including 6526 patients confirmed that RYGB achieved a higher diabetes remission rate (HR = 1.49, 95%CI: 1.04-2.12)[16]. Current data suggesting the long-term superiority of RYGB over LSG in the metabolic control of T2DM could be accounted for by the greater weight loss and by a larger contribution of weight-loss-independent mechanisms[43-45].

In our opinion, the main limitations of this study are the sample size of the series and the heterogeneity of the patients included in the series, precluding to discover significant differences between subgroups of patients (for example, only 15 super-obese patients are included in this series). In addition, only 32% (51/156) of patients reached 5-years of follow-up. The lack of adherence to follow-up was reported previously, and it can be related to several issues, including the distance to the medical office and a lack of trust or rapport with the surgeon or the medical team[46]. However, the most relevant strength of this study is that all patients underwent a standardized LSG operative technique, first, because surgeon expertise is a key issue to lower the complications rate[13,24] and second, because there were no technical differences that may influence the weight loss results. We always tried to perform a more restrictive LSG by using a thinner bougie and beginning the dissection 3 cm from the pylorus to achieve greater weight loss, as suggested by Baltasar *et al*[8,31]. In addition, the long-term follow-up of the patients was always carried out by the same surgeon who performed the procedure.

In conclusion, a LSG built with a narrow 34 F bougie and starting 3 cm from the pylorus, proved to be safe and highly effective in terms of weight loss as a stand-alone procedure, especially in patients with preoperative BMI lower than 40 kg/m^2. In our opinion, LSG could be accepted as the first stand-alone procedure for morbidly obese patients with low BMI. Prospective randomized trials analysing long-term results (beyond ten years of follow-up) will help elucidate whether LSG is comparable to more aggressive techniques.

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COMMENTS

Background

The number of laparoscopic sleeve gastrectomies (LSGs) performed worldwide as a primary bariatric procedure has grown exponentially in recent years, given the simplicity of the technique, the low complication rate and the good short- and mid-term results regarding weight loss and the resolution of co-morbidities. However, the long-term results of LSG still are an ongoing concern because a significant amount of patients may regain weight over time after LSG.

Research frontiers

Bariatric surgery is safe and efficient and allows not only to lose weight but treat conditions such diabetes, hypertension and sleep apnoea in morbidly obese people. Probably, the indications of bariatric and metabolic surgery will increase in the future treating such comorbidities, given its good results and low morbi-mortality.

Innovations and breakthroughs

The current prospective study suggests that LSG could be the procedure of choice for those morbid patients with a low preoperative body mass index (BMI) and without severe comorbidities. However, strict nutritional and behavioural monitoring and follow-up by the surgical team seem to be of paramount importance.

Applications

This study provides additional evidence supporting the role of LSG as a stand-alone procedure for morbidly obese patients, particularly in patients with a low preoperative BMI.

Terminology

Sleeve gastrectomy: Is a left partial gastrectomy of the fundus and body to create a long tubular gastric conduit constructed along the lesser curve of the stomach. The body mass index (BMI) is the main parameter to assess morbid obesity and is defined as the body mass (weight in kilograms) divided by the square of the body height and is universally expressed in units of kg/m^2. The changes in weight and BMI expressed by means of percentage of excess weight loss and percentage of excess of BMI loss help to evaluate the success of bariatric surgery.

Peer-review

The article addresses an important entity and many newly qualified surgeons may find this article interesting.

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MINIREVIEWS

Acute calculous cholecystitis: Review of current best practices

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Abstract

Acute calculous cholecystitis (ACC) is the most frequent complication of cholelithiasis and represents one-third of all surgical emergency hospital admissions, many aspects of the disease are still a matter of debate. Knowledge of the current evidence may allow the surgical team to develop practical bedside decision-making strategies, aiming at a less demanding procedure and lower frequency of complications. In this regard, recommendations on the diagnosis supported by specific criteria and severity scores are being implemented, to prioritize patients eligible for urgency surgery. Laparoscopic cholecystectomy is the best treatment for ACC and the procedure should ideally be performed within

72 h. Early surgery is associated with better results in comparison to delayed surgery. In addition, when to suspect associated common bile duct stones and how to treat them when found are still debated. The antimicrobial agents are indicated for high-risk patients and especially in the presence of gallbladder necrosis. The use of broad-spectrum antibiotics and in some cases with antifungal agents is related to better prognosis. Moreover, an emerging strategy of not converting to open, a difficult laparoscopic cholecystectomy and performing a subtotal cholecystectomy is recommended by adept surgical teams. Some authors support the use of percutaneous cholecystostomy as an alternative emergency treatment for acute Cholecystitis for patients with severe comorbidities.

Key words: Cholecystitis; Cholelithiasis; Biliary stones; Cholecystectomy; Laparoscopy

Core tip: This paper presented herein is a practical and comprehensive review of the acute cholecystitis. This common intra-abdominal infection can proceed to severe complications due to its natural history and requires operative treatment. Surgeons should keep in mind some basic concepts to allow them to make correct decisions about ideal operative strategy including timing.

Gomes CA, Junior CS, Di Saverio S, Sartelli M, Kelly MD, Gomes CC, Gomes FC, Corrêa LD, Alves CB, Guimarães SF. Acute calculous cholecystitis: Review of current best practices. *World J Gastrointest Surg* 2017; 9(5): 118-126 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i5/118.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i5.118

INTRODUCTION

Acute calculous cholecystitis (ACC) represents the second source of complicated intra-abdominal infection (18.5%), according to the World Society of Emergency Surgery complicated intra-abdominal infections Score study[1]. Biliary stones are the main etiology and are present in 6.5% of men and 10.5% of women[2]. The risk of complications, like ACC, gallstone pancreatitis, and choledocholithiasis is 1% to 4% per year. Furthermore, it is recognized that patients with symptomatic cholecystolithiasis will develop ACC more frequently than their asymptomatic counterparts; thereby, effectively raising the risk of complications to five times higher (*i.e.*, 20%)[3].

ACC is the most common complication of cholecystolithiasis accounting for 14% to 30% of cholecystectomies performed in many countries[4]. The disease can be diagnosed at any grade of severity including wall inflammation, local complication and systemic organ dysfunction. Moreover, complicated grades of the disease increase with age, with a peak between 70 and 75 years[5].

The aim is of this manuscript is to provide a practical and comprehensive review of the most important aspects of ACC and its complications. In parallel, to highlight the current evidence that helps the surgeons bedside decision making, on how best to manage the disease, to improve outcomes.

PATHOPHYSIOLOGY

ACC is caused by an inflammatory/infectious process involving the gallbladder wall, in many cases due to an impacted gallstone in the infundibulum or in the cystic duct[2]. The continued mucin production from epithelium and the gallbladder distention, results in micro and macro circulatory perfusion deficits. The subsequent events are serosa edema, mucosal sloughing, venous and lymphatic congestion, ischemia and necrosis with regional or diffuse peritonitis. Acute inflammation may be complicated by secondary bacterial infection, from the bile duct, *via* the portal lymphatic or vascular system. The microorganisms present in the gastrointestinal tract are the most common pathogens[5].

CLINICAL DIAGNOSIS

There is no unique marker capable of definitively indicating the diagnosis of ACC with high accuracy. The key aspects for diagnosis are upper left side signs of inflammation (pain and tenderness) and positive Murphy's sign, as well as clinical and biochemical indicators of systemic inflammatory response. These data must be nowadays supported with positive imaging such as abdominal ultrasound (AUS)[6,7].

Acute cholecystitis severity

The Tokyo Guidelines (TG13) is practical and in accordance with the pathophysiological aspects involved in the inflammation progression from gallbladder wall to regional and systemic complications. Therefore, the grade I represents a mild disease with only wall inflammation. The grade II is associated with local sign of complications such as palpable mass, pericholeystic fluid; onset of symptoms > 72 h; laboratory data showing leukocytosis > 18000/mm^3 and elevated C-reactive protein level. Finally, grade III is associated with organ dysfunction: Cardiovascular (refractory hypotension to volemic resuscitation at 30 mL/kg per hour), decrease of consciousness, respiratory failure (PaO2/FiO2: < 300), oliguria (creatinine: > 2.0 mg/dL), PTT/INR > 1.5 and platelets count below 100.000/mm^3[6].

The American Association of Surgery of Trauma proposes a uniform grading system for eight intra-abdominal infectious diseases including ACC. The grades range from I to V, considering the progressive anatomic inflammation severity (from mild to serious widespread

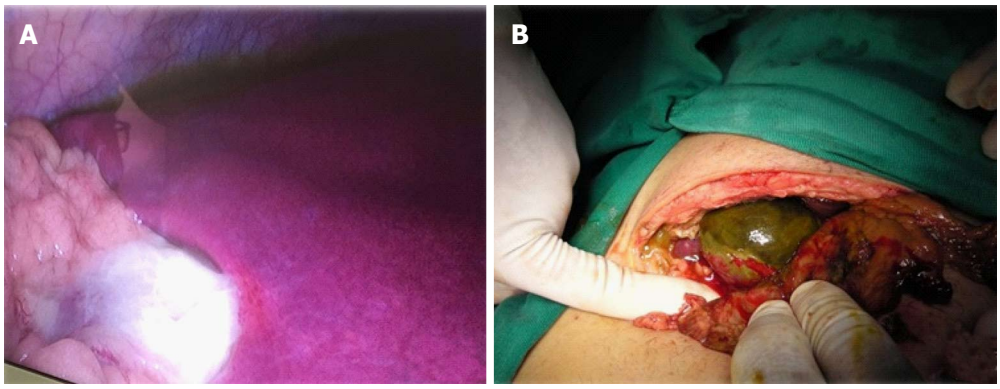

Figure 1 Complicated acute cholecystitis. A: Laparoscopic approach; B: Laparotomic approach.

complications)[8].

Yacoub *et al*[9] have developed five parameters to score and stratify patients under risk of gangrenous ACC (Figure 1). They are age > 45 years, heart beat > 90/min and gallbladder thickness > 4.5 mm (1 point for each parameter), leukocyte count > 13000 mm^3 (1.5 points) and male (2 points). Among their patients with ACC, 13% received 0-2 points (low probability), 33% received 2-4.5 points (intermediate probability) and 87% received > 4.5 points (high probability). The authors concluded that this fast bedside checklist could schedule patients for emergency cholecystectomy[9].

Currently the WSES is in the process of validating a new acute cholecystitis severity score. It takes into account the patient's clinical state, previous surgical intervention and intra-abdominal adhesions, degree of sepsis and regional inflammation[10]. While the paper highlights the initial operative severity score during laparoscopic cholecystectomy to help standardize reporting results of one of the most commonly performed surgeries worldwide, the score also assesses disease severity in the perioperative period and not exclusively in the preoperative period.

IMAGING DIAGNOSIS

Planar radiography is not so effective in the context of gallstones diagnosis, because they are radiolucent in the majority of cases (80%-85%)[11]. Instead, AUS is the first-line imaging requested in suggestive cases of ACC. It allows easy and practical bedside diagnosis due its compelling findings such as: Gallstones, lumen distension, three-phase wall thickening (Figure 2), sonographic Murphy's, perivisceral fluid and hyperemia on Color Dopller[12-15]. However, Kiewiet *et al*[12] have shown that AUS does not have the same accuracy in the diagnosis of ACC as it has in diagnosing cholecystolithiasis. The findings of gallstones, gallbladder wall thickness and Murphy's signal on AUS show high predictive value for ACC diagnosis (95%)[16]. However, not always all signals are present at the same time and gallbladder wall thickening may be observed in other systemic diseases, such as liver, renal and heart failure, probably because portal hypertension[17].

Computed tomography (CT) is useful for the diagnosis of complicated forms of ACC (emphysematous and gangrenous cholecystitis)[18,19], besides it is value in the differential diagnosis with other intra-abdominal diseases, especially in obese patients or when gaseous distention limits the use of AUS. In addition, CT cholangiography (when not jaundiced) in diagnosing common bile duct stones (CBDS) is less employed, with a reported sensitivity from 50% to 90%[20-22].

Cholescintigraphy is an excellent method to diagnose ACC, but it is limited to some centers. It uses the principle that radiopharmaceuticals (diisopropyl iminodiacetic acid) should fulfill the gallbladder content in half an hour. Therefore, if gallbladder is not contrasted, few hours later, the diagnosis of ACC is highly probable, because there is cystic duct obstruction. Shea *et al*[23] showed in their meta-analysis that cholescintigraphy is the imaging of choice in difficult cases and has the highest diagnostic accuracy (Figure 3).

ASSESSING ASSOCIATED CBDS

The presence of associated CBDS should be stratified in all cases of cholecystectomy into low, moderate and high risk. The American Society of Gastrointestinal Endoscopy, has recently confirmed that the presence of choledocholithiasis on AUS and/or bilirubin > 4 mg/dL + dilated CBD criteria had higher specificity (more than 50%) for the CBDS diagnosis[24]. Padda *et al*[25] found in a cohort study that patients with ACC and CBDS present changes in liver function tests. So, the alkaline phosphatase is increased in 77% of the times, bilirubin in 60% and aminotransferase levels in 90%.

In fact, the enzymes could be affected by gallbladder inflammation secondary the acute transient hepatocellular injury, and even their use alone is of limited value[26]. Patients of moderate risk for choledocholithiasis should be underwent a magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) in the preoperative period. The use of intra-operative cholangiography (IOC), and/or laparoscopic ultrasound are effective alternative

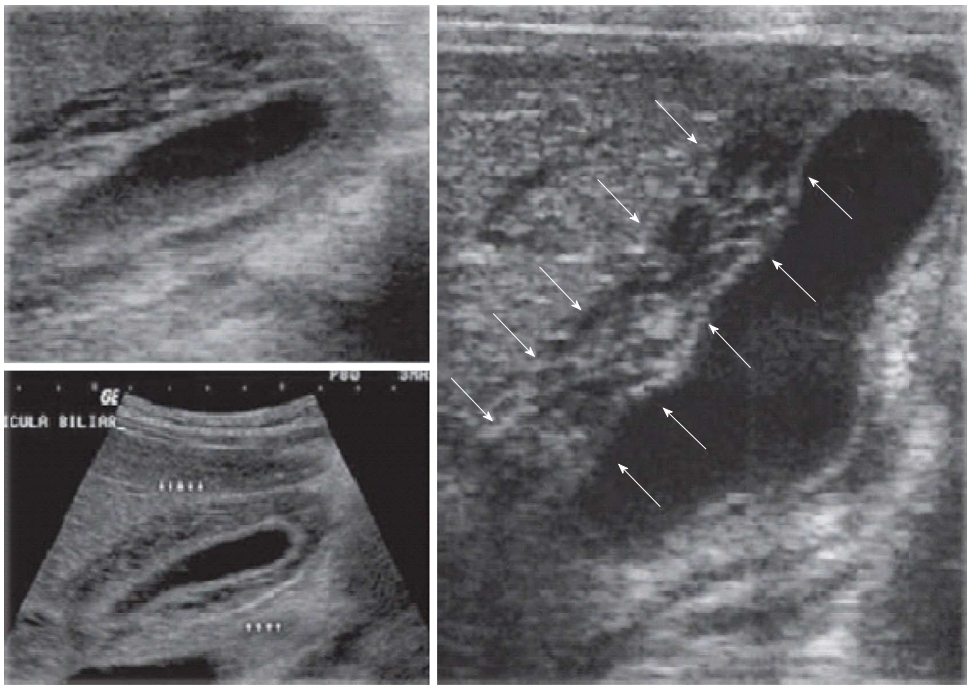

Figure 2 Transabdominal ultrasound in acute cholecystitis.

Figure 3 Cholescintigraphy in acute calculous cholecystitis.

for decrease the incidence of missing CBDS during cholecystectomy too. Therefore, the use of endoscopic retrograde cholangiopancreatography (ERCP) should be reserved for patients that are stratified into the high-risk groups[24,27].

Giljaca *et al*[28], in the recent Cochrane meta-analysis, compared the level of diagnostic accuracy between MRCP and EUS and concluded that both tests are highly accurate and able to exclude the presence of CBDS with high sensibility and specificity (95%). They therefore recommend routinely avoiding the use of the more invasive ERCP, when possible, and instead reserving it for patients already graded as high risk for CBDS[24,28].

Amouyal *et al*[29] have shown that EUS is an excellent approach for detecting CBDS and could replace ERCP in many instances. It prevents the risk of overlooking them, when there are normal biochemical predictors and an absence of CBD enlargement on AUS. The exam is less invasive than ERCP, and has excellent sensitivity and specificity for the detection of CBDS including small stones (< 5 mm)[29].

HOW TO MANAGE ASSOCIATED COMMON BILE DUCT STONE

Patients with symptomatic ACC and CBDS detected during preoperative and/or intraoperative studies should be candidates to undergo CBDS extraction. The choice of treatment depends on the level of surgical expertise, equipment, and the availability of multidisciplinary facilities at each hospital[30]. The options include: open cholecystectomy (OC) with open common bile duct exploration; laparoscopic cholecystectomy (LC) with laparoscopic common bile duct extraction (LCBDE); and LC with endoscopic stone extraction (ESE) performed either preoperatively, intraoperative or post-operatively[31,32]. A systematic review of randomized controlled trials has shown that OC with open CBDE has the lowest incidence of retained stones, but is associated with high morbidity and mortality, especially in elderly patients[30,32]. In addition, there was no difference in the retained CBDS among preoperative or intra-operative ERCP and LCBDSE[30,31]. The procedure, either *via* the transcystic duct (more than 50% success), or *via* choledochotomy (considered to be the more difficult group) is safe and effective to perform in units that are set up for this type of intervention[33,34]. Therefore,

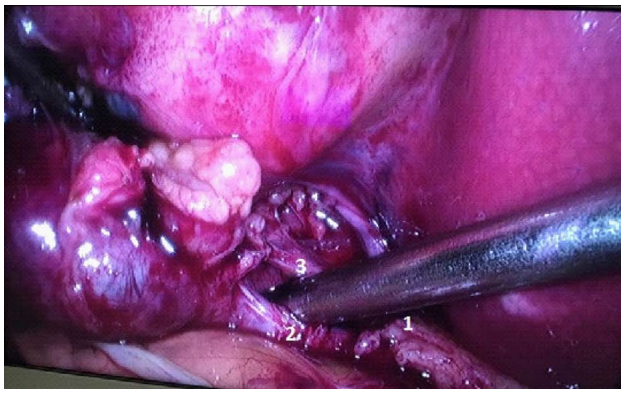

Figure 4 Laparoscopic cholecystectomy showing the critical view of safety. 1: Common hepatic duct; 2: Cystic duct; 3: Cystic artery.

LCBDE is a safe and effective approach for managing option CBDS, has been demonstrated to shorten the hospital stay and should be encouraged as a possible salvage procedure following cases of ESE failure[34].

As a rule, however, operations for severe ACC should focus on dealing with the problem at hand, as CBDS can be removed later. The severity of the local inflammatory process near the bile duct can mean that LCBDE would be difficult to perform. A temporary fenestrated transcystic catheter, inserted *via* the cystic duct into the duodenum (antegrade stent) is an option. Should this be considered, the definite treatment of CBDS would be postponed until the patient recovers and the catheter in the duodenum favors the ERCP. Nonetheless, this approach has not been tested yet prospectively and for coincidental CBDS that are not actively causing obstruction; critics have suggested it seems to be over-treatment, and complications from this technique have been known to occur.

LAPAROSCOPIC OR OPEN APPROACH

Laparoscopy has significant advantages over open surgery in managing septic patients. The immune response and the levels cytokines yielded, which are associated with systemic inflammatory response severity, are smaller and influence the clinical outcomes[35].

Recent systematic reviews and meta-analyses from the WSES concluded that in the setting of ACC post-operative morbidity, mortality, and hospital stay were significantly decreased after LC, as was the incidence of pneumonia and wound infection. Severe haemorrhage, bile leakage rates, and/or operative times were not significantly different between patients undergoing OC and LC. The group of experts concluded that cholecystectomy in ACC should be preferably managed by laparoscopy in the first instance[36]. Though other relevant treatment modalities include mini-cholecystectomy, reduced-port cholecystectomy, single-port cholecystectomy and robotic cholecystectomy, these were determined to be neither practical nor cost-effective in severe cases of ACC.

Because the surgeon's commitment is primarily to their patient and not to the laparoscopy procedure itself, the operation cannot be performed if the "critical view of safety" (CVS) is not obtained during cholecystic pedicle dissection, regardless of the chosen approach (*i.e.,* laparoscopy *vs* laparotomy). Failure to identify the CVS is a strong indication of IOC for the complete understanding of the biliary anatomy (Figure 4). The reported incidence of bile duct injury (CBDI) during LC ranges from 0.16% to 1.5%, and has not decreased over time. Stefanidis *et al*[37] studied how often surgeons resort to the consideration of the CVS during LC and their results were disappointed. Only 20% of observed surgeons achieved adequately the CVS during LC; that is, CVS criterion was not routinely used by majority of surgeons. Furthermore, one-fourth of those who claimed to obtain the CVS did so inadequately[37].

Retrograde laparoscopic cholecystectomy (RLC) or "fundus first" laparoscopic cholecystectomy, a procedure that sometimes utilizes a liver retractor, does have a role in cases in which the standard technique (*i.e.*, cephalad fundic traction and antegrade dissection) fails to provide good exposure[38]. Another emerging strategy that refrains from the need to convert to opening a difficult LC and performing a subtotal cholecystectomy (SCL) is also underway. There is increasing evidence about the feasibility and safety of this procedure, which employs a strategy of "calculated retreat is not defeat[39]. SCL procedures are nominated "fenestrating" and "reconstituting" types and are good alternative in difficult cases. Laparoscopic subtotal cholecystectomy has its advantages but may require advanced laparoscopic skills[39].

An alternative approach aimed at preventing bile duct injury (BDI) is laparoscopic partial cholecystectomy (LPC). A recent systematic review concluded that, when a difficult gallbladder is encountered during LC, LPC is a safe alternative to conversion and closing of the cystic duct, gallbladder remnant, or both seems to be preferable[40]. Currò *et al*[41] (2017) conducted a prospective randomized study comparing three-dimensional *vs* two-dimensional imaging for LC and, despite their small sample, concluded that three-dimensional approach does not improve the performance time of LC in experienced hands. Further study is necessary, however, to verify if it can reduce biliary complications[41].

TIMING OF SURGICAL TREATMENT

Gurusamy *et al*[42] (2010) in their meta-analysis compared early laparoscopic cholecystectomy (ELC - 1 wk of onset of symptoms) X delayed laparoscopic cholecystectomy (DLC - at least 6 wk after symptoms free) in patients with ACC. They concluded that the two groups presented similar results regarding bile duct injury and conversion rate, but the hospital stay was shorter by 4 d for ELC and recommend the approach[42].

Table 1 The choice of antibiotics for treatment of acute calculous cholecystitis according the WSES proposal in two different scenarious

Community acquired		Health care associated	
Infections situations	Drug	Infections situations	Drug
No severe Sepse ESBL -	Amoxicilin Clavulanate	No severe sepse	Piperacilin Tazobactan + Tigecicline + - Fluconazol
No severe Sepse ESBL +	Tigecicline		
Severe Sepse ESBL -	Piperacilin Tazobactan	Severe sepse	Piperacilin Tazobactan + Tigecicline + Echinocandin
Severe Sepse ESBL +	Piperacilin Tazobactan + Tigecicline + Fluconazole		or Carbapenen + Teiclopanin + Echinocandin

From: Campaline *et al*[47], 2014. WSES. ESBL: Extended spectrum β-lactamase.

Cao *et al*[43] (2015) in their meta-analyses studied if ELC is superior to DLC for ACC management. They showed that ELC group has presented reductions in mortality, bile duct complications and improvement in many other parameters analyzed.

Although the procedure should be performed within the first 72 h, patients still benefit from early surgery compared to delayed surgery. Therefore, the period of onset of symptoms should not influence the surgeons' willingness to perform an ELC. They suggest that ELC is the standard of care in the treatment of ACC[43].

According to TG13, for patients with grade Ⅰ disease, cholecystectomy at an early stage (*e.g.*, within 72 h of onset of symptoms) is recommended. If non-operative treatment (antimicrobial therapy) is chosen and no improvement is observed within 24-48 h, reconsider ELC first. For patients classified as grade Ⅱ (*i.e.*, they demonstrate local complications), emergency surgery must be expedited (*via* laparotomy or laparoscopy) and in the absence of adequate facilities, skilled personnel or technical equipment, patient transfer should be considered. For patients with grade Ⅲ and/or those unfit to undergo an emergency cholecystectomy, gallbladder drainage may be an attractive alternative. This therapy is typically complemented with antibiotics and intensive care; an interval cholecystectomy may also be performed at three months, following improvement in the patient's health status[6]. However, Amirthalingam *et al*[44] (2016) suggested that these recommendations are too restrictive, stating instead that patients with moderate and severe ACC can be managed by ELC and sometimes, even those that fall into the category of grade I should be managed using percutaneous drainage because of potential underlying.

In addition, the 2016 WSES guidelines on ACC identify two important aspects in the management. First of all, they conclude that "surgery is superior to observation of ACC in the clinical outcome and shows some cost-effectiveness advantages due to the gallstone-related complications (33% in relapse) and to the high rate of readmission and surgery in the observation group". Second, they confirm that "cholecystectomy is the gold standard for treatment of ACC"[45].

ANTIMICROBIAL TREATMENT

The role of therapeutic antibiotics in ACC is controversial, but seems appropriate in non-operative treatment, which should be reserved for patients with mild disease[6]. The use of preoperative prophylactic antibiotics is not suitable for low-risk patients undergoing LC. The main purpose of starting antibiotics in surgically managed cases of ACC is to prevent perioperative infectious complications[46], however, according to van Dijk *et al*[47] in recent systematic review, which assessed its effect in the course of ACC conclude: They are not effective for patients undergone to non-operative treatment neither in those one selected for cholecystectomy.

When antibiotics are indicated, the choice of antimicrobial agent is guided by the likely type of pathogen being targeted, taking into consideration whether it was acquired in the community or a healthcare setting, whether it is extended spectrum β-lactamase (ESBL) producing, the presence of sepsis, as well as the agent's pharmacodynamics and pharmacokinetics. Blood cultures are not always positive and many times the prescription is based on empiric approach. As we know, critically-ill patients need acute care measures and the intravenous antibiotics administration within the first hour. Microbiological data take at least 48 h for the identification of the microorganisms. In addition, the Hospital based Antibiotic Stewardship Programs should be involved to provide the most frequent pathogens and their susceptibility/resistance profiles[48].

The most important pathogens in ACC originate in the patient's indigenous flora and include Enterobacteriaceae: *E. coli* and *Klebsiella sp*, *Streptococcus sp*, and anaerobes such as *Bacteroides fragilis* group. In these cases, narrower spectrum activity antimicrobials targeting the previously mentioned pathogens are the best option. However, in patients with ESBL-producing Enterobacteriaceae infections, agents against ESBL-producing bacteria need to be warranted[48]. Campanile *et al*[49] (2014) recommend the use of antibiotics and antifungal agents in high-risk patients with gangrenous cholecystitis as their use is tied to lower incidence of infection at the surgical site and better prognosis. The Table 1 illustrates more clearly their antimicrobial recommendations[49].

COMPLICATIONS

Bile leak from a duct of Luschka is more common than true bile duct injury and occurs in 0.1%-0.5% of patients after cholecystectomy. Other complications include peritonitis (0.2%), hemorrhage and surgical site infection including spaces and organs. Operative complication rates are comparable between the laparoscopic and laparotomic approaches. In addition, there is less concern for contamination and lower rates of

wound infection when the gallbladder is taken out in a retrieval bag during laparoscopic cholecystectomy[50-53].

A recent systematic review assessed the associated factors linked to the conversion of LC to OC. The results showed that male patients, age 60-65 years, sclerotic gallbladder or wall thickness (4-5 mm) and acute cholecystitis, were significant risk factors for conversion[54].

WHEN TO PERFORM CHOLECYSTOSTOMY

Percutaneous cholecystostomy (PC) is an alternative to emergency cholecystectomy in complicated cases of high risk patients, however, there are yet no evidences supporting this claim[55,56]. Gurusamy *et al*[56] (2013) in a Cochrane Database systematic review included two trials with 156 participants. The first trial compared PC followed by ELC *vs* DLC (70 participants). The results showed that the mortality, morbidity and conversion rate were the same among the two groups[56].

The second trial (86 participants), compared PC *vs* conservative treatment (86 participants). Again, the result of the study showed no difference in the same parameters[56].

It has been difficult to establish the role of percutaneous gallbladder drainage because of the different existing definitions for the "high-risk patient"[42,54]. In an attempt to clarify the conflicting evidences, Yeo *et al*[57] 2017 in a retrospective review, studied 103 aged patients (median: 80 years), who had undergone PC procedures. The study results showed that the patients with higher APACHE Ⅱ scores, higher Charlson index, delay in diagnosis and carrying out the procedure had higher in-hospital mortality. On the other, the absence of these findings was associated with eventual cholecystectomy[57].

CONCLUSION

Presented herein is a practical and comprehensive review of the ACC. This common intra-abdominal infection can proceed to severe complications due to its natural history and requires operative treatment. Surgeons should keep in mind some basic concepts to allow them to make correct decisions about ideal operative strategy including timing.

The clinical diagnosis should be based on strictly criteria and the patient should be stratified according grade and the possibility of local and systemic complications. Laparoscopy is the suggested first approach for cholecystectomy guaranteeing significant advantages over open surgery. In select cases, percutaneous cholecystostomy may be used as a lifesaving manoeuvre. In addition, the possibility of choledocholithiasis should be kept in mind and its therapeutic alternatives considered. Finally, to recognize the basic principles that guide the antimicrobial use for prophylactic and therapeutic proposes.

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SYSTEMATIC REVIEWS

International scientific communications in the field of colorectal tumour markers

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Abstract

AIM

To analyze scientometrically the dynamic science internationalization on colorectal tumour markers as reflected in five information portals and to outline the significant journals, scientists and institutions.

METHODS

A retrospective problem-oriented search was performed in Web of Science Core Collection (WoS), MEDLINE, BIOSIS Citation Index (BIOSIS) and Scopus for 1986-2015 as well as in Dervent Innovations Index (Derwent) for 1995-2015. Several specific scientometric parameters of the publication output and citation activity were comparatively analyzed. The following scientometric parameters were analyzed: (1) annual dynamics of publications; (2) scientific institutions; (3) journals; (4) authors; (5) scientific forums; (6) patents - number of patents, names and countries of inventors, and (7) citations (number of citations to publications by single authors received in WoS, BIOSIS Citation Index and Scopus).

RESULTS

There is a trend towards increasing publication output on colorectal tumour markers worldwide along with high citation rates. Authors from 70 countries have published their research results in journals and conference proceedings in 21 languages. There is considerable country stratification similar to that in most systematic investigations. The information provided to end users and scientometricians varies between these data-bases in terms of most parameters due to different journal coverage, indexing systems and editorial policy. The lists of the so-called "core" journals and most productive authors in WoS, BIOSIS, MEDLINE and Scopus along with the list of the most productive authors - inventors in Derwent present a particular interest to the beginners in the field, the institutional and national science managers

and the journal editorial board members. The role of the purposeful assessment of scientific forums and patents is emphasized.

CONCLUSION

Our results along with this problem-oriented collection containing the researchers' names, addresses and publications could contribute to a more effective international collaboration of the coloproctologists from smaller countries and thus improve their visibility on the world information market.

Key words: Colorectal tumour markers; Scientometrics; International scientific communications; Web of Science; MEDLINE; BIOSIS; Scopus; Derwent

Core tip: Colorectal tumour markers represent a promising option for the early diagnosis and prognostic evaluation of colorectal cancer patients. Dynamically changing environment of the communication infrastructure in this significant interdisciplinary field deserves comprehensive scientometric assessment. By means of this specific approach, valuable and relatively objective information about the trends and perspectives of research and publication output worldwide has been provided. The results obtained and the comprehensive collection of abstracts and full texts of relevant publications on colorectal tumour markers could contribute to the further improvement of the international visibility on the world information market of coloproctologists from smaller countries.

Ivanov K, Donev I. International scientific communications in the field of colorectal tumour markers. *World J Gastrointest Surg* 2017; 9(5): 127-138 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i5/127.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i5.127

INTRODUCTION

At present, primary colorectal cancer is diagnosed in > 1.4 million subjects annually and incidence is increasing[1]. Recently, much effort focuses on screening and earlier detection of colorectal cancer, which reduces the cancer-related mortality rate[2]. Several screening markers are currently applied to help diagnosing the early-stage colorectal cancer or even the premalignant lesions. They are divided into two different categories: stool markers, such as FOBT/FIT and blood-based markers as DNA/RNA and proteins[3]. DNA methylation-based biomarkers should be widely used to improve the current diagnosis, screening, prognosis and treatment prediction in colorectal cancer[4]. Detection of epigenetic and genetic alterations of circulating cell-free DNA as DNA methylation or DNA mutations and related ribonucleic acids improves cancer detection based on unique, colorectal cancer-specific patterns which serve as biomarkers in screening and diagnosis[5].

The analysis of a panel of 92 candidate cancer protein markers measured in 35 clinically identified colorectal cancer patients and 35 ones identified at screening colonoscopy proves the importance of the validation of the early detection markers in a true screening setting for limiting the number of false-positive findings[6]. Serum expression levels of miR-17, miR-21, and miR-92 represent valuable markers for recurrence after adjuvant chemotherapy in colon cancer patients[7].

A plasma-based protein marker panel for colorectal cancer detection was identified by multiplex targeted mass spectrometry using multiple reaction monitoring technology[8]. The usefulness of diagnostic marker panels was already suggested by us, too[9]. The measurement of metabolite porphyrin concentrations in urine could serve as a new screening and recurrence marker for colorectal cancer[10]. Better understanding and elucidation of the various influences provides a more accurate picture of the segmental distribution of some common molecular markers in colorectal cancer such as KRAS, EGFR, Ki-67, Bcl-2, and COX-2, potentially allowing the application of a novel patient's stratification for treatment based on particular molecular profiles in combination with tumour location[11].

The main objectives of this article were to comparatively analyze by means of scientometric methods the dynamic science internationalization in the actual topic of colorectal tumour markers as reflected in five information portals (data-bases), to outline the most significant primary information sources, scientists and institutions in this interdisciplinary field and thus attempt at contributing to the further improvement of the international scientific communications in smaller countries.

MATERIALS AND METHODS

In July 2016, a retrospective problem-oriented search on this topic using the term of "colorectal marker(s)" in publication titles only was performed. Information retrieval covered the following information portals (data-bases): Web of Science Core Collection (WoS), MEDLINE and BIOSIS Citation Index (BIOSIS) (Thomson Reuters, Philadelphia, PA, United States) as well as Scopus (Elsevier, the Netherlands) for the period from January 1st, 1986 till December 31st, 2015. Information about patents indexed in Dervent Innovations Index (Derwent) (Thomson Reuters, Philadelphia, PA, United States) between 1995 and 2015 was analyzed, too.

The following scientometric parameters were analyzed: (1) annual dynamics of publications - total number and thematic belonging of abstracted publications as well as languages and types of primary publications; (2) scientific institutions - number of abstracted publications and country belonging; (3) journals - total number and number of abstracted articles

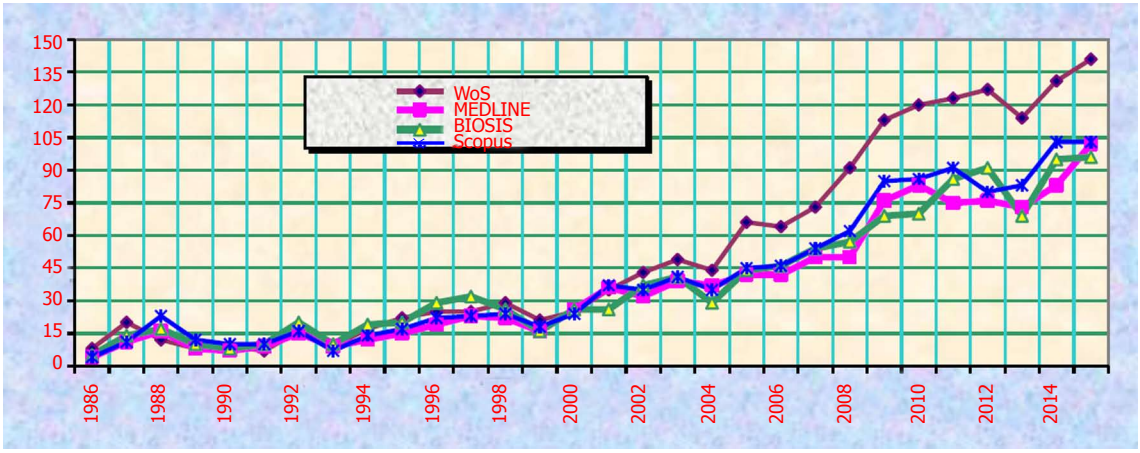

Figure 1 Annual dynamics of the number of publications on the topic abstracted in four data-bases.

Table 1 General bibliometric characteristics of four data-bases concerning the topic

Parameter	WoS	BIOSIS	MEDLINE	Scopus
Total number of publications	1587	1172	1108	1221
Total number of journals	334	265	364	N/A
Total number of journals with one article only	163	140	201	N/A
Total number of languages (n = 21)	5	11	17	19
Total number of countries of authors (n = 70)	63	55	N/A	63
Total number of research areas (WoS categories)	48	42	49	21

N/A: Not available.

from single journals as well as narrow-profile specialized journals containing the term of "(bio)marker(s)" in their titles; (4) authors - number of unique names and number of publications; (5) scientific forums - titles and publications in them; and (6) patents - number of patents, names and countries of inventors and assignees as well number of claims in single patents, and (7) citations - number of citations to publications by single authors received in WoS, BIOSIS Citation Index and Scopus. Purposeful combinations of such quantitative parameters enabled a comprehensive assessment of the unity of the institutionalization, interdisciplinarity and internationalization of modern science in this narrow field of rising socio-medical importance[12].

RESULTS

Our results revealed several essential peculiarities of the dynamic structure of the publication and citation output on this topic during these three decades.

The amounts of relevant papers, journals containing them, and countries of authors varies between the data-bases (Table 1). There are 106 patents indexed in Derwent during the period of the observation

The annual dynamics of the number of publications on this topic which have been abstracted in WoS, BIOSIS, MEDLINE and Scopus and that of the patents abstracted in Derwent are illustrated on Figures 1 and 2. There is a considerable recent increase of the publication output, especially in WoS.

The distribution of some leading countries according to the number of publications in WoS, BIOSIS, and Scopus indicates a considerable stratification typical of most scientometric investigations (Figure 3). The corresponding figures for the United States are 314, 228, and 223 publications; for Canada - 36, 17, and 21; for Switzerland - 34, 21, and 20; for Poland - 17, 13, and 24; for Bulgaria - only five, three, and three, respectively, etc. Meanwhile, the aforementioned paper of ours[8] has received six citations in WoS.

The distributions of document types (Table 2) and languages (Table 3) display an obvious variability between these four data-bases. This is mainly due to the strict restrictions of journal coverages permanently applied by the editors of WoS.

The lists of the so-called "core" journals containing the greatest number of relevant papers on the topic (Table 4) and the most productive authors in WoS, BIOSIS, MEDLINE and Scopus (Table 5) along with the list of the most productive authors - inventors in Derwent (Table 6) represent a particular interest not only to the beginners in the field but also to the institutional and national science managers and the journal editorial board members as well. It should be added that among the top 20 journals, there are two titles equally represented in four data-bases, three titles are omitted in one data-base but one title, Lab Invest is omitted in both MEDLINE and Scopus. On the other hand, most journals in the scientometric "tail", *i.e.*, presenting with one article abstracted only, are

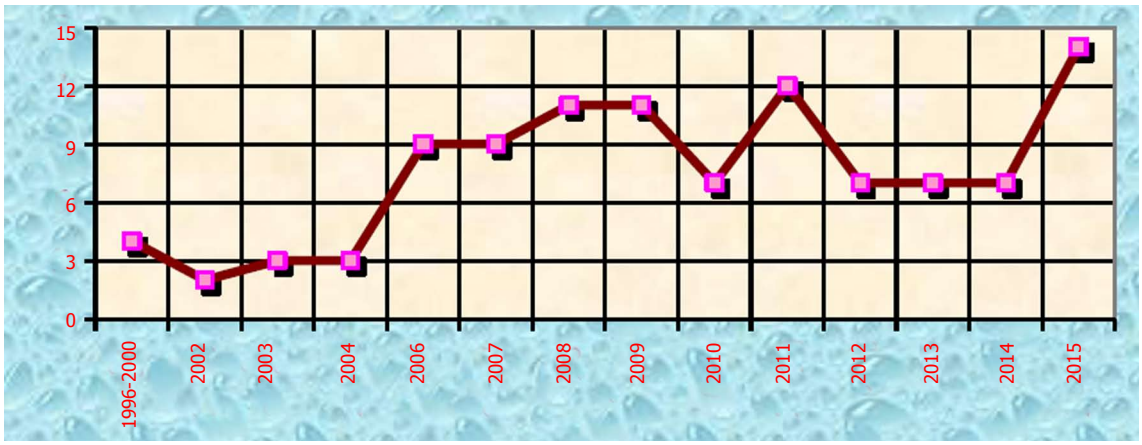

Figure 2 Annual dynamics of patents on the topic.

Table 2 Document type distribution in four data-bases

Document type	WoS	BIOSIS	MEDLINE	Scopus
Journal article	870	700	1057	970
Review	63	38	118	114
Congress proceedings	57	6	1	39
Meeting abstract	543	313	0	0
Editorial	34	6	17	18
Letter-to-the-editor	37	9	28	32
Book chapter	6	9	0	8
Evaluation study	0	0	28	0
Multicenter study	0	0	19	0
Randomized controlled trial	0	0	15	0
Meta-analysis	0	0	13	0
Validation study	0	0	11	0
Patent	0	19	0	0

Table 3 Language distribution of publications on the topic abstracted in four data-bases

Language	WoS	BIOSIS	MEDLINE	Scopus
English	1545	1136	1017	1095
German	17	5	10	17
French	14	9	12	14
Spanish	9	2	9	12
Japanese	0	7	17	21
Chinese	0	6	11	27
Italian	2	1	6	7
Polish	0	0	5	7
Czech	0	1	4	5
Danish	0	0	4	4
Other (11)	0	3 (5)	7 (15)	9 (15)

Table 4 "Core" journals on the topic in four data-bases

Rank	Journal title	WoS	BIOSIS	MEDLINE	Scopus
1	*Gastroenterology*	115	100	15	15
2	*J Clin Oncol*	96	4	12	13
3	*Br J Cancer*	52	47	45	47
4	*Anticancer Res*	46	54	39	39
5	*Cancer Res*	43	45	14	14
6	*Eur J Cancer*	38	36	20	20
7	*Clin Cancer Res*	36	9	34	34
8	*Dis Colon Rectum*	33	4	24	19
9	*Oncol Rep*	28	28	28	28
10	*Int J Cancer*	27	25	26	26
Total "core" journals - *n* (%)		10 (2.99)	10 (3.76)	10 (2.75)	10 (N/A)
Total publications - *n* (%)		514 (32.39)	352 (30.03)	255 (23.01)	257 (21.05)

N/A: Not available.

Table 5 Most productive authors on the topic in four data-bases

Rank	Author's name	WoS	BIOSIS	MEDLINE	Scopus
1	Ahlquist DA	25	31	10	8
2	Mori M	22	14	16	20
3	Doki Y	17	11	13	16
4	Nielsen HJ	17	12	2	11
5	Lugli A	16	14	5	6
6	Mimori K	16	10	11	14
7	Zlobec I	16	14	5	6
8	Inoue Y	14	4	10	10
9	Ishi H	14	8	11	14
10	Mahoney DW	14	11	1	2

almost equally indexed in these four data-bases thus confirming Bradford's law of journal scattering in any research field. In this case, these journals amount to 48.80% in WoS, to 52.83% in BIOSIS, and to 55.22% in MEDLINE (their absolute counts are shown in Table 1).

Only a small number of most productive scientific institutions in WoS and Scopus (Table 7) and institutions - assignees in Derwent (Table 8) is provided in order to indicate their undoubtedly high relative share on the world information market.

The computerized analysis published online by Thomson Reuters of the main research areas (in BIOSIS and MEDLINE) and of the Web of Science categories (in WoS itself) has identified significant differences concerning several indexing results between there three data-bases, Table 9). We would like only to mention the figures for "gastroenterology and hepatology", "biochemistry and molecular biology", and "immunology" and to emphasize the achievements in these interdisciplinary fields in clinical medicine and

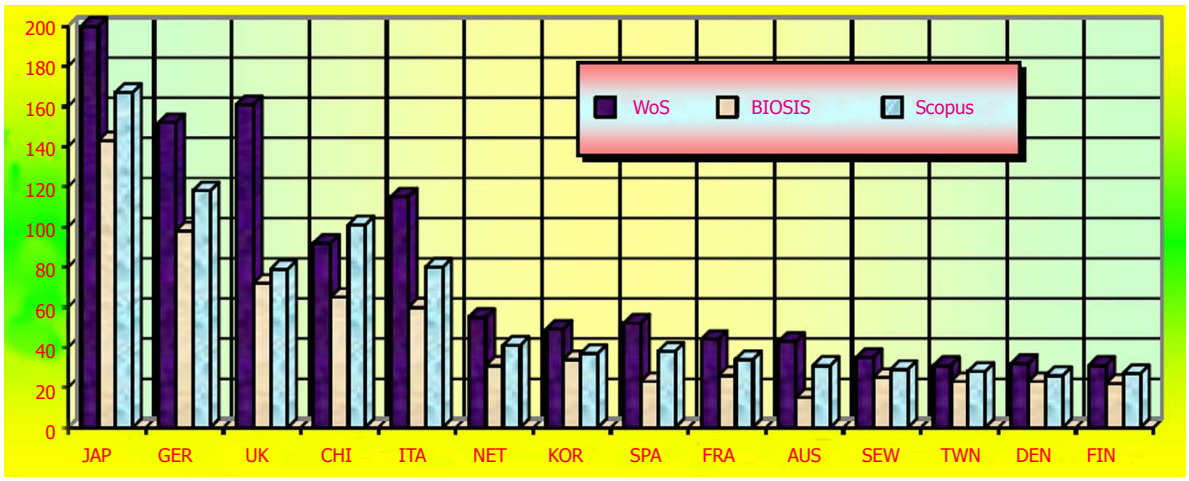

Figure 3 Country distribution according to the number of publications on the topic abstracted in three data-bases.

Table 6 Most productive authors - inventors on the topic in Derwent

Name	Country	City	Institution	Patents
Karl J	Germany	Penzberg	Roche Diagnostic GmbH	9
Choquet-Kastylevsky G	France	Nancy Letoile	Biomerieux SA	9
Charrier JP	France	Nancy Letoile	Biomerieux SA	9
Ataman-Oenal Y	France	Nancy Letoile	Biomerieux SA	6
Beaulieu C	France	Nancy Letoile	Biomerieux SA	6
Ahlquist DA	United States	Rochester	Mayo Clinic	4

Table 7 Most productive institutions on the topic in WoS and in Scopus

Rank	Institution	WoS	Scopus
1	German Cancer Research Center	29	26
2	Mayo Clinic	29	17
3	Harvard University	28	14
4	Osaka University	25	25
5	Kyushu University	22	22
6	Universität Heidelberg	25	19
7	Ludwig-Maximilians-Universität München	21	23
8	Memorial Sloan-Kettering Cancer Center	20	12
9	Kaohsiung Medical University	15	22
10	University of Copenhagen	23	9

Table 8 Most productive institutions - assignees on this topic in Derwent

Nomination	Country	Patents
Biomerieux SA	France	9
Hoffmann La Roche	Switzerland	9
Mayo Medical Education and Research	United States	4
Ruiqu Biotechnology Shanghai Co. Ltd	China	3
Signature Diagnostics GmbH	Germany	3
Shimadzu Corporation	Japan	3
Ver Christelijk Wetenschappel Onderw	The Netherlands	3
Fudan University	China	3

Table 9 Dominant research areas (WoS categories) on the topic in three data-bases

Rank	Research area (WoS category)	WoS	BIOSIS	MEDLINE
1	Oncology	834	1153	1034
2	Gastroenterology and hepatology	297	1084	166
3	Surgery	301	55	132
4	Pathology	169	55	74
5	Cell biology	47	42	231
6	Biochemistry and molecular biology	42	266	703
7	Medical laboratory technology	33	393	48
8	Pharmacology and pharmacy	27	144	190
9	Radiology, nuclear medicine and medical imaging	25	15	30
10	Genetics and heredity	24	402	490
11	Public, environmental and occupational health	23	22	29
12	Immunology	10	77	454
13	Hematology	7	22	43
14	Nutrition and dietetics	5	16	17
15	Endocrinology and metabolism	3	98	22

biomedicine.

The distributions of the number of authors according to the number of their patents (Figure 4) and that of the declared claims in their patents (Figure 5) demonstrate a significant research activity on the topic of colorectal tumour markers. This specific scientometric evaluation contributes to the identification of the players at the fore-front of clinical medicine-related technological progress.

Several common citation patterns on this topic as reflected in WoS and BIOSIS are listed in Table 10. The percentages of the times cited without self-citations and of the citing articles without self-citations are extraordinarily high, indeed. The so-called "h-index" introduced by Hirsch[13] is very high - 75 and 57 in WoS and in BIOSIS, respectively.

The comparative assessment of ten articles which have been most cited in WoS, in BIOSIS, and in Scopus (Table 11)[14-23] identifies two weird discrepancies. The

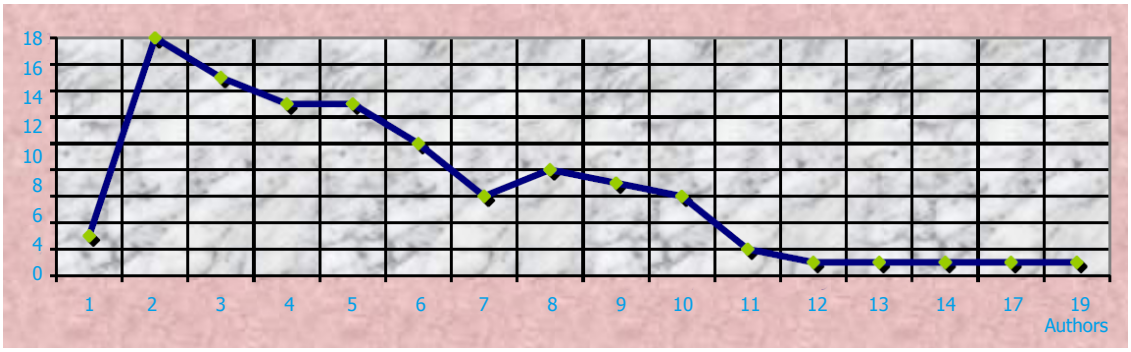

Figure 4 Distribution of the number of authors according to the number of their patents on the topic.

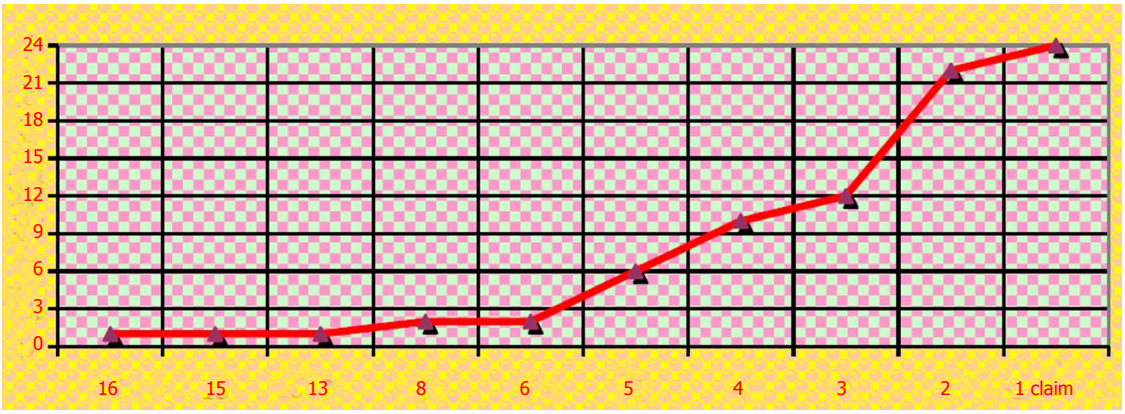

Figure 5 Distribution of the number of declared claims in the patents on the topic.

Table 10 Cumulative citation patterns on the topic in WoS and BIOSIS

Citation parameter	WoS	BIOSIS
Total number of publications	1587	1172
Sum of the times cited	25116	13297
Sum of the times cited without self-citations	24092	12777
Percentage of these times cited	95.92	96.09
Citing articles	19607	11061
Citing articles without self-citations	19120	10779
Percentage of these citing articles	97.52	97.45
Average citations per item	15.83	11.35
Average citations per year	810.19	443.23
Articles cited at least once	961	643
Percentage of these articles	60.55	54.86
H-index	75	57

article published in the "core" journal *J Clin Oncol*[17] has not been indexed in Scopus at all (as opposed to the other 13 articles in this journal) as well as the article co-authored by Sturgeon *et al*[22] and published in the journal *Clin Chem* has not been indexed in BIOSIS at all (as opposed to the other nine articles in this journal ranked 15th among a total of 265 journals).

The comprehensive scientometric analysis of the bibliographic information about the congresses, symposia, meetings, and conferences held in many countries which proceedings have been abstracted in WoS and in BIOSIS clearly outlines the rising role of these forums for the intensive development of the international scientific communications and science advancement as well (Tables 12 and 13).

In WoS and in BIOSIS, we have identified six scientific forums containing the terms of "tumour or cancer (bio) markers" in their titles (Table 14) and, in four data-bases, we have found out eight specialized journals meeting this criterion (Table 15). The annual dynamics of these 51 articles is characterized by two peak values (in 2010 and in 2014) (Figure 6). The considerable relative share (78.43%) of the papers published in foreign specialized journals stresses, indeed (Figure 7) and testifies to the substantial role of this particular aspect of science internationalization.

DISCUSSION

Our results convincingly outline the rising publication output on colorectal tumour markers worldwide and the significant citation activity as substantial features of quality and international prestige under the conditions of science globalization.

Modern colorectal tumour markers are used either for diagnostic, or for prognostic purposes. In addition, they could be applied for therapeutic evaluations.

The combined detection of two tumour markers, serum p53 antibody and carcinoembryonic antigen (CEA), improves the diagnostic sensitivity and prognosis

Table 11 Ten most cited articles on the topic in three data-bases

Ref.	Journal title, volume, year and pages	WoS	BIOSIS	Scopus
Ng *et al*[14]	*Gut* 2009; 58: 1375-1381	593	447	656
Bast *et al*[15]	*J Clin Oncol* 2001; 19: 1865-1878	552	314	670
Cui *et al*[16]	*Science* 2003; 299: 1753-1755	472	400	530
No author list[17]	*J Clin Oncol* 1996; 14: 2843-2877	388	234	Absent
Walther *et al*[18]	*Nat Rev Cancer* 2009; 9: 489-499	315	243	348
Duffy[19]	*Clin Chem* 2001; 47: 624-630	253	141	289
Duffy *et al*[20]	*Eur J Cancer* 2007; 43: 1348-1360	245	160	276
Nakamori *et al*[21]	*Gastroenterology* 1994; 106: 353-361	234	179	219
Sturgeon *et al*[22]	*Clin Chem* 2008; 54: E11-E79	211	Absent	255
Duffy *et al*[23]	*Eur J Cancer* 2003; 39: 718-727	202	120	235

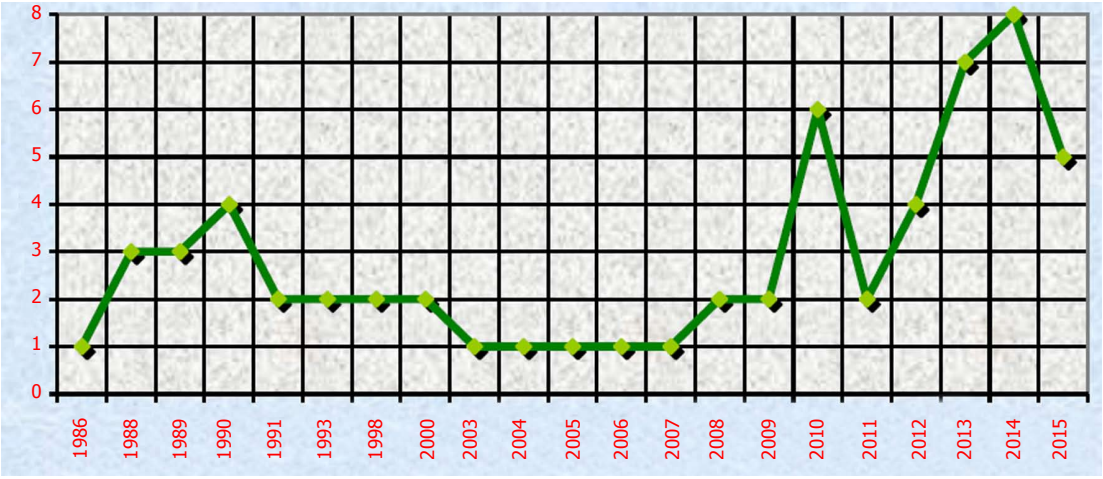

Figure 6 Annual dynamics of papers on the topic in specialized journals.

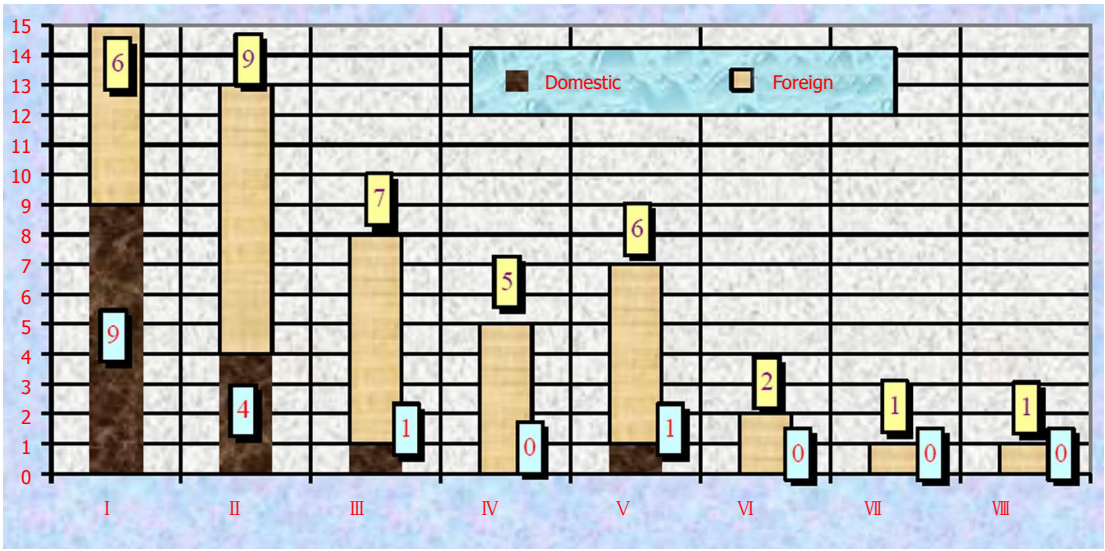

Figure 7 Papers on the topic published in domestic and foreign specialized journals. I: Cancer Epidemiol Biomarkers Prev; II: Int J Biol Markers; III: Cancer Biomarkers; IV: Disease Markers; V: J Tumor Marker Oncol; VI: Biomarkers; VII: Biomarkers Med; VIII: Genet Testing Mol Biomarkers.

of early-stage colorectal cancer patients[24].

A diagnosis strategy of serum tumour markers, an artificial intelligent algorithm, provides decision support for physicians on the usage of different tumour markers and diagnosis of colorectal cancer[25].

CEA containing macrophages combined with C-reactive protein possesses diagnostic potential in early colorectal cancer[26]. The diagnostic models based on the logistic regression analysis, support vector machine and back-propagation neural network demonstrate

Table 12 Bibliometric characteristics of scientific forums on the topic in WoS and BIOSIS

Parameter	WoS	BIOSIS
Number of forum titles	95	73
Number of unique forums	170	203
Number of publications	377	432
Number of forums with a single event only	71	52
Number of forums with two events	9	5
Number of forums with three events	5	2
Number of forums with one publication only	57	117
Number of forums with two publications	10	34
Number of forums with three publications	5	16
Maximal number of events of a unique forum	12	27
Maximal number of publications in a unique forum	58	102

Table 13 Scientific forums with most events and papers in them on the topic in WoS and BIOSIS

Scientific forum title	WoS		BIOSIS	
	Events	Papers	Events	Papers
Digestive Disease Week	12	58	25	90
Annual Meeting of the American Association for Cancer Research	4	17	27	102
Annual Meeting of the United States and Canadian Academy of Pathology	10	34	11	29
Annual Meeting of the American Society of Clinical Oncology	8	49	0	0
European Society for Medical Oncology Congress	7	17	1	5
World Congress of Gastrointestinal Cancer	7	24	0	0
Meeting of the International Society for Oncodevelopmental Biology and Medicine	3	6	9	16
Meeting of the Pathological Society of Great Britain and Ireland	5	5	11	11
European Congress of Pathology	0	0	11	22
Annual Meeting of the American College of Gastroenterology	4	5	5	6

Table 14 Scientific forums with "tumour or cancer (bio)markers" in their titles in WoS and BIOSIS

Scientific forum title	WoS		BIOSIS	
	Events	Papers	Events	Papers
Hamburg Symposium on Tumor Markers	2	3	5	8
Congress (Meeting) of the International Society of Oncology and Biomarkers	3	4	2	2
Annual Meeting of the EORTC/NCI/ASCO on Molecular Markers in Cancer	1	2	1	2
Annual Conference on Diet and Cancer: Markers, Prevention, and Treatment	1	1	0	0
International Symposium on Tumor Markers - From Biology to Therapy	1	1	0	0
Joint Meeting on Markers in Cancer of ASCO, EORTC and NCI	0	0	1	1

a higher early diagnostic value of the combination of serum tumour markers, *e.g.*, CEA, cancer antigen (CA) such as CA 19-9, CA 242, CA 125, and CA 15-3 for colorectal cancer[27]. SATB2 protein is a diagnostic marker for tumours of colorectal origin and provides a new and advantageous supplement for clinical differential diagnostics[28]. In combination with CK7 and CK20, its specificity increases from 77% up to 100%. The most common markers for such tumours include the expression of CK20, often along with lack of CK7, *i.e.*, the $CK20^{+}/CK7^{-}$ phenotype[28].

MYBL2 gene is an independent prognostic marker with tumour-promoting functions in colorectal cancer and its overexpression may play an important role in tumourigenesis[29]. HLA class Ⅱ antigen expression in colorectal cancer is a reliable prognostic marker as it is related with a favourable clinical course of the disease[30]. The combined high levels of some inflammatory cytokines such as CXCL8, vascular endothelial growth factor and Pentraxin3 are potential prognostic markers as they are associated with increased risk of colorectal cancer recurrence independently of TNM staging and with worse survival[31]. The circulating microRNAs markers miR-122 and miR-200 family members could be used in the development of a multi-marker blood test for colorectal cancer prognosis and survival[32]. The decreased erythropoietin expression, high vascular endothelial growth factor levels and elevated cyclin B1 expression, predominant moderate tumour differentiation, absence of metastasis, and negative lymph node status are reliable proliferation and differentiation markers indicating the low level of aggressiveness, better prognosis, and longer colorectal adenocarcinoma patient's survival[33]. By means of solid-phase proximity ligation assay, 35 protein markers were simultaneously analyzed in a small amount of blood of stage Ⅰ to Ⅳ colorectal cancer patients, however, these markers did not give better prognostic information than CEA[34].

An outlined correlation exists between the differentiation degree and expression of aldehyde dehydrogenase 1, a stem cell marker, in colorectal carcinoma cells[35]. Low-stage tumours exhibit a higher expression of aldehyde dehydrogenase 1 or CD133 compared with high-stage tumours while CD133 expression is associated with lymph node metastasis-positive cases thus predicting the disease prognosis. Aldehyde dehydragenase 1 and Nodal are important prognostic markers in colorectal cancer as there is a significant correlation between their expression and the differentiation degree, metastasis, number of tumour-positive lymph nodes and disease stage[36].

Science internationalization includes not only direct research interaction between single scientists from different countries and their teams organized through official contracts or within informal collectives but also several essential components[12]: (1) continuous creation of new international scientific societies and international associations of national societies, of new international scientific journals and international publishers or publish-

Table 15 Specialized journals with the term of "(bio)markers" in their titles in four data-bases

Rank	Journal title	WoS	Scopus	MEDLINE	BIOSIS	Total
1	*Cancer Epidemiol Biomarkers Prev*	0	0	0	15	15
2	*Int J Biol Markers*	5	0	11	9	13[1]
3	*Cancer Biomarkers*	7	8	7	8	8[1]
4	*Disease Markers*	5	5	5	5	5[1]
5	*J Tumor Marker Oncol*	0	3	0	6	6[1]
6	*Biomarkers*	2	0	2	2	2[1]
7	*Biomarkers Med*	0	0	1	0	1
8	*Genet Testing Mol Biomarkers*	1	0	1	0	1[1]
Total number of publications		20	16	27	45	51[1]
Total number of journals		5	3	6	6	8[1]
Countries of authors		19	13	20	20	25[1]
Countries of journals		5	2	4	5	5[1]
Articles in domestic journals		2	1	2	14	11[1]
Articles in journals published abroad		18	15	25	31	40[1]

[1]The sum of unique items is smaller than the total amount of single items due their duplication in several data-bases.

ing houses; (2) publishing of scientific papers, reviews and book reviews in foreign journals and periodicals; (3) translation and publishing of monographs by foreign authors; (4) organization of international scientific forums and participation in them of authors from numerous foreign countries; (5) enrichment of the forms of immediate exchange of scientists from other countries; (6) unlimited dissemination of new scientific information through modern information-communication technologies; (7) modernization and automatization of scientific libraries; and (8) introduction of electronic journals and monographs; and (9) overcoming of the traditional barriers for interpersonal communication between scientists from different countries.

Similarly to other authors[37], we face not only advantages but also disadvantages in the comprehensive activity of both editors and staff in these two widely recognized information centres in the United States and in the Netherlands. There is user-friendly uninterrupted online access to the information portals providing a rising amount of full-text articles. The computerized data processing facilitates automated problem-oriented information retrievals and large-scale scientometric analyses as well. However, several unfavorable features deserve a special attention. Some author's affiliations are incomplete, even within one and the same scientific institution. Single significant publications are missing in at least one of these four data-bases although the corresponding journals are covered. The incorporation of proceedings from congresses, conferences and symposia is insufficient. The indexing of primary document types and research areas should be further improved, too.

There is a stable research interests in the issues of a variety of peculiarities of the modern international scientific communications and collaboration worldwide.

Publication coverage in Scopus or WoS, English as a specific international language, and journal articles as a specific type of publication, are indicators of research quality and internationalization in the social sciences and humanities[38]. There is a different extent of internationalization of peer reviewed and non-peer reviewed book publications in the social sciences and humanities in Belgium[39].

The analysis of the dynamics of journal internationality using using 1398 journals and 2557229 papers during 1991-2014 demonstrates that journals' papers and references have become more globalized over time[40]. For both national and multinational publishers, most of the changes in journal internationalization occur between the fourth and sixth year of indexing in *WoS*. Natural sciences as well as engineering and technology have the most international papers but the journals in medical and health sciences, natural sciences, and agricultural sciences contain the most international references.

The emergence of a new transnational demand in health research dealing with global regenerative medicine and parallel markets is analyzed according to relevant theoretical dilemmas in medical anthropology and the sociology of science and health[41].

The investigation of the international and domestic coauthorship relations of all citable items in the Social Sciences Citation Index 2011 demonstrates that the international networks in the social sciences have grown during the last decades in addition to the national ones but not by replacing them[42]. The comparison of the internationalization of more than one thousand academic journals in six fields of science indicates that social sciences literature is still nationally and linguistically fragmented more than natural sciences one[43].

A standardization method that transforms all fractions of internationally coauthored papers from a dataset of the National Science Foundation into a comparable framework is applied to examine the evolution and convergence of the patterns of international scientific collaboration between 1973 and 2012[44]. The convergence of these long-run collaboration patterns between the applied and basic sciences might be a contributing factor that supports the evolution of modern

scientific fields.

The promises and challenges of international collaboration in achieving success towards poverty, environment, education, science, and medicine are reviewed comprehensively[45]. A model for sustainable university-based international plastic surgery collaboration between plastic surgery consultants from abroad and a hospital in a developing country is implemented[46]. The analysis of China's international publications on healthcare science and services research identifies a rapid recent increase[47]. Collaboration among countries, institutions and authors increase, too. The academic impact of publications with partners from European and American countries is relatively higher than of those with partners from Asia. The most prominent actors are Peking University, Fudan University, Chinese University of Hong Kong, and University of Hong Kong. The significance of the international scientific collaboration in the field of minimally invasive general surgery is highlighted[48].

The bibliometric analysis of Cuban scientific publications listed in PubMed during the period between 1990 and 2010 proves that Cuban science policy and practice ensure the application of science for social needs by harnessing human resources through national and international collaboration, building stronger scientific capacity[49]. The research output and impact of 479 Mexican researchers working abroad and included in the Mexican National System of Researchers are investigated in terms of production, mobility and scientific collaboration[50]. Mobility exerts a strong effect on scientists' international collaboration.

The dynamic internationalization of modern science is analyzed by Bulgarian authors in different interdisciplinary fields such as haemorrhagic stroke prevention[51], paediatric sleep apnea[52], applications of the geographical information systems in health planning[37], *etc.*

In conclusion, contemporary colorectal tumour markers are more and more widely studied and routinely applied in clinical coloproctology worldwide thus promoting the further improvement of individualized patient's management. We have revealed a series of discrepancies in the coverage and computerized processing of the recent scientific literature on colorectal tumour markers by these powerful information centres that necessitates refinements in their editorial policy. The creation of this comprehensive problem-oriented collection with purposefully systematized files containing the researchers' names, addresses and publications is designed mainly for specialists in coloproctology from smaller countries who strive for a more effective collaboration with colleagues from eminent centres abroad and, in this way, to achieve an improved international visibility on the world information market.

COMMENTS

Background

A summary of the increasing role of screening and early detection of colorectal cancer with a variety of specific colorectal serum markers that is reflected in five modern information portals covering world literature on this hot topic during the recent decades.

Research frontiers

Nowadays, science stratification in terms of individual researchers, teams, institutions, journals, and countries deserves a special attention to be paid by the comprehensive scientometric approach to the structure and dynamics of international scientific communications in the field of colorectal tumour markers. Such a particular analysis is capable of identifying the most productive authors representing a true interest to the beginners in oncological coloproctology and related fields, the institutional and national science managers and the journal editorial board members. By providing systematized factual information to end users, the scientometric results outline the emerging opportunities for fruitful interdisciplinary and international collaboration.

Innovations and breakthroughs

Under the conditions of enormous globalization and competition in contemporary science, timely orientation in and awareness of the promising advances in colorectal tumour markers can substantially contribute to new scientific achievements not only by leaders working in powerful countries but also by the scientists from the rest of the world. Thus the collaboration trends can be further empowered and expanded.

Applications

In the era of telecommunication technologies, the new scientific information on colorectal tumour markers published in the ocean of journals, conference proceedings, monographs, patents and other primary literature sources is very easy to access in case one could be trained in information science and applied scientometrics. Besides science policy managers at different levels and journal editors could successfully apply these scientometric results, too.

Terminology

At the first glance, the particular terminology used in this article looks nearly strange to gastrointestinal surgeons, coloproctologists, and oncologists. On the other hand, there is a rising amount of meta-analyses, systematic reviews and scientometric papers on different topics recently published in various journals. All these publications make specific contributions to the uninterrupted world science advancement of benefit to patients.

Peer-review

The authors explored five information portals for the topic of colorectal tumour markers and outlined the significant journals, scientists and institutions. The authors made tremendous efforts on searching and comparing the five information portals, and showed the detailed results. This paper is interesting.

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REVIEW

Recent advances in the management of rectal cancer: No surgery, minimal surgery or minimally invasive surgery

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Abstract

Over the last decade, with the acceptance of the need for improvements in the outcome of patients affected with rectal cancer, there has been a significant increase in the literature regarding treatment options available to patients affected by this disease. That treatment related decisions should be made at a high volume multidisciplinary tumor board, after pre-operative rectal magnetic resonance imaging and the importance of total mesorectal excision (TME) are accepted standard of care. More controversial is the emerging role for watchful waiting rather than radical surgery in complete pathologic responders, which may be appropriate in 20% of patients. Patients with early T1 rectal cancers and favorable pathologic features can be cured with local excision only, with transanal minimal invasive surgery (TAMIS) because of its versatility and almost universal availability of the necessary equipment and skillset in the average laparoscopic surgeon, emerging as the leading option. Recent trials have raised concerns about the oncologic outcomes of the standard "top-down" TME hence transanal TME (TaTME "bottom-up") approach has gained popularity as an alternative. The challenges are many, with a dearth of evidence of the oncologic superiority in the long-term for any given option. However, this review highlights recent advances in the role of chemoradiation only for complete pathologic responders, TAMIS for highly selected early rectal cancer patients and TaTME as options to improve cure rates whilst maintaining quality of life in these patients, while we await the results of further definitive trials being currently conducted.

Key words: Rectal cancer; Watchful waiting; Transanal minimal invasive surgery; Transanal total mesorectal excision

Core tip: Over the last decade several additional surgical

options have become available in the management of rectal cancer. These extend from non-surgical management with chemoradiation only, local excision for selected cases of early rectal cancer and the standard total mesorectal excision but now by a transanal approach. Although long-term outcome studies are ongoing, it is the duty of the multidisciplinary team treating these patients to be familiar with these options, as they may be of benefit to selected patients with this disease.

Plummer JM, Leake PA, Albert MR. Recent advances in the management of rectal cancer: No surgery, minimal surgery or minimally invasive surgery. *World J Gastrointest Surg* 2017; 9(6): 139-148 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i6/139.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i6.139

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer affecting males and females in most western countries and is a leading cause of cancer related deaths with rectal cancer accounting for up 40000 of these new cases in the United States[1]. Rectal cancer is more common in men and until recently compared to cancer in the more proximal large intestines mid and lower rectal cancer was traditionally associated with higher rates of local recurrence and reduced disease free survival[2]. In addition curative surgery is associated with higher risk of morbidity and greater long-term consequences, including a poorer quality of life compared to colon cancer surgery. Up to 40% of affected patients are treated with a permanent stoma especially when performed by general surgeons[3].

Over the last few decades significant strides have been made in the treatment of rectal cancer with the adherence to strict anatomical dissection as popularized by Heald *et al*[4], the recognition of the importance of neoadjuvant therapy in reducing local recurrence rates as led by the Swedish and Dutch trials[5,6], and the fusion of surgery with technology in effecting minimally invasive surgery being the most critical. The various European structured intervention programs have all led to a reduction in local recurrence rates, lower permanent stoma rates and higher cure rates[7-9]. The acceptance of the need for similar interventions in the United States and hopefully its benefits has since led to the introduction of initiatives such as the OSTRiCh[10,11] and its National Accreditation Program for Rectal Cancer (NAPRC) that was established jointly with the Commission on Cancer and adopted as a quality program by the American College of Surgeons[12]. This program's goal is to ensure that all (> 95%) of rectal cancer patients receive appropriate individualized evidence-based care using a multidisciplinary team of qualified doctors, and offering appropriate magnetic resonance imaging (MRI) based staging, detailed pathologic assessment and delivering quality TME, whilst tracking adherence to these standards and patient outcome. The net effect is that more rectal cancer patients will receive their high quality care in fewer centers that will be advantageous for recruitment into clinical trials to address current areas of uncertainty.

The introduction of laparoscopic colonic surgery for malignant disease has been supported by good level evidence of short-term benefits to patients without compromising oncologic outcome[13-15], but this can not be said to be the same with mid and low rectal cancer surgery. While the short-term indicators may be superior, various studies[15,16], have not always supported equivalence in oncologic outcomes with high circumferential resection margin (CRM) positivity being an initial concern. As such, patients undergoing surgery for rectal cancer must be informed of all treatment options and preferably be treated in a high volume center.

Difficulty with rectal cancer surgery is especially evident in the narrow male pelvis, and given that obesity is now endemic, the bulky mesorectum that must be excised completely for mid and low rectal cancers often pose challenges laparoscopically, when done in the usual "top-down" manner. The importance of a detailed pathologic report to inform quality of surgery [grade of the total mesorectal excision (TME)] and adjuvant therapy (degree of differentiation and lymphovascular invasion in addition to nodal status) has also been recognized in recent times, as is appropriate local preoperative staging with pelvic MRI. Modern high-resolution MRI techniques can accurately predict depth of spread within 1mm of histopathology assessment and therefore predicting the likelihood of a clear CRM[17,18], and unlike endorectal ultrasound (ERUS), it can identify nodal disease in the entire mesorectum and the pelvic side-wall compartment[19] which are markers of local recurrence and overall survival. Nowadays, MRI and ERUS are complementary and when used simultaneously, will result in a significant increase of the overall accuracy for the T stage of the rectal cancer[20].

In the last decade, three innovations of the surgical care of rectal cancer care have been introduced with the potential to revolutionalize the treatment of rectal cancer patients. These are watchful waiting after neoadjuvant chemoradiotherapy for complete pathologic responders, that is, no surgery or primary treatment (by default) with chemoradiotherapy, transanal minimally invasive surgery (TAMIS), minimal surgery, and transanal total mesorectal excision (TaTME) the latest version of minimally invasive surgery. They are promising options that in the appropriately selected patient have a role as we strive to optimize cure rates whilst maintaining optimal quality of life in the individuals affected by this disease. In addition to the evolution of surgical techniques, the continued standardization of therapy as determined in a multidisciplinary tumor board (MDT) has lead to the practice of more evidence-based medicine applied to rectal cancer management to the benefit of patients. While the role of the MDT will not be addressed further in this

review it is fair to say that compared to a single surgeon management, better decisions are more likely to be made and the patients are more likely to complete all aspects of their therapy, thus achieving the mandate of the NAPRC.

NO SURGERY

Preoperative local staging with a rectal MRI is mandatory in all patients with a diagnosis of rectal cancer, complemented by ERUS especially in the evaluation of early rectal lesions, where it may be superior to MRI[20]. The performance of ERUS is operator dependent and limited in the presence of a stricture[20]. Therefore the determination of tumour thickness, the precise mesorectal fascial margin, the presence of extramural venous invasion provided by MRI facilitate patient selection for neoadjuvant chemoradiotherapy in an attempt to reduce local recurrence rates. Following neoadjuvant chemoradiotherapy, patients have traditionally proceeded to radical surgery with TME (APR or LAR) in the following 6-12 wk. With refinements in chemoradiotherapy approximately 10%-30% of rectal cancer patients who receive neoadjuvant chemoradiotherapy demonstrate complete resolution of their tumor on final pathologic evaluation, pathologic complete responders (pCR). Patients treated with TME after achieving ypT0 status have local recurrence rates of less than 1% and 5-year survival rates of more than 95%[21]. All other options must be comparable to this standard with respect to cancer survival.

Led by the persistence of Habr-Gama *et al*[22], it has been demonstrated that following long-course neoadjuvant chemoradiotherapy, patients with a complete clinical response can be managed by "watchful-waiting" rather than radical resection[23-26]. This is especially attractive in elderly patients, those with excessive comorbidities and for patients whose curative surgery may require a permanent stoma. One must also carefully consider the significant gastroenterologic, sexual and urologic functional outcomes associated with radical surgery which alter quality of life, as we know that poor functional outcome is more likely in patients receiving radiotherapy and radical resection[26-28].

Patients are treated with 1.8-2.0 Gy in 25 daily fractions to a total of 45-50 Gy and given concurrently with fluropyrimidine-based chemotherapy. Extended dose of chemoradiation therapy with additional chemotherapy cycles and 54 Gy of radiation may result in higher (> 50%) sustained complete clinical response rates that may ultimately avoid radical resections[29]. Assessment of response to neoadjuvant chemoradiotherapy is ideally done initially 8-10 wk after completion of chemoradiotherapy. A pale, white scar including telangiectasiss, along with the absence of ulceration or any mucosal abnormality is considered a complete clinical response[29]. The use of the previous strict diagnostic criteria remains challenging and repeatedly has demonstrated underestimating the number of complete pathologic responders secondary to persistent mucosal irregularities at the initial cancer site[30]. This has led many to extend the period of observation prior to surgery outward of 20 wk. On the contrary, approximately 25% of patients determined to have a complete clinical response ultimately develop tumor regrowth within one year. Radiological restaging is often utilized but not sensitive or specific because of the post-treatment changes making interpretation difficult. Improvements in radiologic technique and modality should continue to resolve this troublesome problem while the finding of minimal radiological response should prevent undue delays to radical resection.

Residual mucosal abnormality is predictive of luminal recurrence and should be carefully documented and biopsied. Coupled with clinical examination, endoscopic assessment and biopsy has been shown to possess a false negative rate of 69%[31]. ERUS has a low specificity 33% for luminal disease but has a 81% negative predictive value for lymph node involvement[31]. Like pre-treatment staging, MRI has been named the gold standard post neoadjuvant therapy[32]. The use of T2 weighted MRI may have an accuracy of 92% in identifying complete responders in terms of local disease but it has a tendency to over stage nodal spread[32]. The use of MRI diffusion weighted imaging has become a superior technique to evaluate tumor resolution and fibrosis. While it may be superior to ERUS for advanced T stages, in a recent meta-analysis looking specifically at T0 disease it showed 19% sensitivity and 94% specificity[33].

In the largest meta-analysis to date involving 2224 patient, de Jong *et al*[34] concluded radiological evaluation by ERUS, MRI and CT, while still performed, have a poor accuracy at predicting complete tumor response and the accuracy of these modalities to predict the presence of metastatic lymph node disease is also low. This has led to the investigation of various tools such as magnetic resonance tumor regression grade-which is reportedly 10 times better than clinical assessment in identifying complete responders)[29]. This tool needs further validation and for now these investigations cannot be used in isolation to accurately predict response to therapy, but rather they have to be taken in context of the overall assessment.

Watchful-waiting as primary treatment for rectal cancer requires meticulous follow-up. In the first year patients are seen at one to three-months intervals for clinical examination and this must include digital and endoscopic rectal examination. Patients with a sustained cCR after one year will have continued surveillance every three months for an additional year and every six months thereafter[22-24]. Various local and systemic radiological investigations are performed at 3-6 mo intervals for 5 years. A positive result mandates crossover to radical resection. The majority of patients who develop non-metastatic local re-growth can undergo salvage surgery without adversely affecting their survival[35]. In the meta-analysis by Li *et al*[36], while patients treated with watchful-waiting had an increased risk of local recurrence compared to radical resections these patients had similar overall survival at 1, 2, 3 and 5 years after their diagnosis and treatment once they receive appropriate follow-up and timely intervention when indicated.

Table 1 Publications of "no surgery" for rectal cancer including minimum 20 patients in their study (2006-2016)

Ref.	No. of patients	Local recurrence (%)	Systemic recurrence	%undergoing salvage surgery	Disease free survival	Overall survival %
Habr-Gama *et al*[23]	90 (183)	28/90	14%	93	68	91 at 5 yr
Maas *et al*[24]	21	1/21	0	100	93	91 at 2 yr
Smith *et al*[25]	32	6/32	3/32	NA	88	96 at 2 yr
Araujo *et al*[26]	42	5/42	7/42	80	60.9	71.6 at 5 yr
Renehan *et al*[35]	129	44/129	3	36/41	88	96 at 3 yr

NA: Not reported.

There are several areas of uncertainty regarding this management approach. These include optimal timing and best method of assessment of response to therapy, the role of extended chemoradiation, standardization of follow-up to detect recurrences early for the best outcome and the role of further local resection *vs* radical surgery for salvage of failures. The reports of success with this management approach are from a few highly specialized centers (Table 1). Review of the literature will show that the patient numbers are small relative to the burden of the disease and outcome, albeit limited follow-up in most series, is not as good as if the patients were treated with radical resection. It is fair to say that while there is a role for this line of management in up to 20% of rectal cancer patients, they must be fully informed about the possible need for radical resection and it all should be done whilst adhering to a strict protocol.

MINIMAL SURGERY

Increasingly patients with CRC are being diagnosed on screening colonoscopies and at an earlier stage with localized disease being the most common stage at presentation[37] both in the United States and worldwide[38]. The number of patients diagnosed with localized rectal cancer has increased over the last three decades with localized rectal cancer being more commonly diagnosed than localized colon cancer[39]. There is also greater understanding of tumor biology and other harbingers of biologically aggressive disease. With this comes the acceptance that there may be a role for less radical surgery in patients with early rectal cancer and good prognostic features such as the absence of lymphovascular invasion. Favorable T1 cancers have less than a 10% chance of having lymph node metastasis[40,41] and complete local excision only can be curative. Early rectal cancer is defined as rectal cancer confined to the submucosa[42] and is subdivided by Kikuchi *et al*[43] based on the depth of invasion into: sm1: Slight submucosal invasion from the muscularis mucosa (upper 1/3); sm2: Intermediate (middle 1/3) invasion; and sm3: Carcinoma near the inner surface of the muscularis propria (lower 1/3).

There are several acceptable local options to treat early rectal cancer including transanal excision (TAE), transanal endoscopic microsurgery (TEM) and TAMIS. They all avoid the consequences of radical excision of the rectum but also have the disadvantages of the need for increase vigilance after treatment and greater local failure rates even in appropriately selected patients. TAE and TEM have both been available options before TAMIS was described by Atallah *et al*[44] but compared to TAE, TAMIS carries the advantages of wider application to lesions further away from the anal verge and with less fragmentation[45], while the use of a flexible laparoscopic platform gives it benefits of reduced capital expenditure for equipment acquisition and less post-procedural sphincteric complications compared to TEM[46,47]. TAMIS therefore has distinct advantages above its competitors and since its introduction its use has grown exponentially[48]. Local excision with an advanced platform should be an option in the care of all patients with early rectal cancer patients. While some patients having local recurrence can undergo salvage radical resection without any reduction in expected survival[45,49], some patients may not be as fortunate[50]. Data from patients undergoing TEM and followed by radical resection show a reduction in the quality of the TME performed when compared to similar patients treated by TME alone[45]. Poor quality TME leads to increase local recurrence and a reduction in survival, emphasizing the importance of patient selection as an important determinant of outcome from local excision.

The patients undergoing TAMIS are placed in lithotomy position and the operative monitor is placed at the patient's head. Basic laparoscopic instrument required are a long 5 mm angled camera, a grasper, eletrocautery, needle drivers and one of two Food and Drug Administration approved ports for TAMIS[47] (SILS Port and the GelPOINT Path). A good suction device is important for smoke evacuation such as the recently introduced insufflators like AirSeal Insufflation System which provide improved stability of pneumorectum at lower pressures and reduced intraluminal smoke.

The procedure begins with the marking out of the lesion with at least a 1 cm margin in all directions using eletrocautery. Care must be taken to ensure a full thickness division of the rectal wall without coning by dissecting perpendicular to the rectal wall until the mesorectal fat entered. The majority of the dissection is done with eletrocautery and during excision and manipulation the specimen must be grasped on the edge of normal mucosa to prevent fragmentation of the tissue. Particular attention

must be taken for anterior lesions as to avoid injury to the urethra, prostate, or vagina. The resected specimen must be appropriately oriented, pinned and labeled for adequate pathological evaluation and reporting.

Adequate hemostasis is obtained before closing the rectal wall defect and in fact best method of handling the defect is debatable. There is evidence that defects of the extraperitoneal rectum do not have to be closed if they are in a posterior location and these have little consequence[51]. If the decision is to close the defect this is done transversely so as not to narrow the lumen significantly. Sigmoidoscopy can be done at the end of the procedure so as to assess the luminal diameter if there are any concerns.

Patients are usually fed once they have recovered from anaesthesia and there are no dietary restrictions. Post-operative pain is negligible and most patients are discharged after one night in hospital. The frequency of clinical review maybe institution based but there is general agreement that the patients are seen once the histology of the resected specimen is available for a full discussion. In the event that the patients were upstaged after TAMIS (sm3 with high-grade histologic features or more advanced disease on the final resected histology), these patients must be offered the ideal option of a more radical resection involving TME. This may take the form of an anterior or abdominoperineal resection[44]. Repeat TAMIS is also an option for patients with T1 disease and a positive margin microscopically. Some patients may opt for treatment with adjuvant radiotherapy[52]. There is no consensus about the timing of the radical surgery and role of adjuvant radiotherapy in this setting[53].

TAMIS is a relatively new procedure and as expected several complications have been described. They are all of limited morbidity and occurring in an average of 7.5% of patients[54]. Intra-operative complications include bleeding and entry into the peritoneal cavity, especially for anterior placed and higher lesions. Entry into the peritoneal cavity occurs in about 1% of cases and usually the rectum is closed immediately once the specimen is removed. In these patients it is recommended that gastrografin enema is done on day-3 postoperatively to document the absence of leaks before discharge. Antibiotics may have to be extended if there was significant gross peritoneal contamination. Hemorrhoidal thrombosis, bleeding, pneumoperitoneum, subcutaneous emphysema, urinary retention and urinary tract infections have all been reported immediately post-operatively[45,55]. Later complications include rectal stenosis and rectovaginal fistula[45]. Incontinence, if it occurs is rare and usually self-limiting. Albeit that grossly 100% of specimens have negative margins, there is a 4.1% and 4.4% incidence of microscopic positive margins and tissue fragmentation respectively[54].

Clinical and endoscopic appraisal of the rectum for marginal recurrence should be done at 3, 6, 9 and 12 mo after surgery, and repeated 6-monthly for the next 2 years. Radiological evaluation by MRI for nodal recurrence should be done at 6 mo. Other aspects of the follow-up can be guided by specific criteria such as the NCCN guidelines.

Although there has been significant growth in the use of TAMIS, the majority of reports are for benign disease, specifically villous and tubulovillous adenomas in the lower and mid rectum. Currently the majority of studies report short-term results with limited follow-up and these are case series and small prospective comparative studies. Listed in Table 2 are publications involving more than 15 patients diagnosed with early adenocarcinoma and subjected to TAMIS. These results revealed that the majority of patients have a successful operation, with operative time of about 80 min, length of stay in hospital is one day, positive resection margins is less that 10% and less than 10% of patients have complications[56-59]. The few studies looking at quality of life and functional outcomes reveal that overall quality of life was improved or not impaired after TAMIS, probably due to the removal of the tumor, and at 6 mo was equal to the general population[56,60]. TAMIS can be used after neoadjuvant chemoradiotherapy[61,62] but care should be taken because of the high incidence of wound complications in this setting[46]. We anticipate an increase in the use of TAMIS in these patients given the accumulating evidence that patients with excellent response after neoadjuvant therapy can be managed more conservatively without compromising their survival[63]. The more important role of TAMIS however was as a launching pad for TaTME.

MINIMALLY INVASIVE SURGERY

On the background of the explosion of laparoscopic surgery for colon cancer, there has been similar enthusiasm for its application to rectal cancer where the laparoscopic approach was performed from a standard transabdominal "top down" approach. However, numerous technical difficulties related to operating in the pelvis have often led to longer operative times, a steep learning curve and high conversion rates. In addition, poor ergonomics in the use of an endoscopic linear stapler to divide the distal rectum, often resulted in multiple firings and the concurrent risk of anastomotic leaks[64]. Anastomotic leaks are always to be minimized as mortality from septic complications, increased local recurrence rates in addition to decreased survival have all been well established. Furthermore, albeit with exceptions[14,64] laparoscopic proctectomy has demonstrated increased circumferential margin positivity and concerns of the long-term oncologic outcomes[65,66]. These problems were thought to be resolved with the introduction of the robot to aid with proctectomy[67] but the increased cost prevented its widespread adoption[68]. There maybe some advantage to the use of the robot with a reduction in urinary and sexual dysfunctions after proctectomy, but this remains to be proven with randomized prospective studies[69]. The results of the Robotic *vs* Laparoscopic Approach for the Resection of Rectal cancer (ROLARR) trial are highly anticipated in an attempt to demonstrate any statistical significant advantage conferred by the robotic approach with respect to long-term oncologic outcomes[67]. At the moment robotic-assisted

Table 2 Publications of transanal minimal invasive surgery for early rectal cancer including minimum 15 patients with invasive adenocarcinoma in their study (2010-2016)

Ref.	No. of patients (# with cancer)	Distant from AV	Duration of surgery (min)	Length of stay (d)	Complications (%)	Positive margin: Local recurrence (%)
Albert *et al*[47]	50 (23)	8.1 cm	? NA	0.6	6	6:4
McLemore *et al*[57]	32 (16)	NA	123	2.5	15	NA
Hahnloser *et al*[51]	75 (38)	6.4	77	3.4	19	NA
Gill *et al*[58]	32 (21)	7.5	131	1.1	6	NA
Rega *et al*[59]	55 (26)	NA	78	NA	4	?9
Keller *et al*[49]	75 (17)	10	76	1	4	7:1
Quaresima *et al*[55]	31 (17)	NA	NA	3	9.6	3 (3)

NA: Not reported.

proctectomy for cancer is better confined to educational programs in high volume hospitals in order to avoid an increase in cost and complication rates[68]. Still there are the short-term benefits of reduced analgesic requirements, shortened length of stay in hospital, less wound related complication such that the laparoscopic approach is being widely utilized and to the advantage of the patients[70-72]. Concerns remain despite more recent studies[16,73], and high quality evidence in favor of a standard laparoscopic approach for its routine application to rectal cancer are still elusive. It is in this setting that trans-anal TME "down-to-up approach" was introduced[74,75]. Transanal TME is purported to confer distinct advantages of greater visibility, and a more complete mesorectal excision for mid and low rectal cancer patients, natural orifice specimen extraction with less post-operative pain and fewer wound complications. It was developed to improve the oncologic and functional outcomes of patients with mid and low rectal cancers[76,77]. Other advantages include being able to clearly demarcate the distal resection margin and more options for anastomosis (intersphincteric resection, stapled or hand sewn anastomosis). That the TME (the most important part of the operation) is being performed at an earlier phase in the procedure may also be advantageous with respect to surgeon fatigue.

TaTME occurs when at least the lower third of the rectum is mobilized and resected transanally according to TME principles. It is said to take all the major surgical developments of the last three decades in CRC care (TME, laparoscopy, NOTES) and roll them into one procedure[77]. It is purported to be particularly helpful in patients with a narrow pelvis or significant visceral obesity in whom laparoscopic pelvic dissection is challenging[48]. Still the procedure has a steep learning curve and familiarity with laparoscopic TME and transanal approach to lesions are important pre-requisites. Previously rare complications such as urethral injuries have emerged as the most common major complication of this procedure[78]. Fortunately with proper training and understanding of the anatomy this can be avoided. Experts have also recommended an initial experience preferably with benign disease, female patients and without prior pelvic irradiation[79].

Since its introduction in 2010 there has been several publications on TaTME and the majority of short-term results have demonstrated equivalence or superiority when compared to standard open or laparoscopic surgery[78,80-83]. This is also supported by meta-analyses done by Xu *et al*[84] and Ma *et al*[85] reinforced in the recent systematic review by Arunachalam *et al*[86] showing lower risk of a positive CRM and better quality TME with shorter operative times, and reproducible in patients undergoing neoadjuvant chemoradiation[87]. To date the largest single series is of 140 patients[64] and although the results were of limited follow-up and did not include an evaluation of functional outcome, there were no conversions, operative complications were comparable to the "top-down" laparoscopic and 97% of the resected specimens macroscopically had complete TME. Still there must be a word of caution as the results of the international registry of the first 720 procedures from 66 registered units in 23 countries were recently published showing that conversion occurred in 9.1%, intact TME specimens was achieved in 85% and postoperative mortality and morbidity occurred in 0.5% and 32.6% respectively[88].

TaTME has its detractors[89,90], the operative technique is not standardized, and involves dissecting from within the rectum outwards into the mesorectum with the theoretical risk of contaminating this space and the peritoneal cavity with bacteria[91] or worse malignant cells[90], even when there is routine performance of iodine-based distal rectal washout. While the two-team approach offers efficiency in execution, the procedure calls for just that, two teams, or at least two sets of instruments for the transanal and transabdominal approaches. This again is at least associated with a theoretical risk of increased cost, even if it is reduced by shorter operative times. The already mentioned urethral injury is one possible complication, but anastomotic leaks, bowel injuries, urinary dysfunctions and bleeding have all been described[92]. All these occur in a setting where 98% of cases were diverted proximally with a stoma[70].

There is a concern as to whether TaTME may worsen low anterior resection syndrome but there is a dearth of studies about functional outcome and the quality of life impact of this approach[92]. Studies of long-term superiority (or at least non-inferiority) compared to the usual "top-down" laparoscopic approach are sparse and for now we

await the results of multicenter randomized prospective trials like the COLOR 3 trial[76] and the long-term results of the various registries before this method of rectal cancer resection can be universally recommended.

CONCLUSION

Global trends suggest that the prevalence of rectal cancer will continue to increase in the next few decades with marked geographic variations in the stage of diagnosis and treatment options available. As such the surgical community must strive to continue to provide quality care as dictated by high cure rates and minimal impact on their quality of life for this disease. Watchful waiting after complete pathologic response to neoadjuvant chemoradiotherapy, TAMIS and TaTME all are exciting new options for the management of selected patients with rectal cancer. They add to the gold standard that remains open TME with neoadjuvant chemoradiotherapy or adjuvant chemotherapy where indicated. These newer options all have in common limited evidence in support of their universal adoption and a limited number of skilled surgeons who are experienced in their efficient execution. For now, whilst the evidence accumulates, their widespread introduction should be well controlled and regulated in an environment of well trained practitioners, thus allowing the informed patient to benefit from the advantages these options promise.

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ORIGINAL ARTICLE

Case Control Study

Utility of routine blood tests after elective laparoscopic cholecystectomy for symptomatic gallstones

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Abstract

AIM

To evaluate the value of blood testing after elective laparoscopic cholecystectomy and its association with procedure related complications.

METHODS

Charts of all patients undergoing elective laparoscopic cholecystectomy from January 2013 through December 2014 were reviewed retrospectively for demographics, indication for surgery, operative course and outcome. In our institution the decision to perform postoperative blood analysis is left for the discretion of the surgeon, therefore we had the possibility to compare the results of those who had blood analyses results to those who did not. Analysis was performed to identify variables associated with the decision to perform postoperative blood tests. Subsequently a univariate and multivariate analyses was performed comparing the two cohorts. Secondary subgroup analysis was performed to identify factors associated with procedure related complications.

RESULTS

Five hundred and thirty-two elective laparoscopic cholecystectomies for symptomatic gallstones were performed during the study period. Sixty-four percent of the patients (n = 340) had blood tests taken post operatively. Patients that had laboratory tests taken were older (P = 0.006, OR = 1.01), had longer surgery (P < 0.001, OR = 3.22) had more drains placed (P < 0.001, OR = 3.2) and stayed longer in the hospital (P < 0.001, OR = 1.2). A subgroup analysis of the patients who experienced complications revealed longer stay in the hospital (P < 0.001), higher body mass index (BMI) (P = 0.04, OR = 1.08),

increased rates of drain placement (P = 0.006, OR = 3.1) and higher conversion rates (P = 0.01, OR = 14.6). Postoperative blood tests withdrawals were not associated with complications (P = 0.44). On Multivariate analysis BMI and drain placement were independently associated with complications.

CONCLUSION

The current study indicate that routine postoperative blood tests after elective laparoscopic cholecystectomy for symptomatic gallstones does not predict complications and may have an added benefit in diagnosis and management of cases were the surgeon encountered true technical difficulty during surgery.

Key words: Cholecystectomy; Blood tests; Laparoscopy; Complications; Post-operative; Gallstones; symptomatic

Core tip: Laparoscopic cholecystectomy is the procedure of choice for patients with symptomatic gallstones. Although some patients will need overnight observation many of the younger patients, with low body mass index (BMI), that did not have severe gallbladder infection may be performed under day surgery, in institutions that have the necessary setup. The current study show that postoperative blood analyses does not predict nor correlate with postoperative complications and has no impact on outcome. The only independent predictors of complications on multivariate analysis are BMI and drain placement that was used a surrogate for technical difficulty during surgery. Intuitively length of surgery is thought to be in correlation with technical difficulty. In centers were supervised residents perform high percentage of the operations, length of surgery does not correlate with difficulty or post operative complications and by itself does not seem to indicate need for post-operative blood analyses.

Ben-Ishay O, Zeltser M, Kluger Y. Utility of routine blood tests after elective laparoscopic cholecystectomy for symptomatic gallstones. *World J Gastrointest Surg* 2017; 9(6): 149-152 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i6/149.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i6.149

INTRODUCTION

Cholelithiasis is a common disease affecting millions of people around the world. Laparoscopic cholecystectomy (LC) is the procedure of choice for symptomatic gallstones and more than 500000 procedures are performed annually worldwide. The need for blood tests evaluation after LC is seldom discussed in the literature[1,2]. In our institution postoperative follow-up blood testing is left for the discretion of the attending surgeon in charge of the case. Departmental protocols exist for the treatment of procedural related complications. Post LC liver function tests have been previously shown to be slightly and transiently elevated with no clinical significance[3-6]. We sought to evaluate whether routine blood tests after elective laparoscopic cholecystectomy have any impact on patient's outcome and whether they are predictive of postoperative complications.

MATERIALS AND METHODS

Charts of all patients undergoing elective laparoscopic cholecystectomy from January 2013 through December 2014 were reviewed retrospectively for demographics, indication for surgery, operative course and operative outcome. Post-operative laboratory analyses order during the time frame of the study were left for the discretion of the attending surgeon in charge of the case. Data was compared between the two groups (lab *vs* no lab) to identify factors associated with the surgeon threshold to order blood work postoperatively. A second subgroup analysis was performed to evaluate the differences between patients who experienced complications and patients who did not. Variables that were significant by univariate analysis were subjected to a multivariate logistic regression model to evaluate variables that are independently associated with complications. Primary measure of outcome was surgical complications and secondary measure of outcome was the association of postoperative blood tests with factors such as age, body mass index (BMI), length of surgery and the positioning of a drain.

Statistical analysis

Potential associations were assessed by Fisher's exact test for percentages, *t*-test for means, and Mann-Whitney *U* tests for medians. A series multivariable logistic regressions were applied to identify independent characteristics with a $P < 0.10$ from univariate analysis; these were treated as candidate variables in the models[7]. Factors included in the final regression models were assessed for significance by the likelihood ratio test (LRT). Two-tailed P value < 0.05 was considered statistically significant. Statistical analysis was performed with JMP version 12.1.0 (64 bit), SAS institute inc.

RESULTS

During the study period 532 elective LC for symptomatic gallstones were performed. Mean age of the patients was 48 years; the majority of the patients (73%) were females. Most patients were overweight (71.7%, n = 302) with a mean BMI of 28.6 (Table 1). Two patients (0.4%) were operated for gallstone and had incidental finding of adenocarcinoma of the gallbladder. Both were confined to the mucosa (T1) and were submitted for follow-up alone. Five patients (0.9%) required conversion to open approach. Sixty four percent of the patients (n =

Table 1 General data and demographics *n* (%)

	n = 532
Age (yr)	48.9 ± 17.3
Gender (female)	386 (72.56)
LOS (d) (median)	1.5 (1-7)
Time of Surgery (min) (median)	50 (14-178)
Drain	134 (25.2)
Laboratory analysis	340 (63.9)
BMI (kg/m^2)	28.6 ± 5.6
> 25.1	302 (71.73)
> 30.1	138 (32.8)
> 35.1	52 (12.35)

LOS: Length of stay; BMI: Body mass index.

Table 2 Detailed rate and type of complications *n* (%)

	n = 532
Overall complication rate	21 (3.9)
Biliary damage	5 (0.9)
Hemorrhage	10 (1.9)
Post-operative abscess	5 (0.9)
Urinary tract infection	1 (0.2)

340) had blood tests (complete blood count and routine chemistry including electrolytes, renal and liver function tests) withdrawn post operatively. Overall complications rate was 3.9%. Postoperative bleeding was the most common complication (1.9%, *n* = 10). Three patients were re-operated for this complication. Biliary duct injury and intra-abdominal infection were equally common (0.9%, *n* = 5) (Table 2).

Patients who had post-operative laboratory tests taken were older (*P* = 0.006, OR = 1.01), had longer surgery (*P* < 0.001, OR = 3.22) and stayed longer in the hospital (*P* < 0.001, OR = 1.2) (Table 3). Closed suction drain was placed in 25.2% (*n* = 134) of the patients. Post-operative blood tests were more commonly withdrawn in this subgroup of patients (*P* < 0.001, OR = 3.2) (Table 3).

The primary outcome of the study was complications and the ability of postoperative blood tests to predict them. A subgroup analysis of the patients who experienced complications compared to the ones who did not showed that complications were associated intuitively with longer stay in the hospital (*P* < 0.001), but also with higher BMI (*P* = 0.04, OR = 1.08), higher rate of drain placement (*P* = 0.006, OR = 3.1) and higher conversion rate (*P* = 0.01, OR = 14.6). Interestingly postoperative blood tests were not associated with complications (*P* = 0.44). On Multivariate analysis BMI (0.05) and drain placement (0.02) were both associated independently with complications (Table 4).

To evaluate the differences in pre and postoperative liver function tests we performed the Wilcoxon signed rank test. We found statistically significant increase in aspartate transaminase (AST) and a decrease in alkaline phosphatase (ALP), both with no clinical significance.

Table 3 Comparison of patients with and without laboratory test post operatively *n* (%)

	Laboratory (*n* = 340)	No laboratory (*n* = 192)	*P* value
Age (yr)	50.4 ± 17.7	46.1 ± 16.4	0.006
Gender (female)	239 (70.3)	147 (76.6)	0.12
LOS (d)	1.9 ± 0.99	1.3 ± 0.56	< 0.001
Length of surgery	55 (15-178)	43 (14-100)	< 0.001
BMI (kg/m^2)	28.9 ± 5.8	28.1 ± 5.2	0.17
Complications	18 (3.4)	4 (0.8)	0.07
Conversion	5 (0.3)	0	0.16
Drain	109 (20.5)	25 (4.7)	< 0.001

LOS: Length of stay; BMI: Body mass index.

DISCUSSION

Laparoscopic cholecystectomy is the standard of care for patients with symptomatic gallstones. Preoperative evaluation and its importance are vastly discussed in the literature and are beyond the scope of this article. We sought to focus on the postoperative follow-up of patients and to evaluate the surgeons' threshold to order these tests.

In many institutions LC is performed in day surgery setup. Routine blood testing post-operatively may result in inconvenience to the patient and his family as well as increased overall costs. In the current study we evaluate the surgeons' threshold to order post- operative blood tests. Older age, prolonged surgery and the need for more than one day of hospitalization triggered the need for postoperative blood work. Drain placement is a good surrogate to the complexity encountered by the surgeon during the procedure especially if done electively. In fact patients who had drains placed had significantly more blood test taken. Subgroup analysis to identify factors associated with complications showed that postoperative blood tests were not independently associated with increased rate of complications. In fact the only factors independently associated with increased risk for complications were BMI and drain placement.

Length of surgery was associated with increased risk of complications on bivariate analysis but not on multivariate analysis correcting for BMI, drain placement, length of surgery and postoperative blood withdrawal. Our institution is a university center and residents perform high percentage of the procedures with the supervision of an attending surgeon. Length of surgery may be affected therefore by our teaching duties and not necessarily a true complexity of the cases.

We also evaluated the utility of the blood test taken and whether they have actually changed the management of the patients. In the complication group (*n* = 21), 12 patients were discharged on day one or two. Blood tests were taken to 75% (*n* = 9) of 21 patients in the complication group. All blood work returned normal and the patients were discharged. All these patients were readmitted for complications. This observation

Table 4 Subgroup univariate and multivariate analysis comparing patients who experienced complications with those who did not *n* (%)

	Complications (*n* = 22)	No complications (*n* = 510)	*P* value (univariate)	*P* value (multivariate)
Age (yr)	53 ± 17	48.7 ± 17.4	0.26	
Gender (female)	15 (68.2)	371 (72.8)	0.63	
LOS (d)	2.45 ± 1.2	1.7 ± 0.9	< 0.001	
Length of surgery	57.3 ± 20.7	53.4 ± 23.3	0.44	0.08
BMI (kg/m^2)	31.5 ± 8.1	28.5 ± 5.5	0.04	0.05
Postop labs	18 (81.8)	322 (63.1)	0.07	0.06
Conversion	2 (9.0)	3 (0.6)	0.01	
Drain	11 (50.0)	123 (24.1)	0.006	0.02

LOS: Length of stay; BMI: Body mass index.

suggests that the immediate postoperative blood work did not change the management and did not predict the complications.

In conclusion, the results of our study suggest that routine postoperative blood tests after elective laparoscopic cholecystectomy are unnecessary and should be carried out only in selected cases where the surgeon encountered true technical difficulty during surgery. Length of surgery by itself does not seem to indicate need for blood test postoperatively only when it is accompanied by high level of difficulty. Future prospective studies that address the matter are needed.

COMMENTS

Background

Laparoscopic cholecystectomy (LC) is the procedure of choice for patients with symptomatic gallstones and thousands of these procedures are performed every year worldwide.

Research frontiers

The current study explore the need for routine post operative blood analysis.

Innovations and breakthroughs

Although many places do not take blood samples after uneventful laparoscopic cholecystectomy, gives the evidence for such routine.

Applications

Laparoscopic cholecystectomy may be performed safely under day surgery setup.

Peer-review

This article is an interesting study and suitable for publication in this journal. Authors described utility of routine blood tests after LC.

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ORIGINAL ARTICLE

Observational Study

Value of multi-disciplinary input into laparoscopic management of rectal cancer - An observational study

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Abstract

AIM

To assess the impact of multi-disciplinary teams (MDTs) management in optimising the outcome for rectal cancers.

METHODS

We undertook a retrospective review of a prospectively maintained database of patients with rectal cancers (defined as tumours $\leqslant$ 15 cm from anal verge) discussed at our MDT between Jan 2008 and Jan 2011. The data was validated against the national database to ensure completeness of dataset. The clinical course and follow-up data was validated using the institution's electronic patient records. The data was analysed in terms of frequencies and percentages. Significance of any differences were analysed using χ^2 test. A Kaplan-Meier analysis was performed for overall survival and disease free survival.

RESULTS

Following appropriate staging, one hundred and thirty-three patients were suitable for potentially curative resections. Seventy two (54%) were upper rectal cancer (URC) - tumour was > 6 cm from the anal verge and 61

(46%) were lower rectal cancers (LRC) - lower extent of the tumour was palpable ⩽ 6 cm. Circumferential resection margin (CRM) appeared threatened on pre-operative MRI in 19/61 (31%) patients with LRC requiring neo-adjuvant therapy (NAT). Of the 133 resections, 118 (89%) were attempted laparoscopically (5% conversion rate). CRM was positive in 9 (6.7%) patients; Median lymph node harvest was 12 (2-37). Major complications occurred in 8 (6%) patients. Median follow-up was 53 mo (0-82). The 90-d mortality was 2 (1.5%). Over the follow-up period, disease related mortality was 11 (8.2%) and overall mortality was 39 (29.3%). Four (3%) patients had local recurrence and 22 (16.5%) patients had distant metastases.

CONCLUSION

Management of rectal cancers can be optimized with multi-disciplinary input to attain acceptable long-term oncological outcomes even when incorporating a laparoscopic approach to rectal cancer resection.

Key words: Rectal cancer; Multi-disciplinary management; Laparoscopic rectal resection outcomes

Core tip: Recently, management of rectal cancer has undergone a process of standardization with introduction of total mesorectal excision and use of neo-adjuvant long course chemo-radiotherapy. In the United Kingdom, multimodal therapy is provided under the auspices of multi-disciplinary teams (MDTs). This is the first study to report on the benefits of managing patients jointly within such an MDT.

Dhruva Rao PK, Peiris SPM, Arif SS, Davies RA, Masoud AG, Haray PN. Value of multi-disciplinary input into laparoscopic management of rectal cancer - An observational study. *World J Gastrointest Surg* 2017; 9(6): 153-160 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i6/153.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i6.153

INTRODUCTION

Rectal cancer accounts for a third of patients with large bowel cancer[1,2]. Historically, management of rectal cancers has been of variable standard with significant differences in local recurrence rates[3-6]. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the National Institute for Health and Care Excellence (NICE) have both recommend that rectal cancer should be managed by a multi-disciplinary team (MDT)[7,8]. This has led to initiatives to standardize MDT practises across the country.

Currently, nearly 90% of patients with colorectal cancer undergo discussion and treatment planning at an MDT in the United Kingdom[2]. Total mesorectal excision (TME) has been established as the gold standard for the management of mid and lower rectal cancers over the last few years following the results of numerous trials such as the MR CR07 and Dutch TME trials[5,6,9]. The role of neo-adjuvant therapy is also well established in patients with threatened margins[7,8].

We have had an established MDT team managing colorectal cancer since 1997. Our unit has been performing laparoscopic rectal resection under the auspices of the MDT since 2000, initially in selected cases and since 2008, with increased experience, as the default approach. NICE recommends laparoscopic rectal resection by experienced surgeons[10].

We undertook this retrospective analysis of a prospectively maintained database to assess the effectiveness of our MDT rectal cancer management outcomes.

MATERIALS AND METHODS

Definitions

Rectal cancer = All cancers ⩽ 15 cm from anal verge as measured during rigid sigmoidoscopic examination were classified as rectal cancers. These were further categorized as below: Lower rectal cancer (LRC) = All palpable tumours (⩽ 6 cm from anal verge); upper rectal cancer (URC) = All other tumours (6-15 cm from anal verge); Circumferential resection margin (CRM) positivity = if CRM < 1 mm (Both on pre-op MRI and at histopathology); Local or distant metastasis was defined on the basis of radiological evidence.

MDT

Our MDT consists of 3 colorectal surgeons, 1 specialist GI clinical oncologist, 2 specialist radiologists, 1 pathologist, 1 colorectal specialist nurse, 1 enhanced recovery co-ordinator, 2 enterostomal therapists, 1 palliative care consultant/specialist nurse and 2 gastroenterologists. This team meets every week and has been active since 1997 with a track record of publications, awards and innovative solutions to enhancing quality of care and patient experiences[11-13]. Non clinical business meetings of the team are held to facilitate the formulation and agreement of local protocols for colorectal cancer diagnosis, investigations and treatment.

Staging

All patients diagnosed with rectal cancer were staged with a computerized tomography (CT) scan of thorax, abdomen and pelvis. They also underwent either a colonoscopy or a CT colonogram (done as a part of staging CT). All patients with LRC and some with URC underwent a magnetic resonance imaging (MRI) of rectum for local staging as per the T2 weighted fast spin echo protocol, in 5 mm slices in the axial, coronal and sagittal planes in addition to oblique axials targeted at right angles to the axis of the tumour, using 3 mm slices and smaller "Field of View" for maximal resolution. As per common practice

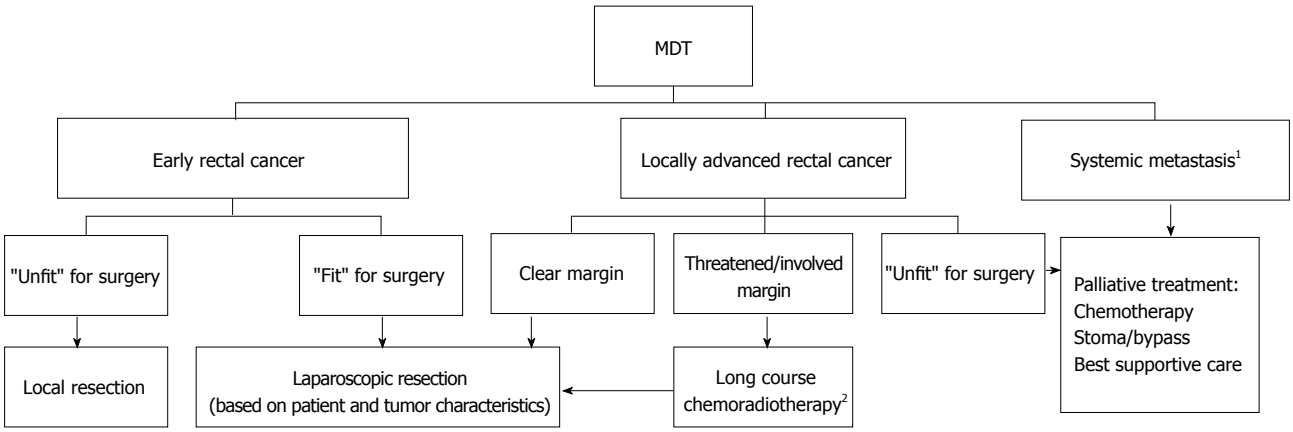

Figure 1 Multi-disciplinary team protocol. [1]If metastases were deemed resectable, referral made to appropriate specialty and primary treated with curative intent. [2]45 Gy in 25 fractions to the pelvis over 5 wk with concurrent capecitabine chemotherapy. MDT: Multi-disciplinary team.

in the United Kingdom, none of our patients underwent endo-rectal ultrasound scanning.

Treatment planning

The staging investigations of all patients were reviewed by the MDT and treatment plans formulated according to the MDT protocol (Figure 1). Patients with threatened CRM were offered neo-adjuvant therapy (NAT) given as a pre-operative Long Course Chemo-Radiotherapy (LCRT), 45 Gy in 25 fractions to the pelvis over 5 wk with concurrent Capecitabine chemotherapy. In addition, short course radiotherapy 25 Gy in 5 fractions over 1 wk was considered in patients with moderate risk rectal cancers. The patients were then restaged and reviewed at MDT prior to surgery. Cases considered suitable for resection were scheduled for surgery 6-10 wk following NAT.

All patients with URC were planned for an anterior resection (AR). Planned surgical options for patients with LRC were either total mesorectal excision with de-functioning ileostomy (TME + I) or when the sphincters or levators were threatened, an abdomino-perineal excision (APER).

Post-operative histology was reviewed by the MDT and clinically fit patients with poor prognostic features on histology were offered adjuvant treatment (AT) with Oxaliplatin and 5 fluorouracil based combination chemo-therapy.

Surgical procedure

The default surgical approach was laparoscopic resection except when the patient had had multiple previous surgery, anaesthetic considerations precluded a laparoscopic approach and occasionally due to technical issues such as particularly obese male patients with bulky tumours not responsive to neo-adjuvant treatment. We defined conversion as previously published[12]: (1) If the final incision made was longer than planned pre-operatively; (2) If the incision needed to be made at an earlier stage of the operation than planned pre-operatively; and (3) If the incision was made at a site other than that planned pre-operatively.

All laparoscopic procedures were performed by one of two consultant surgeons (each with experience of over 100 colorectal resections at the beginning of the study period) or by senior trainees under direct supervision (consultant scrubbed). All procedures were performed with the patient in the Lloyd Davies position with steep Trendelenburg tilt, following a step-wise approach (Table 1)[14,15]. The open procedures and the converted cases followed a similar step-wise approach through a midline laparotomy.

Follow-up protocol

All patients were reviewed initially at 6 wk after their surgery. The follow up protocol was a 6 monthly clinical review with haematological and biochemical tests including tumour marker CEA for 5 years, an annual CT scan of thorax, abdomen and pelvis for 3 years and a surveillance colonoscopy at 3 and 6 years. The length of follow-up was recorded in months from the date of operation.

Patients included in this study

After appropriate institutional approvals, all patients with rectal cancer discussed at our MDT meeting between Jan 2008 and Jan 2011 were identified and the patient demographics, treatment, post-operative histology and follow-up data were studied.

Outcome measures

The primary outcome measures of the study were local recurrence rates and disease free survival. The secondary outcome measures included post-operative length of stay, major complications and overall survival.

Statistical analysis

The data was analysed in terms of frequencies and percentages. Significance of any differences were analysed using χ^2 test. A Kaplan-Meier analysis was performed for overall survival and disease free survival.

RESULTS

During these 3 years, a total of 141 patients [median age 67 years (range 45-89); M:F = 1.7:1] were diagnosed

Table 1 Stepwise approach to rectal dissection

1	Port positions: 10-12 mm - sub-umbilical, RUQ (camera), RIF and LIF; patient in Lloyd-Davies position
2	Omentum to supracolic compartment and small bowel stacking
3	Identify right ureter
4	Start medial dissection at the promontory
5	Identify left ureter, then left gonadal, pelvic nerves
6	Protect left ureter with surgicel® and Pedicle dissection
7	Identify ureter through both windows of mesentery either side of pedicle
8	Transect pedicle, confirm haemostasis
9	Left lateral dissection, identify left ureter and proceed up to peritoneal reflection; IMV high tie and splenic flexure mobilisation, if required
10	Mesorectal Dissection and preparation of rectum for division1
	Right mesorectal dissection up to peritoneal reflection
	Posterior dissection (presacral plane down to levator), keep left ureter in view
	Divide peritoneal reflection anteriorly and dissect till seminal vesicles/vaginal fornix
	Complete both lateral dissection, identify the ureters all the way
	Anterior dissection keeping to the plane just posterior to the vesicles/vagina
	Rectal Cross stapling (achieve antero-posterior staple line) or proceed to perineal dissection[1]
11	Intra-corporeal cross stapling of rectum at appropriate level protecting lateral and anterior structures and Grasp stapled end of specimen
12	Left iliac fossa port extended as a transverse incision for specimen delivery; protect wound and deliver specimen by the stapled end
13	Complete mesenteric ligation, proximal bowel division and prepare proximal bowel for anastomosis
14	Close wound, re-establish pneumoperitoneum
15	Intra-corporeal bowel anastomosis with no tension, no twist and vital structures protected
16	Close incisions

[1]In patients undergoing laparoscopic abdomino-perineal excision, the left sided port is placed at the site of the planned colostomy and the laparoscopic dissection stopped at the mid rectal level, the proximal colon divided intra-corporeally with a stapler and proceed to a wide excision of the anal sphincter complex to obtain a cylindrical specimen.

with rectal cancer. Of these, there were 2 patients with locally advanced disease invading prostate and so were referred for exenteration elsewhere. A further 6 patients went on to have palliative treatment due to either advanced presentation or significant medical co-morbidities. The remaining 133 patients were staged as suitable for potentially curative resections. Of these, 72 (54%) were upper rectal tumours (URC) and 61 (46%) were lower rectal tumours (LRC). Three (2%) patients had resectable metastases at diagnosis and were treated with primary rectal resection, followed by chemotherapy and surgery for metastases.

The pre-operative (putative) CRM was threatened in 19 (14%) patients (4 patients due to presence of nodes close to the CRM). Of these, 14 patients had LCRT; 1 had short course radiotherapy (25 Gy in 5 fractions over 1 wk). Four patients did not receive any Neoadjuvant therapy: 1 female patient with an anterior tumour where there was lack of consensus on preoperative staging being T2 *vs* T4 and 3 patients where there was a small node of doubtful significance threatening the margin.

Interval between completion of NAT and surgery was a median 10 (6-24) wk. One patient had a radiological complete response to neo-adjuvant therapy and opted initially for a watch and wait policy prior to eventually opting to receive surgery.

Table 2 summarizes the operations performed. All 72 patients with URC underwent an AR. Of the 61 with LRC, 29 had TME + I, 1 patient had a TME Hartmann's procedure and 27 had APER. Four patients had TME and anastomosis without covering ileostomy. Surgery following NAT was either APER (8/15) or TME + I (7/15).

Laparoscopic resection was attempted in 118/133 (89%). Conversion rate was 5% (6 out of 118 patients).

Table 2 Operations (n = 133)

Operations	Laparoscopic (conversion)	Open	Total
Anterior resections	66 (2)	6	72
TME	4		4
TME + I	25 (1)	4	29
TME Hartmann's	1 (1)		1
APER	26 (2)	1	27

TME: Total mesorectal excision; APER: Abdomino-perineal excision.

The reasons for conversion were uncontrollable bleeding from the IM pedicle (n = 1), low tumour in a male pelvis, requiring a suprapubic incision rather than the planned left iliac fossa incision for specimen delivery (n = 1) and dense adhesions (n = 4), requiring incisions either larger than planned or at an earlier stage of the operation). The remaining 15 patients (11%) underwent a planned open procedure due to previous extensive surgery, locally advanced tumour in an android pelvis or poor response to LCRT.

Median post-operative length of stay was 5 d (3-49). Major complications needing re-operation within 30 d occurred in 8 (6%) patients [Anastomotic leak: 2, Pelvic haemorrhage requiring packing: 2, Small Bowel Obstruction: 2 (1 - port site; 1 - pelvic), Intra-abdominal collection: 1, Wound dehiscence: 1].

Post-operative histology is shown in Table 3. One hundred and twenty four patients (93.3%) had R0 resection and 9 (6.7%) had an R1 resection (CRM positive - 6 due to tumour, 3 due to nodes). There were no R2 resections in this cohort. Median LN harvest was 12 for the laparoscopic group and 10 for the open group (P < 0.01). Of the 9 patients with positive CRM 4 were URC

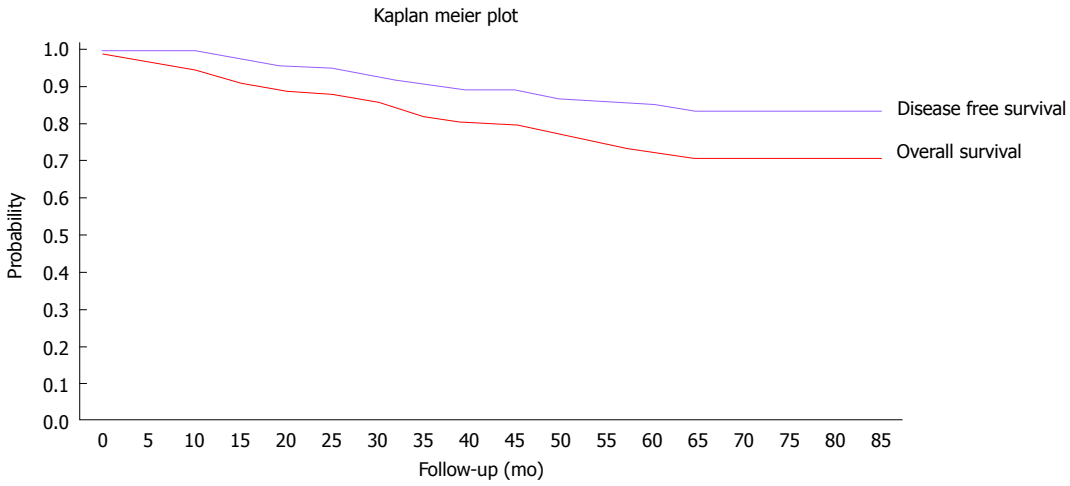

Figure 2 Survival curves for the cohort.

Table 3 Post-op stage (n = 133)

Post-op stage	*n*
R0 resection	124
R1 resection (CRM + ve)	9
R2 resection	0
T1	14
T2	42
T3	58
T4	17
N0	85
N1	31
N2	15

and 5 were LRC. The pre-operative MRI had accurately predicted this in all 5 LRC patients, 4 of whom had received NAT. None of the URCs had had pre-operative MRI as per our practice at that time and so could not be predicted and they did not receive any NAT.

Fifty-six patients had adverse features on histology making them eligible for adjuvant therapy (AT). Of these, 13 were unfit and 3 declined the offer of further chemotherapy. The remaining 40 patients underwent AT.

Median follow up was for 53 mo (0-82). Long-term complications occurred in 9 (6.7%) patients (parastomal hernia: 6, port site hernia: 1, anastomotic stricture: 1, late onset left ureteric obstruction due to fibrosis: 1).

The 90-d mortality was 1.5% (2 patients: 1 in-hospital due to anastomotic leak; 1 patient post discharge - cause unknown). Disease related mortality over the follow-up period was 11 (8.2%); however, overall mortality for the follow-up period was 39 (29.3%).

Four patients (3%) had local recurrence. The durations to development of local recurrence were 15, 23, 33 and 39 mo. On further analysis of the sub-group with local recurrence, only 1 patient had had a histologically positive CRM. This patient had an upper rectal tumour and had not been considered for NAT. The other 3 patients having local recurrence were all T3 URC and all had had a R0 resection with CRM clearance of between 1-2 mm. In this cohort, we had no local recurrence in any patients with LRC.

Twenty two patients (16.5%) developed distant metastases and one patient developed metachronous colonic cancer. Four of these had no poor prognostic factors on histology such as node positive disease, extra-mural lympho-vascular invasion and/or poor differentiation. Of the 18 with poor prognostic markers, 3 had declined and 5 had been deemed unfit for AT. Figure 2 shows the Kaplan-Meier curve for our cohort.

DISCUSSION

Patients in our unit have been receiving care under the MDT umbrella since 1997. Our unit has a relatively high uptake of laparoscopic rectal resections with 89% undergoing laparoscopic resection with a relatively low conversion rate using strict definitions for conversion. The median length of stay was 5 d and is comparable to most enhanced recovery programmes. Oncological results too are acceptable with a CRM positivity rate of 4% for sphincter saving resections (4 out of 106 patients) and 18% for APER (5 out of 27 patients). LNH was higher following laparoscopic resection, in keeping with other studies[16].

MDT management is a concept propagated by practice with no "research/trial" based evidence. There is no level 1 evidence that supports MDT, no grade of recommendation is provided for its use in national guidelines and yet, this concept is gaining acceptance worldwide. MDT management has been a mandatory requirement for treatment of cancers in United Kingdom since 2000. For this reason, we cannot perform a meaningful comparative analysis of patients who have not received care under the MDT umbrella. The management of the rectal cancer has also undergone a significant change over this period. This precludes use of a historical cohort for comparison as there could be other confounding factors that influence outcomes.

We believe that this the first observational study attempting to clarify the role of various MDT members who make individual specialist contributions, based on

Table 4 Comparison of circumferential resection margin positive

Type of operation	Dutch TME trial[6]	CLASICC trial[5]	MR CRO7 trial[9]	Our series
Sphincter saving resection	13%	10%	8%	3% (4/106)
APER	29%	21%	17%	18% (5/27)

TME: Total mesorectal excision; APER: Abdomino-perineal excision.

consensual decisions arrived at by a group of experts, resulting in improved clinical effectiveness.

Lap TME has been shown to be safe with acceptable short-term clinical and oncological outcomes[5,17-19]. The 2 most recent trials, ALaCaRT and the ACOSOG Z6051, have not been able to demonstrate the non-inferiority of laparoscopic resections compared to open resections in terms "completeness of excision" using a composite scoring system[20,21]. However, they are still accruing data on long term oncological outcomes. Laparoscopic TME can be technically challenging and should be undertaken by experienced surgeons[12,20-22]. Caution should therefore be exercised when evaluating results of laparoscopic TME when the expertise of the surgeons has not been defined. The senior surgeons have had a mean experience of 6 years between them with over 100 laparoscopic resections each prior to the commencement of this study. From this study, we see that acceptable long-term oncological results can be safely achieved when laparoscopic approach is pragmatically applied by appropriately trained surgeons in the context of multimodal therapy overseen by MDT.

The few RCTs reporting 5 year survival were not specifically designed or powered for long term outcomes[3]. More recently several meta-analyses published have not come up with any strong conclusions either way with respect to long-term survival[3,4,19,23,24]. However, laparoscopic resection seems to be associated with a lower local recurrence rate[24]. This lack of clarity has been the cause for variable uptake of Lap TME ranging from 0%-100%[2,25].

We believe that this study is one of the first to report on outcomes of laparoscopic rectal resections outside of RCTs or case control studies. Tables 4 and 5 show our results which compare favourably to other published studies. Figure 2 shows the Kaplan Meier curves for our cohort which shows an overall survival of 81% and disease free survival of 90% at median follow-up. This compares favourably with other series with similar follow-up which have reported a predicted overall survival of 81% and disease free survival of 70%[26]. Our survival figures show that our cohort of patients were more likely to die from other causes than from disease recurrence, in keeping with the high co-morbidity of our catchment population[27], most of which falls within the highest quintile of the deprivation index in the United Kingdom.

A 12-year follow-up of Dutch TME trial cohort showed local recurrence of 6.5% (68 patients) in 1082 patients who had an R0 resection[28]. In comparison, we observed a local recurrence rate of 2.4% (3 patients) in 124 patients having an R0 resection. All recurrences were in patients with URC with no recurrences in LRC. We observed only 1 local recurrence in 9 patients who had an R1 resection (11.1%). However extrapolating similar data from the Dutch TME trial would give a figure of 20.8% patients with involved margins developing a local recurrence. This comparison however, may be misleading as the follow up in our study (53 mo) is shorter than the Dutch TME trial (12 years).

Traditionally, local recurrence after rectal cancer resection usually presents within 2 years[2,28]. In our series, we have had a median follow up of 53 mo and have not noticed any local recurrence in the LRC group. The follow-up of the Dutch TME trial cohort confirmed that pre-operative radiotherapy not only reduced local recurrence but was especially effective in preventing anastomotic recurrences[28]. The same effect probably accounts for the absence of local recurrence noted in our study for the low rectal cancers in spite of 10% (6 of 61 LRC) CRM positivity. Another hypothesis worth considering could be that CRM positivity due to lymph nodes may carry a lesser risk of local recurrence when compared with cases where the CRM was involved by the primary tumour.

We believe this observed low rate of local recurrence is due to effective working within a well-established specialist MDT, resulting in appropriate use of NAT for our cohort of patients.

In conclusion, this study demonstrates that good long term oncological outcomes can be achieved for patients with rectal cancer when appropriate multi-disciplinary expertise is combined with surgery being performed by adequately trained surgeons. Neo-adjuvant chemo-radiotherapy improves the oncological outcomes without precluding the routine use of the laparoscopic approach to rectal resection.

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COMMENTS

Background

Rectal cancer accounts for a third of patients with large bowel cancer. Historically, management of rectal cancers has been of variable standard with significant differences in local recurrence rates. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the National Institute for Health and Care Excellence (NICE) have both recommend that rectal cancer should be managed by a multi-disciplinary team (MDT). This has led to initiatives to standardize MDT practises across the country. The authors undertook this retrospective analysis of a prospectively maintained database to assess the effectiveness of the MDT rectal cancer management outcomes.

Table 5 Comparison of local recurrence

	Meta-analysis[4] (*n* = 1544)	Dutch TME trial[6] (*n* = 1586)	CLASICC trial[5] (*n* = 400)	MRC CR07 trial[9] (*n* = 1350)	Our series (*n* = 133)
Local recurrence	13%	8%	6.80%	7%	3% (4/133)

TME: Total mesorectal excision.

Innovations and breakthroughs

Providing evidence to the concept of multidisciplinary management of rectal cancer; optimizing outcomes following laparoscopic rectal resection.

Applications

This study adds evidence to the increasing evidence in the evolving management of rectal cancers

Terminology

MDT consists of Colorectal Surgeons, Specialist GI Clinical Oncologist, Specialist GI Radiologists, Specialist GI pathologist, Colorectal Specialist Nurse, Enhanced Recovery co-ordinator, Enterostomal Therapists, Palliative care specialists and Gastroenterologists.

Peer-review

This is a good paper, showing that excellent results can be achieved by dedicate teams. This retrospective analysis focus on the MDT (several related specialities coming together every week) on rectal cancer management and they suggest MDT for better early and late outcomes and for laparoscopy.

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Retrospective Study

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ORIGINAL ARTICLE

Retrospective Cohort Study

Perforation associated with endoscopic submucosal dissection for duodenal neoplasm without a papillary portion

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Author contributions: Matsuda Y designed the research and wrote the paper; Sakamoto K designed the research and provided treatment; Sakamoto K, Kataoka N, Yamaguchi T, Tomita M and Makimoto S provided treatment and analyzed the data.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of Kishiwada Tokushukai Hospital for ethical issues.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment without additional invasion.

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Abstract

AIM

To investigate predictors of perforation after endoscopic resection (ER) for duodenal neoplasms without a papillary portion.

METHODS

This was a single-center, retrospective, cohort study conducted between April 2003 and September 2014. A total of 54 patients (59 lesions) underwent endoscopic mucosal resection (EMR) (n = 36) and endoscopic submucosal dissection (ESD) (n = 23). Clinical features, outcomes, and predictors of perforation were investigated.

RESULTS

Cases of perforation occurred in eight (13%) patients (95%CI: 4.7%-22.6%). Three ESD cases required surgical management because they could not be repaired by clipping. Delayed perforation occurred in two ESD cases, which required surgical management, although both patients underwent prophylactic clipping. All patients with perforation who required surgery had no postoperative complications and were discharged at an

average of 13.2 d after ER. Perforation after ER showed a significant association with a tumor size greater than 20 mm (P = 0.014) and ESD (P = 0.047).

CONCLUSION

ESD for duodenal neoplasms exceeding 20 mm may be associated with perforation. ESD alone is not recommended for tumor treatment, and LECS should be considered as an alternative.

Key words: Duodenal neoplasm; Endoscopic submucosal dissection; Laparoscopic and endoscopic cooperative surgery

Core tip: Duodenal neoplasms are relatively rare, and endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) of the duodenum poses a high risk of complications. In our study, 54 patients (59 lesions) underwent EMR (n = 36) and ESD (n = 23). Cases of perforation occurred in eight (13%) patients (95%CI: 4.7%-22.6%), and perforation showed a significant association with a tumor size greater than 20 mm (P = 0.014) and ESD (P = 0.047). ESD for duodenal neoplasms exceeding 20 mm may be associated with perforation. ESD alone is not recommended as a treatment for tumor treatment, and laparoscopic and endoscopic cooperative surgery should be considered as an alternative.

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INTRODUCTION

Duodenal neoplasms are relatively rare. Duodenal polyps are found in 4.6% of patients referred for upper gastrointestinal endoscopy[1]. Primary adenocarcinoma represents only 0.3% of all gastrointestinal tract malignant neoplasms and 0.042% of all malignant neoplasms[2,3]. Therefore, no method of treatment for duodenal neoplasm has been established.

Recently, cases of endoscopic resection (ER) for superficial neoplasms without lymph node metastasis have been reported. ER may consist of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). However, ER for the duodenum poses a high risk of complications, such as perforation and bleeding, due to the abundant blood vessels in the submucosal layer and thin muscle layer in the duodenum compared with the digestive tract[4-7]. Specifically, patients with perforation undergo emergency surgery in many cases, and it is unclear whether ER for duodenal tumors is appropriate. In this study, we investigated predictors of perforation after ER for duodenal neoplasms without a papillary portion.

MATERIALS AND METHODS

Patients

This study included a retrospective cohort of 54 patients (59 lesions) in a single center. We recruited patients (without ampullary duodenal tumors) who underwent ER between April 2003 and September 2014. These patients were preoperatively diagnosed with adenoma or carcinoma. The database included patient information such as age, sex, treatment method (EMR or ESD), prophylactic clipping (applied or not applied), and tumor characteristics, such as histological diagnosis (adenoma or carcinoma), location (pre-ampulla or post-ampulla), size (under 20 mm or over 20 mm), and type (polyploid or superficial). When a patient had multiple duodenal tumors, the largest lesion was included in the analysis. When a tumor was located on the opposite side of the ampulla of Vater, it was categorized as post-ampullary. The clinical features of complications (perforation and bleeding) were investigated.

All patients were provided with an explanation of the endoscopic procedure before treatment, including complications and alternative treatments, and written informed consent was obtained.

Endoscopic resection techniques

The endoscopic procedures were performed with a single-channel endoscope (GIF-Q240 or PCF-PQ260I; Olympus Medical Systems Co., Tokyo, Japan) or a double balloon sigmoid scope (EN-450T5/W; FUJIFILM, Saitama, Japan) by carbon dioxide insufflation. The choice of scope depended on the distance to the lesion.

EMR was indicated for small lesions (< 2 cm) or pedunculated lesions. Simple snarectomy was performed after the injection of 0.4% sodium hyaluronate solution (MucoUp; Johnson and Johnson K.K., Tokyo, Japan). The mucosa bulge is important for the safety of the procedure because the wall of the duodenum is thin. ESD was indicated for large lesions (≥ 2 cm) or flattened lesions. The ESD technique consisted of three steps. First, the periphery of the lesion was marked using a 2.0 mm short needle knife with a water jet function (Flush Knife, DK2618JB20; FUJIFILM, Saitama, Japan). Second, MucoUp was injected into the submucosal layer to achieve sufficient mucosal elevation. Third, a mucosal incision and submucosal dissection were performed with the Flush Knife (1.5 mm or 2.0 mm). Additionally, an electric current generator (VIO300D; ERBE, Tübingen, Germany) was used for hemostasis.

Prophylactic clipping using hemoclips (HX-110/610; Olympus Medical Systems Co.) was performed for mucosal defects after ER.

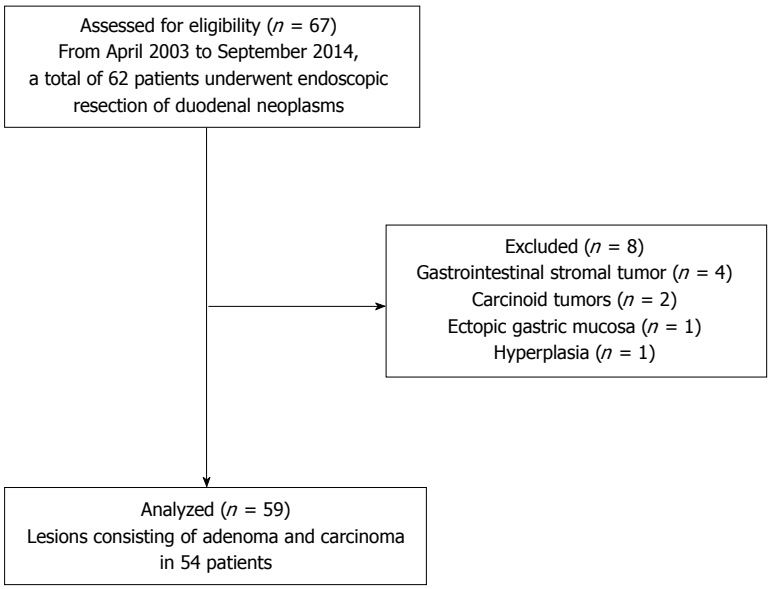

Figure 1 Flow diagram of patients with duodenal neoplasms treated by endoscopic resection.

Definition of complications

Intraoperative perforation was defined as the ability to recognize a perforation during the EMR and ESD procedures. Delayed perforation was defined as the inability to recognize a perforation during the EMR and ESD procedures, and patients had no symptoms immediately after the procedures. The diagnosis of delayed perforation is reached using enhanced computed tomography, which was performed for patients with abdominal pain. Delayed bleeding was defined in patients who required endoscopic hemostasis or transfusion after ER.

Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS 22.0 Package; SPSS Inc., Chicago, Illinois, United States). Continuous variables are expressed as the means and were analyzed using Student's *t* test. Categorical variables were compared with a χ^2 test or, if appropriate, Fisher's exact test. A probability value of < 5% was considered statistically significant.

RESULTS

From April 2003 to September 2014, a total of 62 patients underwent ER of duodenal tumors. Four cases with gastrointestinal stromal tumors, two cases with carcinoid tumors, one case with an ectopic gastric mucosa, and one case with a hyperplasia were excluded. As a result, 59 lesions due to adenoma and carcinoma in 54 patients were analyzed (Figure 1).

The 59 cases included 39 males and 20 females. The average age was 61.3 years (range 40-79 years). Thirty-eight lesions were diagnosed as adenoma, and 21 lesions were diagnosed as carcinoma. The accuracy of the preoperative biopsy was 96.6% (57/59). Thirty-five lesions were located in the pre-ampulla region, and 24 were in the post-ampulla region. The average tumor size was 14.2 mm (95%CI: 11.6-16.8 mm). The macroscopic types included 12 polyploid and 47 superficial tumors. All lesions were confined to the mucosa. Thirty-six lesions underwent EMR. Piecemeal EMR was performed in four cases, and en-bloc EMR was performed in 32 cases. Among the piecemeal EMR cases, three lesions were removed in two pieces, and one lesion was removed in four pieces. Twenty-three lesions underwent ESD. Prophylactic clipping was applied in 46 patients.

Complications included perforation and bleeding (Table 1). Perforation occurred in eight (13%) patients (95%CI: 4.7%-22.6%). Four lesions were located in the pre-ampulla region, and four lesions were in the post-ampulla region. The mean size of lesion in cases of perforation was 22.9 mm, which was significantly different from the non-perforated group ($P < 0.05$). Intraoperative perforation occurred in six cases, and delayed perforation occurred two cases. Intraoperative perforation occurred in two EMR cases and ESD four cases. All cases in the EMR group and one case in the ESD group underwent conservative management after clipping. Three ESD cases required surgical management because they could not be repaired by clipping. Delayed perforation occurred in two ESD cases, and these patients required surgical management, even though both patients received prophylactic clipping. Perforation after ER was significantly associated with tumor size greater than 20 mm and ESD (Table 2). Bleeding occurred in two (3.4%) cases. One required endoscopic hemostasis, and the other patient received a transfusion after ER.

For the surgical procedures, three cases consisted of suturing and covering with omentum. Two patients underwent Billroth I anastomosis after pyloric ring resection and partial duodenum resection. No patients with perforation who required surgery had postoperative

Table 1 Clinical features and outcomes of patients with complications

Case	Age (yr)	Sex	Method	Complication	Clipping	Treatment	Hospital stay after ER (d)	Tumor characteristics		
								Location	Size (mm)	Type
1	65	M	EMR	IP	Possible	Conservative	7	Post-ampulla	17	Is
2	60	M	EMR	IP	Possible	Conservative	6	Post-ampulla	9	IIa
3	55	M	ESD	DP	Possible	Surgical	12	Post-ampulla	24	IIa
4	60	M	ESD	Bleeding	Possible	Transfusion	9	Pre-ampulla	20	IIa
5	67	M	EMR	Bleeding	Possible	Hemostasis	11	Pre-ampulla	55	Isp
6	40	M	ESD	IP	Impossible	Surgical	11	Pre-ampulla	20	IIa
7	55	M	ESD	IP	Possible	Conservative	18	Pre-ampulla	13	IIc
8	64	M	ESD	IP	Impossible	Surgical	16	Post-ampulla	30	IIa
9	44	F	ESD	IP	Impossible	Surgical	12	Pre-ampulla	30	IIa
10	72	F	ESD	DP	Possible	Surgical	15	Pre-ampulla	40	IIa

ER: Endoscopic resection; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; IP: Intraoperative perforation; DP: Delayed perforation.

Table 2 Predictors of perforation

		Perforation		*P* value
		Did not occur	Occurred	
Sex	M	33	6	
	F	18	2	0.704
Histological diagnosis	Adenoma	33	5	
	Carcinoma	18	3	1.000
Tumor location	Pre-ampulla	31	4	
	Post-ampulla	20	4	0.704
Tumor size	Under 20 mm	42	3	
	Over 20 mm	9	5	0.014
Macroscopic type	Polyploid	11	1	
	Superficial	40	7	0.482
Resection method	EMR	34	2	
	ESD	17	6	0.047
Prophylactic clipping[1]	Not applied	10	0	
	Applied	41	5	1.000

[1]Excluded three cases in which clipping were impossible due to perforation. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; M: Male; F: Female.

complications. The patients were discharged at an average of 13.2 d after ER.

DISCUSSION

The reported incidence of malignant degeneration of duodenal tubulovillous polyps ranges from 35% to 85%, and accurately differentiating cancer from adenoma is difficult based on biopsy findings alone[8]. Even if the histopathological examination of a biopsy specimen reveals an adenoma, it is possible to diagnose an adenoma as carcinoma after ER. In our study, the accuracy of preoperative biopsy was 96.6% (57/59). An ER should be performed if no metastasis is present in the lymph nodes and distant organs; however, an adenoma in the duodenum presents the possibility of carcinoma. Nagatani *et al*[9] reported that the incidence of lymph node metastasis was 0% in cases of intramucosal cancer and 5% in cases of submucosal cancer. Shinoda *et al*[10] reported no cases of lymph node metastasis among 273 cases of early duodenal cancer. Therefore, an early duodenal neoplasm can be treated by ER, unless lymph node metastasis is revealed.

Some reports address ER for duodenal tumors, but none address standard therapy. The surgical methods include piecemeal EMR, *en-bloc* EMR, and ESD. Piecemeal EMR is possible in most tumors that exceed 20 mm, but commonly results in recurrence[11,12]. En-bloc EMR can be performed for tumors exceeding 10 mm, although the resection margins may be histologically positive[8]. Additionally, lesions larger than 20 mm cannot be safely removed en-bloc and closed by any currently available method[4,6,13]. Therefore, EMR is not an ideal treatment for duodenal neoplasms larger than 20 mm. ESD can be performed for tumors exceeding 20 mm and achieves higher rates of en-bloc and curative resection than EMR[5]. In one study, the negative margin rate was 100% for the lateral resection margin in ESD[8]. However, ESD is associated with a higher rate of complications, such as perforation and bleeding, than EMR[5]. Jung *et al*[14] reported that the perforation rates after ESD were very high (35.7%). For example, perforation rates associated with gastric ESD have been reported to be between 1.2% and 8.7%. Inoue *et al*[7] reported that the incidence of delayed perforation was significantly associated with post-ampullary tumor location and resection method (both piecemeal EMR and ESD). In our study, ER of tumors exceeding 20 mm and ESD presented a high risk of perforation. We examined EMR and ESD because piecemeal EMR was only performed in four cases, and therefore the statistical power was insufficient. Additionally, the results were not significantly different according to the tumor location.

As described earlier, ER of a duodenal tumor tends to cause complications (especially perforation), and appropriate treatments for perforation are lacking. Abundant blood vessels in the submucosal layer and a thin muscle layer in the duodenum are thought to be related to a high risk of complications. In addition, exposure of the duodenal wall to pancreatic juice and bile may increase the risk of delayed perforation[5]. Taku *et al*[15] reported that conservative treatment is possible

when patients with perforation are stable. Krishna *et al*[16] reported that if perforation is suspected, abdominal CT should be performed to evaluate the indication for surgery. We have suggested that patients could be evaluated immediately by abdominal CT and receive emergency surgery, if necessary, when abdominal pain or high fever is present.

Prophylactic clipping is not sufficient to prevent perforation after ESD. Recently, a new device (the over-the-scope clip) has been developed for the prevention of perforation after ER, but this method requires further evaluation[17]. We suggest that laparoscopic and endoscopic cooperative surgery (LECS) should be the therapeutic strategy for tumors exceeding 20 mm.

Toyonaga *et al*[18] reported the use of an endo linear stapler for wedge resection. However, it is not possible to appropriately resect tumors of the posterior duodenum using this method (*i.e.,* resection with an inappropriate margin or unnecessary resection of the duodenal wall)[18,19]. Sato *et al*[20] reported LECS of a duodenal carcinoid tumor. Recently, others have reported laparoscopic local excision of a tumor followed by closure of the defect using a hand-sewn technique[21-25]. We performed endoscopic total layer resection or ESD of a duodenal tumor followed by this procedure in three cases. All patients had no complications and were discharged in approximately one week. More cases should be evaluated in the future because the sample size of duodenal neoplasms was relatively small.

In conclusion, ESD for a duodenal tumor exceeding 20 mm may be associated with complications (especially perforation). ESD alone is not recommended for tumor treatment, and LECS should be considered as an alternative.

COMMENTS

Background

Duodenal neoplasms are relatively rare. Primary adenocarcinoma represents only 0.3% of all gastrointestinal tract malignant neoplasms and 0.042% of all malignant neoplasms. Therefore, no method of treatment for duodenal neoplasm has been established.

Research frontiers

Recently, cases of endoscopic resection (ER) for superficial neoplasms without lymph node metastasis have been reported. ER may consist of endoscopic mucosal resection or endoscopic submucosal dissection (ESD). However, ER for the duodenum poses a high risk of complications. Patients with perforation undergo emergency surgery in many cases. It is unclear whether ER for duodenal tumors is appropriate.

Innovations and breakthroughs

The authors investigated predictors of perforation after ER for duodenal neoplasms without a papillary portion.

Applications

ESD for a duodenal tumor exceeding 20 mm may be associated with complications (especially perforation). ESD alone is not recommended for tumor treatment, and LECS should be considered as an alternative.

Peer-review

This paper presents an unique comparison of endoscopic mucosal dissection with endoscopic submucosal dissection in the management of non-ampullary duodenal tumours.

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ORIGINAL ARTICLE

Retrospective Study

Analysis of risk factors - especially different types of plexitis - for postoperative relapse in Crohn's disease

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of University of Szeged.

Informed consent statement: Patients were not required to give informed consent to the study because the data were collected retrospectively, and the analysis used anonymous clinical data. Each patient gave their informed consent to the treatment.

Conflict-of-interest statement: We have no financial relationships to disclose.

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Abstract

AIM

To evaluate the presence of submucosal and myenteric plexitis and its role in predicting postoperative recurrence.

METHODS

Data from all patients who underwent Crohn's disease (CD)-related resection at the University of Szeged, Hungary between 2004 and 2014 were analyzed retrospectively. Demographic data, smoking habits, previous resection, treatment before and after surgery, resection margins, neural fiber hyperplasia, submucosal and myenteric plexitis were evaluated as possible predictors of postoperative recurrence. Histological samples were analyzed blinded to the postoperative outcome and the clinical history of the patient. Plexitis was evaluated based on the appearance of the most severely inflamed ganglion or nerve bundle. Patients underwent regular follow-up with colonoscopy after surgery. Postoperative

recurrence was defined on the basis of endoscopic and clinical findings, and/or the need for additional surgical resection.

RESULTS

One hundred and four patients were enrolled in the study. Ileocecal, colonic, and small bowel resection were performed in 73.1%, 22.1% and 4.8% of the cases, respectively. Mean disease duration at the time of surgery was 6.25 years. Twenty-six patients underwent previous CD-related surgery. Forty-three point two percent of the patients were on 5-aminosalicylate, 20% on corticosteroid, 68.3% on immunomodulant, and 4% on anti-tumor necrosis factor-alpha postoperative treatment. Postoperative recurrence occurred in 61.5% of the patients; of them 39.1% had surgical recurrence. 92.2% of the recurrences developed within the first five years after the index surgery. Mean disease duration for endoscopic relapse was 2.19 years. The severity of submucosal plexitis was a predictor of the need for second surgery (OR = 1.267, 95%CI: 1.000-1.606, *P* = 0.050). Female gender (OR = 2.21, 95%CI: 0.98-5.00, *P* = 0.056), stricturing disease behavior (OR = 3.584, 95%CI: 1.344-9.559, *P* = 0.011), and isolated ileal localization (OR = 2.671, 95%CI: 1.033-6.910, *P* = 0.043) were also predictors of postoperative recurrence. No association was revealed between postoperative recurrence and smoking status, postoperative prophylactic treatment and the presence of myenteric plexitis and relapse.

CONCLUSION

The presence of severe submucosal plexitis with lymphocytes in the proximal resection margin is more likely to result in postoperative relapse in CD.

Key words: Submucosal plexitis; Postoperative recurrence; Crohn's disease; Stricturing disease behavior; Isolated ileal disease

Core tip: This is a retrospective study to evaluate the presence of submucosal and myenteric plexitis and its role in predicting postoperative recurrence (POR) in Crohn's disease. Demographic data, smoking habits, previous resection, treatment before and after surgery, and histological findings were evaluated as possible predictors of POR. We found that the severity of submucosal plexitis was a predictor of the need for second surgery. Other predictors of POR were female gender, stricturing disease behavior, and isolated ileal localization. Our results did not confirm the hypothesis that myenteric plexitis can be predictive of postoperative relapse.

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INTRODUCTION

Surgery is not curative in Crohn's disease (CD), hence postoperative recurrence still remains a significant problem in the treatment of CD. More than 70% of all patients with CD require surgery in the course of their disease. A second surgery is required in 34%-53% of the cases; the highest recurrence rate has been observed in the ileocolic disease location[1]. Farmer *et al*[2] also demonstrated that operative incidence was the highest (91.5%) among patients with ileocolic disease. Therefore it is important to identify the predictors of postoperative recurrence in order to optimize treatment and surveillance after surgery. Currently conflicting data are available on the different risk factors. The IBSEN study group found that the probability of surgery was 37.9% in a 10-year follow-up. Terminal ileal location, stricturing, penetrating behavior, and age younger than 40 years at diagnosis were independent risk factors of subsequent surgery[3]. A large meta-analysis of 2962 patients with CD revealed that smoking significantly increases the risk of clinical and surgical recurrence. This high risk of postoperative relapse and reoperation is significantly reduced if a patient quits smoking[4]. A recently published study only identified preoperative steroid use as a risk factor for early postoperative endoscopic recurrence[5], while another study found a higher risk for postoperative endoscopic recurrence in case of previous use of two or more anti-tumor necrosis factor (TNF)-α agents[6].

Histological changes in the enteric nervous system are common in CD. The major structural abnormalities are irregular hypertrophy and hyperplasia of nerve fibers and alterations of neuronal cell bodies and enteric glial cells in the ganglia of the submucosal and myenteric plexus[7]. Ferrante *et al*[8] showed that the presence of myenteric plexitis in proximal resection margins of ileocolonic resection specimens is highly associated with postoperative CD recurrence, and the severity of myenteric plexitis in the proximal resection margin correlated with the severity of endoscopic recurrence[8-10]. Sokol *et al*[11] revealed an association between submucosal plexitis and early clinical recurrence, moreover lymphocytic plexitis in the proximal surgical margin was related to a higher risk of endoscopic or surgical recurrence after ileocolonic resection[12,13].

Our aim was to evaluate the frequency and predictors of postoperative recurrence and the role of submucosal and myenteric plexitis in predicting postoperative recurrence on the basis of endoscopic findings

and/or the need for additional surgical resection.

MATERIALS AND METHODS

Patients and data collection

Patients were selected retrospectively from the database of the Department of Pathology, University of Szeged (Hungary). All patients who underwent CD-related surgery between 2004 and 2014 were included in the study.

Diagnosis of CD was based on clinical, endoscopic and histological findings. The following data were extracted retrospectively from the medical chart of each patient: Age, sex, year of the diagnosis of CD, phenotype of CD according to the Montréal classification[14], smoking habits, date of the CD-related surgery, type of the anastomosis, CD-related therapy before and after surgery, and the presence of postoperative relapse. Postoperative relapse was defined on the basis of endoscopic and clinical findings, and/or the need for additional surgical resection. Patients were regularly followed up with colonoscopy after the surgery. Postoperative endoscopy findings were classified on the basis of the Rutgeerts score in case of ileocolonic resection[15]; remission was defined as Rutgeerts endoscopic score i0-i1, and recurrence as a score of i2-i4[15].

Postoperative recurrences were defined on the basis of the work of Ng *et al*[10] Clinical recurrence was defined as the presence of CD-related symptoms associated with radiologic or endoscopic findings, considered severe enough to change the current therapy (requires steroid treatment or an increase in existing treatment). Surgical recurrence was defined as a need for further operation (refractory to medical treatment or new complications developed)[10].

Pathologic examination

Histological samples were analyzed retrospectively by two expert pathologists, blinded to the postoperative outcome and the clinical history of the patient. Both resection margins (ileal and colonic margins) were investigated for typical CD lesions (inflammatory infiltrates, granuloma, *etc*). Further investigations focused on the proximal resection margin. Special attention was given to the enteric nervous system, namely to the myenteric and submucosal plexuses. Plexitis was evaluated based on the appearance of the most severely inflamed ganglion or nerve bundle[12]. The severity of plexitis was graded according to the classification proposed by Ferrante *et al*[8]: Mild plexitis if the ganglion or nerve bundle contained 0-4 inflammatory cells (G_1), moderate plexitis if it contained 4 to 9 cells (G_2), or severe if containing $\geqslant$ 10 cells (G_3). Evaluation was performed independently for each cellular type: Mast cell, plasmocyte, lymphocyte, eosinophil and neutrophil cell counts were also evaluated[12]. Each sample was fixed in buffered formalin and analyzed using hematoxylin-eosin staining. Some examples are demonstrated in Figure 1.

Table 1 Patient characteristics *n* (%)

Baseline characteristics of patients	*n* = 104
Mean age at diagnosis (yr)	41.3 ± 14.047
Mean disease duration at the time of the operation (yr)	6.25 ± 6.12
Sex	
Female	50 (48)
Male	54 (52)
Age at index resection (yr)	
Younger than 40	74 (71.2)
40 and older	30 (28.8)
Smoking history at index surgery	
Current smoker	32 (30.8)
Never smoked	68 (65.4)
Ex-smoker	4 (3.8)
Montréal classification	
A1 (< 16 yr)	15 (14.4)
A2 (between 17 and 40 yr)	71 (68.3)
A3 (> 40 yr)	18 (17.3)
B1 (nonstricturing, nonpenetrating)	12 (11.5)
B2 (stricturing)	52 (50)
B3 (penetrating)	40 (38.5)
L1 (isolated ileal disease)	51 (49)
L2 (isolated colonic disease)	22 (21.2)
L3 (ileocolonic disease)	31 (29.8)
L4 (isolated upper disease)	0 (0)
p (perianal disease modifier)	14 (13.5)
Type of index resection	
Ileocolonic resection	76 (73.1)
Colonic resection	23 (22.1)
Small bowel resection	5 (4.8)
Previous resection before index surgery	26 (25)

Statistical analysis

The statistical analysis of the data was performed by a biomedical statistician using SPSS. To identify predictors of postoperative recurrence (clinical recurrence or surgical recurrence) among patients' baseline characteristics, histological findings such as severity of myenteric and submucosal plexitis univariable logistic regression analysis was used. *P* values < 0.05 were considered statistically significant. Survival was examined with the Kaplan-Meier method.

RESULTS

Patient characteristics

One hundred and four patients with CD were enrolled in the study. The baseline characteristics of the patients are reported in Table 1. Mean age at index CD-related surgery was 34.8 ± 13.24 years, mean disease duration at the time of the index surgery was 6.25 ± 6.12 years. 86.5% of the patients were on specific CD-related treatment at the time of the index surgery; 37.5% of patients were on aminosalicylates, 13.5% on anti-TNF-α therapy, 51% on corticosteroid, 12.5% on budesonide, 43.3% on azathioprine, 6.7% on methotrexate, and 35.6% on antibiotics. Operations were performed for specific reasons: abscess (20.2%), fistulas (13.5%), perforation (4.8%), stenosis (67.3%) and other (1%). Ileocecal, colonic and small bowel

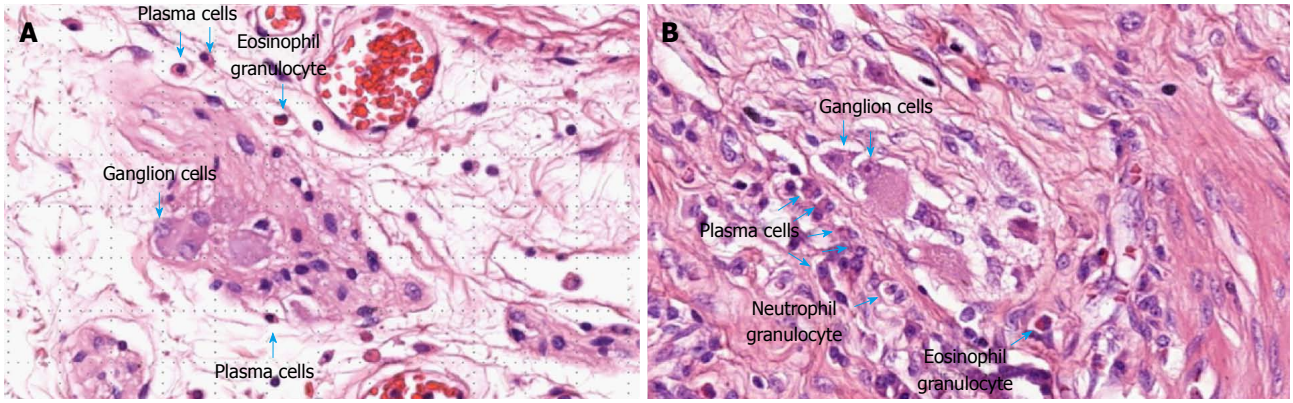

Figure 1 Submucosal plexitis (A) with plasma cells, eosinophil granulocyte surrounding the ganglion cell (hematoxylin-eosin staining); and myenteric plexitis (B) with plasma cells, neutrophil granulocyte, eosinophil granulocyte surrounding the ganglion cell (hematoxylin-eosin staining) in a Crohn's disease resection specimen.

resection were performed in 73.1%, 22.1% and 4.8% of the cases, respectively. Twenty-six patients had undergone previous CD-related surgery. Forty-three point two percent of the patients were on 5-aminosalicylate, 20% on corticosteroid, 68.3% on immunomodulant, and 4% on anti-TNF-α postoperative treatment. Postoperative recurrence occurred in 61.5% of the patients; of them 39.1% had surgical recurrence. 92.2% of the recurrences developed within the first five years after the index surgery. Mean disease duration for postoperative relapse was 2.70 ± 2.11 years.

Histological findings

Typical Crohn's lesions, such as inflammatory cell infiltration, architectural alterations, crypt abscesses, ulcers, and granulomas were detected in both resection margins. Typical CD lesions were found in proximal resection margins (5.8%), distal resection margins (5.8%), and in both resection margins (16.3%). Neural fiber hyperplasia was present in 37.5% of proximal resection margins. The pathological examination focused on proximal resection margins with quantitative evaluation of myenteric and submucosal plexitis. Inflammatory cell count (mastocyte, plasmocyte, lymphocyte, eosinophil and neutrophil granulocyte) for myenteric and submucosal plexuses are summarized in Table 2. Median severity of submucosal plexitis was 1 and median severity of myenteric plexitis was 2. Submucosal plexitis was mainly constituted by lymphocytes (median: 2), while myenteric plexitis was mainly constituted by lymphocytes (median: 2) and plasmocytes (median: 2). Other cell types, such as mastocytes, eosinophils and neutrophil granulocytes were less frequently observed.

We found that perianal disease [odds ratio (OR) = 3.78, 95%CI: 1.164-12.312, P = 0.027] and female gender (OR = 2.21, 95%CI: 0.98-5.00, P = 0.056) are risk factors for postoperative relapse. Stricturing disease behavior (OR = 3.584, 95%CI: 1.344-9.559, P = 0.011) and isolated ileal disease localization (OR = 2.671, 95%CI: 1.033-6.910, P = 0.043) increased the risk of second surgery. Stricturing disease behavior (OR = 6.417, 95%CI: 0.999-41.212, P = 0.050) and ileocecal disease (OR = 6.00, 95%CI: 0.832-43.293, P = 0.076) also increased the risk of relapse in previously operated CD patients.

Higher lymphocyte cell count in the submucosal plexus was a risk factor for surgical or clinical relapse (OR = 1.267, 95%CI: 1.000-1.606, P = 0.050). Moderate submucosal plexitis reduced the risk of second surgery by 85.4% compared to severe submucosal plexitis (OR = 0.146, 95%CI: 0.029-0.738, P = 0.020). No association was revealed between postoperative recurrence and smoking status, postoperative prophylactic treatment and the presence of myenteric plexitis and relapse. Figure 2 shows the survival probability without a second CD-related surgery and the probability without clinical recurrence.

DISCUSSION

We have demonstrated that severity of submucosal plexitis in proximal resection margins, perianal manifestation and stricturing disease behavior, as well as isolated ileal disease were all associated with postoperative recurrence. Over the last few years, several studies focused on plexitis and its role in the postoperative recurrence of CD. Ferrante *et al*[8] demonstrated that inflammation of the myenteric plexus was significantly associated with postoperative CD endoscopic recurrence; moreover they found a positive correlation between the severity of the inflammatory infiltration of the plexus and the severity of endoscopic recurrence. These data are in concordance with the findings of recent studies: Misteli *et al*[9] revealed that severe myenteric plexitis at the proximal resection margin is associated with surgical resection; Ng *et al*[10] demonstrated that myenteric plexitis can be present in otherwise uninvolved proximal resection margins. Sokol *et al*[11] demonstrated an association between submucosal plexitis and early clinical recurrence; they found that mast cell-associated submucosal plexitis

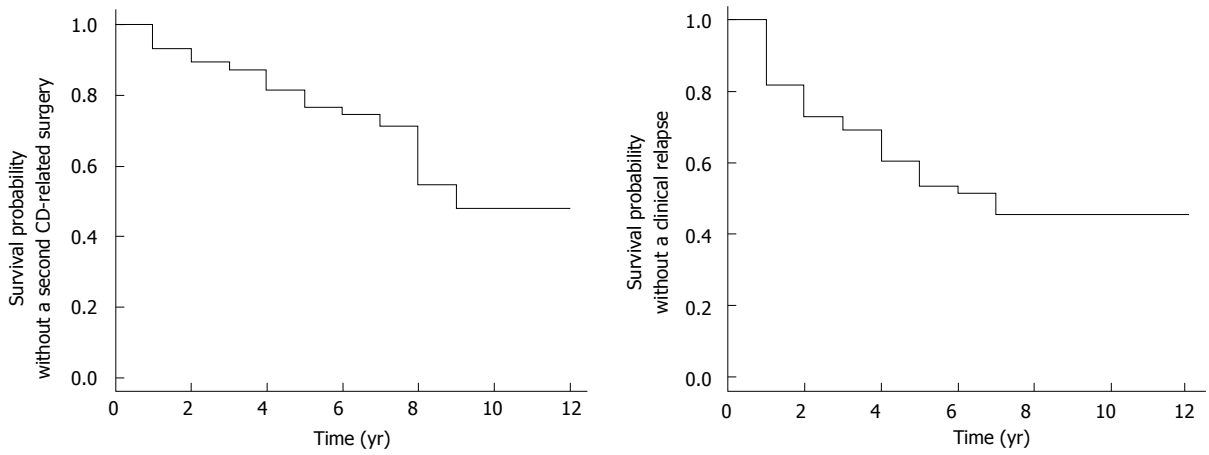

Figure 2 Shows the survival probability without a second Crohn's disease-related surgery and the probability without clinical recurrence with the Kaplan-Meier method. CD: Crohn's disease.

Table 2 Inflammatory cell count of histopathological findings (*n* = 104)

	Median	IQR, 25th to 75th
Myenteric plexus		
Eosinophils	0	0-1
Lymphocytes	2	1-4
Neutrophils	0	0-0
Plasmocytes	2	1-3
Mastocytes	0	0-0
Submucosal plexus		
Eosinophils	0	0-0
Lymphocytes	2	1-3
Neutrophils	0	0-0
Plasmocytes	1	0-3
Mastocytes	0	0-0

in proximal resection margins is a predictor of early postoperative clinical recurrence. Aude *et al*[12] revealed that submucosal plexitis of > 0 eosinophils and/or > 6 lymphocytes in proximal resection margins and early surgical revision after the first ileocecal resection are predictive of a second surgery in CD; Lemmens *et al*[13] found that submucosal lymphocytic plexitis in the proximal surgical margin was significantly associated with a higher risk of endoscopic recurrence after ileocolonic resection. All these studies found that plexitis is more frequent in the proximal resection margin, but data on the prognostic value of histological factors in postoperative CD recurrence are conflicting. This is the reason why we used a comprehensive approach by analyzing all inflammatory cell types in both submucosal and myenteric plexuses in proximal resection margins. Data of the most severely inflamed plexus were involved in the study.

Studies found myenteric plexitis in 42.5%-69.7%-88% of proximal surgical margins[8-10]. We could evaluate myenteric and submucosal plexitis of different severity in every sample, in accordance with Aude *et al*[12], while the rate of typical CD-lesions was low (5.7%) in proximal resection margins. A higher lymphocyte cell count in the submucosal plexus was a risk factor for surgical or clinical relapse (P = 0.050), while moderate submucosal plexitis reduced the risk of a second surgery by 85.4% compared to severe submucosal plexitis (P = 0.020), which is in accordance with other studies. No association was revealed between postoperative recurrence and the presence of myenteric plexitis.

We found no relationship between the presence of granulomas and clinical or surgical recurrence; however, we could find granulomas only in approximately half of the samples. A few studies found a positive association between the presence of granulomas and the likelihood of recurrence or a more aggressive disease process[16-18], while other studies suggested the opposite[19,20]. It has also been reported that the need for immunosuppressive therapy and surgical interventions were significantly higher in patients with granulomas.

We found no association between postoperative recurrence and neural hypertrophy. Ferrante *et al*[8] found that patients who had both neural hypertrophy in the terminal ileum and myenteric plexitis in the proximal resection margin had a tendency to develop a higher endoscopic recurrence rate compared with patients who only had myenteric plexitis.

Postoperative recurrence occurred in 61.5% of patients with a median duration of 2 years between the index surgery and relapse; of them 39.1% had surgical recurrence. Ninety-two point two percent of the recurrences occurred within five years. Our data are similar to previously published data: Surgical recurrence was reported in 11%-32% of patients at 5 years[21]. Mean disease duration for endoscopic relapse on the basis of the Rutgeerts score was 2.70 years. Postoperative recurrence was divided into two groups on the basis of the paper of Ng *et al*[10] Clinical recurrence was defined as the presence of CD-related symptoms associated with radiologic or endoscopic findings considered severe enough to change the current therapy (requires steroid treatment or an increase in existing treatment). Surgical recurrence was defined as a need for further operation if the

disease was refractory to medical treatment or new complications developed.

No association was revealed between postoperative recurrence and preoperative or postoperative prophylactic treatment. Forty-three point two percent of patients were on 5-aminosalicylate, 20% on corticosteroid, 68.3% on immunomodulant, and 4% on anti-TNF-α postoperative treatment. 5-aminosalicylic acid (5-ASA) has been extensively studied in the postoperative management of CD. Studies showed that the early administration of oral mesalazine following surgery is effective in preventing postoperative endoscopic recurrence in CD over a 2-year period[22] and it can also decrease the rate and severity of endoscopic recurrences[23]. In a meta-analysis, 5-ASA significantly reduced the risk of symptomatic relapse[24]. In a prospective, open-label randomized study, azathioprine was more effective than mesalazine in preventing clinical relapse in patients with previous intestinal resections[25]. These studies suggest that 5-ASA is safe in postoperative CD prophylaxis, even if it seems to provide only a small reduction in clinical and endoscopic recurrence[26].

Our study has certain limitations including its retrospective nature, although it is one of the largest series looking at myenteric and submucosal plexitis. As the course of CD may differ from one patient to another, many studies have looked for potential predictors of CD recurrence as these can modify the intensity of surveillance and the type of medical therapy.

In conclusion, the presence of severe submucosal plexitis with lymphocytes in the proximal resection margin is more likely to result in postoperative relapse. Postoperative assessment of plexitis could be performed routinely by every pathologist in every center as proximal resection margins are systematically analyzed. This requires no special immunostaining. Histological analysis of the proximal resection margin may be useful when making a decision on early postoperative treatment without a postoperative follow-up colonoscopy, thus possibly modifying the natural course of CD. However, further studies with a prospective design and a longer follow-up period are needed.

COMMENTS

Background

Crohn's disease (CD) can affect the entire gastrointestinal tract, but the most commonly affected sites are the ileum and the ascending colon. More than 70% of all patients with CD require surgery in the course of their disease, which is not curative; the disease recurs in most cases. Currently, there are no reliable tools to predict when and in whom the disease will recur.

Research frontiers

In the last decade, particular attention was paid to histological features to assess the risk of postoperative relapse (POR). Inflammatory changes in the enteric nervous system (myenteric and submucosal plexus) of the resection margins are probably the most promising factors.

Innovations and breakthroughs

The authors confirmed the significant value of investigating the presence of submucosal plexitis in the proximal resection margin of ileo-colonic resection specimens; the severity of submucosal plexitis (higher lymphocyte cell count in the submucosal plexus) was a risk factor for surgical and clinical POR of CD. These investigations can be performed by analyzing proximal resection margins with routine staining.

Applications

All available data, including ours, suggest that lymphocyte cell count plays the most important role in predicting the POR of CD. Routine histological analysis of the proximal resection margin for submucosal plexitis can be useful to stratify patients according to their risk to decide the need for early postoperative treatment.

Terminology

POR was defined as the reappearance of lesions after complete surgical resection. Clinical recurrence was defined as the presence of CD-related symptoms associated with radiologic or endoscopic findings, considered severe enough to change the therapy (requires steroid treatment or an increase in existing treatment). Surgical recurrence was defined as a need for further operation.

Peer-review

In the article, the clinical and pathological data of 140 postoperative patients with CD were analyzed, so as to study the risk factors of postoperative recurrence of CD.

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MINIREVIEWS

Abdominal tuberculosis: Is there a role for surgery?

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Abstract

It is important that surgeons are familiar with the various manifestations of tuberculosis (TB). Although TB has been declining in incidence in the developed world, it remains an important problem in endemic areas of the developing world. The aim of the review was to elucidate the natural history and characteristics of abdominal TB and ascertain the indications for surgery. TB can affect the intestine as well as the peritoneum and the most important aspect of abdominal TB is to bear in mind the diagnosis and obtain histological evidence. Abdominal TB is generally responsive to medical treatment, and early diagnosis and management can prevent unnecessary surgical intervention. Due to the challenges of early diagnosis, patients should be managed in collaboration with a physician familiar with anti-tuberculous therapy. An international expert consensus should determine an algorithm for the diagnosis and multidisciplinary management of abdominal TB.

Key words: Tuberculosis; Peritoneal; Intestinal; Surgery; Anti-tuberculous therapy

Core tip: It is important to bear in mind the non-specific manifestations of abdominal tuberculosis. There is no gold standard for the diagnosis and high clinical suspicion is required. Diagnostic laparoscopy is increasingly useful but joint decision making with physician familiar with anti-tuberculous therapy is important. Surgery is reserved for abdominal complications.

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INTRODUCTION

Abdominal tuberculosis (TB) continues to represent a diagnostic challenge to clinicians[1]. The abdomen is involved in 10%-30% of patients with pulmonary TB and

accounts for between 5% and 10% of TB notifications in the United Kingdom. Greater than 75% of cases occur in immigrants, with most coming from the Indian sub-continent[2,3]. There is a slight male predominance in abdominal TB with a peak incidence in the 4th and 5th decades in the immigrant population, and in the elderly in the United Kingdom[3,4]. In the United States, among native-born white Americans, abdominal TB is primarily a disseminated disease of elderly, debilitated patients with chronic illnesses. Among foreign-born individuals, abdominal TB occurs in the young, immunocompetent patients from endemic areas[5]. The diagnosis is thus difficult and often delayed[6]. Surgeons must be aware of the wide clinical spectrum of abdominal TB and have a high index of suspicion when confronted with patients from an endemic area presenting with unclear abdominal symptoms[2,6]. The aim of the review is to offer an opinion on the role of surgery in abdominal TB and stimulate debate in an area of ongoing interest.

PATHOGENESIS AND PATHOLOGY

The principal forms of abdominal TB are intestinal and peritoneal but a third form - nodal - is also recognized. In practice, the various forms may coexist[6,7]. In the past, many cases of abdominal TB occurred as a direct result of the ingestion of *Mycobacterium bovis* in unpasteurized milk. In most cases today intestinal TB is due to reactivation of primary disease caused by *Mycobacterium tuberculosis*. The reactivation of *Mycobacterium tuberculosis* and the atypical opportunistic *Mycobacterium avium* intracellulare infection in the acquired immune deficiency syndrome have a poor prognosis because of immunosuppression[8-11]. TB bacteria reach the gastrointestinal tract *via* haematogenous spread (from a pulmonary focus acquired during primary infection in childhood), ingestion of infected sputum, or direct spread from infected contiguous lymph nodes and fallopian tubes. Swallowed bacilli pass through the Peyer's patches of the intestinal mucosa and are transported by macrophages through the lymphatics to the mesenteric lymph nodes where they remain dormant. Reactivation of disease in these nodes especially in the immunocompromised including diabetes, renal failure and malignancy may lead to abdominal TB, with the spread of the bacteria to the peritoneum or intestine[4]. Intestinal TB can involve any part of the alimentary tract (from oesophagus to the anus)[2,11]. Gastro-duodenal TB is uncommon (1%) due to the bactericidal properties of gastric acid, scarcity of lymphoid tissue in the mucosa and rapid emptying of gastric contents[12]. The ileocaecal region is the most common site of involvement (75%) because of increased physiological stasis, fluid and electrolyte absorption, minimal digestive activity and abundance of lymphoid tissue (Peyer's patches)[12]. TB of the ileocaecum presents usually with a palpable mass in the right iliac fossa. Perianal disease with abscesses and fistulas can occur, but is uncommon[3,7]. The naked eye appearance of intestinal TB may resemble Crohn's disease, with skip lesions. The gross pathology is characterized by transverse ulcers, fibrosis, thickening and stricturing of the bowel wall, enlarged and matted mesenteric lymph nodes, omental thickening, and peritoneal tubercle (Figure 1). The histology shows numerous granulomas which are not always caseating, and, often, acid-fast bacilli cannot be found if there is low mycobacterial load (Figure 2)[7,13,14]. Tuberculous peritonitis is usually due to reactivation of a tuberculous focus in the peritoneum with concurrent pulmonary, intestinal or genital TB (especially from the fallopian tubes). This is usually seen in debilitated patients and alcoholics[6,7]. Peritoneal TB occur in three forms: Wet type with ascites, dry type with adhesions, and fibrotic type with omental thickening and loculated ascites[14]. Peritoneal TB is characterized by tubercles that appear as white "seedlings" on the parietal and visceral surfaces of the peritoneum. Inflammation and exudation leads to the formation of straw-coloured ascites (Figure 3). When there is associated infiltration and thickening of the omentum, intestinal walls, and formation of caseous masses it is referred to as "plastic" peritonitis[15-17]. *Mycobacterium tuberculosis* can spread to the genital tract *via* the blood or lymphatics. Granulomata develop in the tubes and subsequently the other genital organs. The endometrium is involved

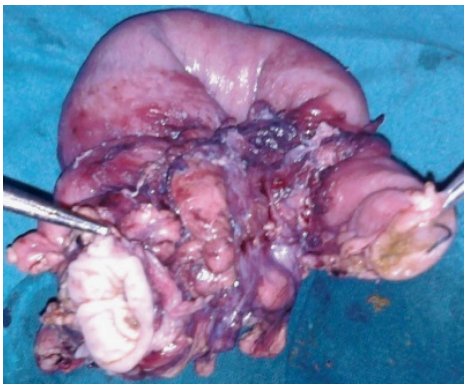

Figure 1 Intestinal tuberculosis (ileocaecal) (with permission from Chumber *et al*[51], 2001).

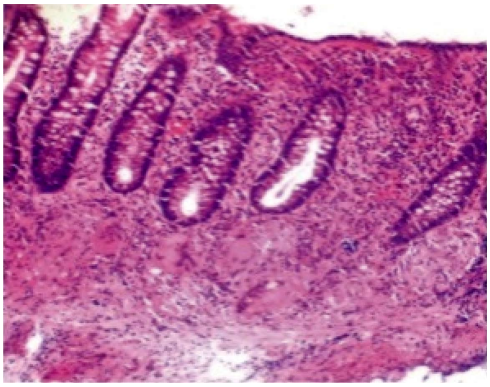

Figure 2 Histopathology (H/E stain): Showing multiple mucosal and submucosal epitheloid cell granulomas with Langhan's giant cells in a case of colonic tuberculosis (with permission from Tandon *et al*[35], 1972).

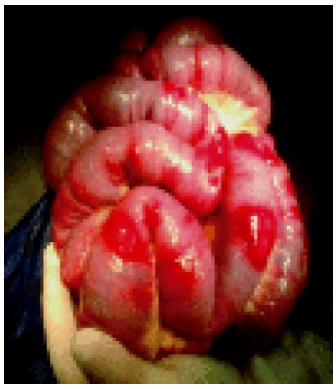

Figure 3 Peritoneal tuberculosis (with permission from Bolognesi *et al*[43], 2013).

in up to 80% of cases and the ovaries in 20%-30%[15]. Fillion *et al*[11] reported in a low incidence country that the main organs involved were the peritoneum (66%), the mesenteric lymph nodes (62%), and the bowel (33%). Atypical presentation of peritoneal TB such as portal vein thrombosis from encasement, with splenomegaly and ascites can delay diagnosis or result in misdiagnosis[14]. Half (50%) of HIV patients with TB have extrapulmonary involvement, compared with only 10%-15% of TB patients who are not infected with HIV[7]. In HIV-infected patients abdominal TB is of a rapidly progressive nature, often fatal though usually treatable.

CLINICAL FEATURES

The clinical symptoms and signs of abdominal TB are non-specific and the diagnosis may be overlooked or mistaken for other disease processes[2]. The clinical picture is different in children to that in adults. About 90% of the features of abdominal TB in children are due to involvement of the peritoneum and lymph nodes and 10% related to intestinal lesions[4-6]. Abdominal pain is common, accompanied by ascites (75%) or an abdominal mass caused by an inflamed mesentery (30%)[2,3]. The most common signs are abdominal tenderness and hepatosplenomegaly. Patients with the "plastic" type of peritoneal TB may have a characteristic "doughy" abdomen but this form is, however, uncommon today[16,17]. Usually the onset of tuberculous peritonitis is insidious with fever, anorexia and weight loss. In a high prevalent area in sub-Saharan Africa, the common presenting symptoms and signs were abdominal pain 76.6%; ascites 59.6%; weight loss 53.2% and fever 29.8%. The average duration of symptoms before presentation was 3 mo and 13% of patients had earlier been treated for pulmonary TB[10].

Intestinal TB presents in a variety of ways. Up to 30% of cases may present as an acute abdomen, either with acute intestinal obstruction or with symptoms and signs suggestive of an acute appendicitis from an obstructing TB lymphadenopathy[11]. Hypertrophic ileocaecal TB is particularly common in the Indian subcontinent as a cause of intestinal obstruction. It must be distinguished from Crohn's disease which is rare in most tropical countries[14]. Tuberculous enteritis may, if the patient recovers, lead to stenotic lesions causing small bowel obstruction[18]. Intestinal perforation and acute bleeds do occur, but are unusual. Classically malabsorption from strictures and sometimes with steatorrhoea, can result from TB of the small intestine, and occasionally when the terminal ileum is involved, patients present with anaemia due to vitamin B_{12} deficiency[14]. Some cases present with disturbance of bowel habit, usually diarrhoea. The remainder of patients with intestinal TB have vaguer symptoms and signs, such as weight loss, malaise and abdominal tenderness. A few patients with only nodal disease present with an abdominal mass consisting of enlarged mesenteric lymph nodes[2,6]. As many as 60% of patients with abdominal TB have evidence of TB elsewhere. Chest X-ray, however, show evidence of concomitant pulmonary lesions in less than 25% of cases[10,11,19,20]. Genitourinary TB may present in a similar manner to pelvic inflammatory disease (PID), with chronic low-grade pelvic pain and ultimately with amenorrhoea and infertility. Abnormal uterine bleeding is a presenting symptom in 10%-40% of patients[15]. Examination is normal in many women but an adnexal mass or fixing of the pelvic organs may be detected[21]. It should be noted that the human immunodeficiency virus (HIV) may alter the manifestations of, and host susceptibility to, other infections[9,15,21]. Other rare clinical presentations include dysphagia, odynophagia and a mid oesophageal ulcer due to oesophageal TB; dyspepsia and gastric outlet obstruction due to gastroduodenal TB; lower abdominal pain and rectal bleeding due to colonic TB; and annular rectal stricture and multiple perianal fistulae due to rectal and anal involvement[2,6].

INVESTIGATIONS

Neither clinical signs, laboratory, radiological and endoscopic methods nor bacteriological and histopathological findings provide a gold standard by themselves in the diagnosis of abdominal TB[10]. The clinical awareness is thus primary[10,22]. Most laboratory tests are unhelpful. The erythrocyte sedimentation rate (ESR) is often moderately raised in 79% of patients, and although there may be a mild normochromic, normocytic anaemia, a leucocytosis is uncommon. Hypoalbuminaemia is not uncommon but liver function tests are usually normal[11,23]. Abdominal TB has a multitude of possible presentations and requires a diagnostic approach adjusted to the individual presentation. This approach should be as little invasive as possible and be based on the best available imaging. Ultrasound scans of abdomen were abnormal in 68%, showing ascites, hepatomegaly and or enlarged nodes. Computed tomography (CT) was the most frequent imaging modality (88%) in the United States. The

findings suggestive of abdominal TB were mesenteric/omental stranding (50%), ascites (37%), and retroperitoneal lymphadenopathy (31%). Seventeen of 18 patients required operative intervention, and one patient underwent CT-guided drainage of a psoas abscess[20]. Mantoux test was positive in 33% and ascitic fluid was diagnostic for TB in 29%. Thus, a positive tuberculin skin test (*e.g.*, Mantoux) may be helpful, though some series have found less than 50% of the cases of proven abdominal TB to be tuberculin positive[23]. Chest X-ray showed abnormal findings in 25% of the patients suggesting past or present pulmonary TB and sputum was positive for acid-fast bacilli (AFB) in 14.3%[10]. A high index of suspicion is, required for the diagnosis of peritoneal TB as the analysis of peritoneal fluid for tuberculous bacilli is often ineffective and may cause mortality due to delayed diagnosis. Examination of the ascitic fluid usually reveals an exudate (protein > 25 g/L) and a raised white blood cell count (WBC) > 0.1×10^9/L consisting principally of lymphocytes. A direct stain for acid-fast bacilli is positive in less than 5% of cases, though up to 40% will be positive if the ascitic fluid is cultured. By centrifuging large volumes of ascitic fluid and culturing the sediment, the diagnostic yield may be increased to up to 80%[23,24]. However, tuberculous peritonitis-associated mortality is high among patients waiting for the results of mycobacterial culture of ascitic fluid samples[24]. Direct stains and culture of stool specimens may sometimes be positive, but the yield is generally low[23]. Barium studies may show some abnormality in about 50% of patients with intestinal TB but are not diagnostic[25]. To confirm the diagnosis, it is important to try to obtain material for culture and histology. As culture may take up to 6 wk, the histological evidence is important. There are a variety of ways of obtaining tissue for histology. Colonoscopy may be useful. Biopsy specimens obtained during colonoscopy of the terminal ileum and ileocaecal valve may show active chronic ileocolitis with ulceration and granuloma formation[25]. Invasive procedures are frequently necessary to obtain samples but also for the treatment of digestive involvement[11]. In light of new evidence, peritoneal biopsy through laparoscopy has emerged as the gold standard for diagnosis and both lymphoma and carcinomatosis can be excluded by this means[26]. Laparoscopy is most reliable as it is minimally-invasive effective modality for diagnosis of peritoneal TB, and can be performed under local anaesthesia. It is rapid, safe, greater than 75% accuracy in diagnosis and spares the patient the discomfort of a laparotomy[11,27]. It allows the biopsy of the typical studded tubercles of the peritoneum and other organs which are sent for culture and histology. However, laparoscopy is costly and is not available in many of the poorer areas of the world. Blind percutaneous peritoneal biopsy with an Abrams or Cope needle biopsy usually in the left lower quadrant just lateral to the rectus muscle is diagnostic in up to 75% of cases of peritoneal TB[3]. The complications of the procedure albeit uncommon include intestinal perforation, bleeding and infection. Thus, for this to be safe, the patient must have clinically detectable ascites. The diagnostic yield can be increased if the peritoneum is exposed by dissection under local anaesthesia[11]. Some patients with abdominal TB without ascites have the diagnosis confirmed indirectly by culture and histology of percutaneously biopsied liver tissue with hepatic TB[3,16]. Diagnostic laparotomy may be resorted to where endoscopic procedures are not available or when they fail to give a definite histopathological diagnosis or for an undiagnosed abdominal mass[16]. While laparotomy will reveal the diagnosis in patients with abdominal TB who present with an acute abdomen, the procedure may be hazardous in sick, emaciated patients with malabsorptive syndrome. It is also not always accurate for the "cold" cases[28] and laparotomy should, thus, essentially be performed only when complications of abdominal TB develop[29]. The suspicion of genitourinary TB in a woman from an endemic area with bilateral tubal calcification from chronic infection seen on abdominal X-ray or radiographic evidence of pulmonary TB should be confirmed if possible, by positive culture of the organisms in endometrial tissue obtained from biopsy or dilatation and curettage[13-15]. Endometrial biopsy does not have 100% sensitivity but the detection rate is greatest towards the end of the menstrual cycle. A Mantoux or Heaf test should be reactive in a woman with active TB unless she is immunosuppressed. The enzyme-linked immunoabsorbent assay (ELISA) using mycobacteria saline-extracted antigen for the serodiagnosis of abdominal TB gives a diagnostic accuracy of 84%[16,23]. Another test for early diagnosis of tuberculous peritonitis is the determination of adenosine deaminase activity (ADA) in the peritoneal fluid[1,13]. New diagnostic procedures, and especially molecular biology-polymerase chain reaction (PCR), may help diagnose unusual clinical presentations of TB[11,23]. As abdominal TB should be considered in all cases with ascites. PCR of ascitic fluid obtained by ultrasound-guided fine needle aspiration is a reliable method for its diagnosis and should at least be attempted before more invasive interventions[13,30].

DIFFERENTIAL DIAGNOSIS

Abdominal TB, with its vague symptoms and signs and non-specific laboratory investigations, can mimic many other diseases (Table 1). The main differential diagnosis to consider with intestinal TB is Crohn's disease. Crohn's disease is uncommon in the immigrant population at risk for TB, and in Caucasians its peak incidence occurs in the 20-40 age group, while that of intestinal TB is in the older age group (50-70 years)[5]. Although perianal disease and enteric fistulas can be due to TB, this is uncommon in comparison with Crohn's disease. Distinguishing between these two entities is a challenge because there is marked overlap in the clinical presentation and the radiographic, laboratory, and endoscopic findings, as well as in the

Table 1 Differential diagnosis of abdominal tuberculosis

Intestinal TB	Peritoneal TB
Crohn's disease	Carcinomatosis
Intestinal lymphoma	Bacterial peritonitis
Carcinoma	Talc peritonitis
Yersinia infections	Chronic liver diseases
Amoeboma	

TB: Tuberculosis.

presence of granulomas on histological examination[31-33]. Misdiagnosis of Crohn's disease in a patient with intestinal TB would result in treatment with steroids and biologic agents, which then has the potential to cause disease progression that leads to increased morbidity and mortality[34]. Misdiagnosis of intestinal TB in a patient with Crohn's disease would lead to prolonged anti-tuberculous therapy and delay the necessary immunosuppression required to induce disease remission[35]. Both diseases have an insidious onset but diarrhoea, rectal bleeding and extraintestinal manifestations are more common in patients with Crohn's disease. Intestinal TB can target extrapulmonary sites in a manner that resembles the classic extraintestinal manifestations of Crohn's disease, such as reactive arthritis, erythema nodosum, and uveitis[36]. Ascites and fever are more commonly seen in patients with intestinal TB. Both diseases involve the ileum and colonic segments of the bowel. Isolated involvement of the terminal ileum is commonly seen in patients with Crohn's disease (terminal ileitis), whereas involvement of the ileocaecal area and a patulous ileocecal valve is seen in patients with intestinal TB (ileo-caecal TB). In patients with Crohn's disease, mucosal injury has a cobblestone appearance with aphthous and longitudinal rake ulcers, whereas in patients with intestinal TB, the ulcers are transverse in orientation[37-39]. Furthermore, the granulomas associated with intestinal TB are more frequent and confluent and larger than those associated with Crohn's disease. As tissue samples are positive for acid-fast bacilli in only 25% to 30% of cases of intestinal TB, the use of molecular techniques such as PCR assays of fresh biopsy specimens, can improve the diagnostic yield[28,40]. Makharia *et al*[38] interestingly developed a scoring system for differentiation of CD and intestinal TB based on clinical endoscopy and histology using the findings of sigmoid colon involvement, blood in stools, weight loss and focally enhanced colitis. Other differential diagnoses are carcinoma, lymphoma, *Yersinia* infections and, in some parts of the world, amoeboma[3]. Peritoneal TB must be differentiated from carcinomatosis, talc peritonitis, bacterial peritonitis, and from ascites due to heart failure or liver disease (Table 1). Although ascites due to cardiac failure is usually easy to distinguish, it is important to realize that there is an increased incidence of abdominal TB in alcoholics, and that liver disease with ascites may coexist with peritoneal TB and the ascites may not have the characteristics of an exudate[5,19]. Some patients may therefore warrant a laparoscopy or diagnostic laparotomy for atypical diagnostic problems especially as diseases such as CD, lymphoma and malignancy can mimic TB in every way[26-28].

MANAGEMENT

Most patients with abdominal TB respond to medical treatment with standard anti-tuberculous chemotherapy and carries good prognosis if promptly diagnosed and treated[8,26]. The drug treatment is identical to pulmonary TB with conventional chemotherapy for at least 6 mo. Rifampicin and isoniazid are given for 6 mo, with two additional drugs-pyrazinamide and streptomycin (given at a dose of 0.75-1.0 g daily depending on body weight, age and renal function) for the first 2 mo[16]. The main cause of failure in medical treatment in the endemic and developing countries is patient defection or poor compliance[10]. Shorter and more effective regimes, based on rifampicin that can be completed in 6 mo have increased patient compliance[16]. For patients in whom the diagnosis is strongly suspected, but for whom the histological proof is unobtainable or inconclusive, it is justifiable to undertake a trial of anti-tuberculous therapy[10,41]. Akinkuolie *et al*[10], reported that 85.1% of patients with clinically diagnosed abdominal TB in a high prevalent area recovered after receiving anti-tuberculous therapy for a period of 9-12 mo. However, all those with HIV infection and not on antiretroviral treatment died from immunosupression[8,10]. A few patients who developed adhesions, obstruction or perforation at some time following chemotherapy required surgery[7]. Intravenous anti-TB therapy in combination with surgery may be needed for severe forms of TB with extensive gastrointestinal involvement[42].

ROLE OF SURGERY

Surgery is essentially reserved for those with acute surgical complications including free perforation, confined perforation with abscess or fistula, massive bleeding, complete obstruction, or obstruction not responding to medical management[6,11,26,27]. Obstruction is the most common complication with multiple and/or long strictures less likely to respond to medical therapy[40,43]. The obstruction may also be exacerbated during anti-tuberculous therapy due to healing by cicatrisation[40]. About 20%-40% of patients with abdominal TB present with an acute abdomen and need surgical management[44]. Chronic patients with subacute obstruction are managed conservatively and surgery is planned after suitable work-up[45]. Being a systemic disease surgical resection should be conservative. Multiple small bowel strictures may be treated by strictureplasty to avoid major resection[46-48]. An alternative is colonoscopic balloon dilatation of readily accessible, short and fibrous tuberculous ileal strictures causing subacute obstructive symptoms. Although the experience is very limited, this technique appears safe and may obviate the need for surgery in this setting[49]. Acute tubercular peritonitis

and mesenteric lymphadenitis need to be managed with caution. If a laparotomy is carried out only a biopsy needs to be performed with peritoneal toilet and the abdomen closed without a drain[50].

The surgery performed in gastrointestinal TB are essentially of three types[14]. The first type is the surgery which is done to bypass the involved segments of bowel such as an enteroenterostomy or an ileotransverse colostomy. As in Crohn's disease, these surgeries are usually complicated by blind loop syndrome, fistula formation and recurrent disease in the remaining segments and hence usually not performed routinely. The second type are segmental resections such as the limited ileo-caecal resection for obstructing ileo-caecal TB with adjuvant anti-tuberculous therapy to eradicate the disease completely[47,51]. However, these surgeries are hindered by the malnourished status of most of the patients which make them poor surgical candidates. Also the lesions can be widely placed and extensive resection may not be possible in all the cases. Postoperative complications include anastomotic leak, faecal fistula, peritonitis, intraabdominal sepsis, persistent obstruction, wound infection and dehiscence[47,48,52]. Re-operation may be required for recurrent obstruction. The third type of surgery is bowel conserving strictureplasty of those stenotic lesions with obstructive symptoms[18,47,48]. Strictureplasty for cases with multiple strictures was introduced as a better technique than multiple resections and enteroanastomoses, as it does not sacrifice any part of the small bowel and avoids the risk of short-bowel syndrome or blind loops[53]. Long strictures with active inflammation or multiple strictures in a segment may require resection unless there is concern about bowel length[18]. With adjuvant anti- tuberculous therapy, microscopic disease at the resection margin should not influence recurrence of disease[14,18-20,54]. The Heineke-Mikulicz pyloroplasty technique is usually used. In a small number of cases with longer strictures where bowel conservation is required, a Finney or a Jaboulay strictureplasty may be used[17-19]. Strictures of recent onset that are not very tight may be left alone, or dilated *via* an enterotomy[53,54]. Tubercular perforations are mostly ileal and proximal to a stricture. If they are close to one another, resection of the segment is performed. If the stricture is not close, the perforation can be closed in layers and the stricture dealt with by strictureplasty or resection, depending on the length of the narrowed segment. Delayed diagnosis and injudicious treatment are responsible for the mortality rate of 4%-12%[50]. The high mortality was partly associated with malnutrition, anaemia and hypoalbuminaemia, the mortality being higher (12%-25%) in the presence of acute complication[47].

Fillion *et al*[11]'s study in a low prevalence country reported that out of 86% presenting with abdominal symptoms, 76% underwent surgery, with 10% in an emergency setting. 81% of patients received six months or more of anti-TB treatment. Seventy-six percent had a positive outcome. Wani *et al*[30] reported a study on surgical emergencies of tubercular abdomen in developing countries. Abdominal pain, vomiting, and constipation were commonest presenting symptoms. About 20% patients had history of pulmonary TB and 16% patients presented with ascites. PCR for blood and ascitic fluid was positive in 72% and 87.5% patients, respectively. As in the low prevalence developed country, the indications and principles of management were the same. About 24% of patients were managed non-operatively and responded to anti-tuberculous therapy. Seventy-six percent needed surgery among which 20% were operated as emergency. Adhesiolysis of gut (47.3%), strictureplasty (10.5%), resection anastomosis (5.2%), right hemicolectomy (5.2%), and ileotransverse anastomosis (7.8%) were performed and peritoneal biopsy and lymph node biopsy in 21% of patients. The tuberculous bowel perforations were usually treated with resection of involved segments with primary anastomosis[17,18]. Generally, emergency surgery in those severely ill patients presenting late carried high mortality from toxaemia, hypoproteinaemia, anaemia and immunosuppression. The mortality rate ranged between 14%-50% in developing countries[10,30], and 6%-37% in developed countries[11,16]. Morbidity included delayed wound healing with occurrence of incisional hernia, recurrent obstruction and faecal fistula[14,47]. Both medically and surgically managed patients responded dramatically to anti-tuberculous therapy with increase in haemoglobin level and fall in ESR[28-30].

CONCLUSION

Abdominal TB is generally responsive to medical treatment, and early diagnosis and management can prevent unnecessary surgical intervention. However, abdominal TB should be considered a surgical problem in the acute and chronic abdomen. Laparoscopy is emerging as the gold standard for diagnosis since diseases such as Crohn's disease, lymphoma and malignancy can mimic TB. Due to the challenges of early diagnosis, patients should be managed in collaboration with a physician familiar with anti-tuberculous therapy. An international expert consensus should recommend an algorithm for the diagnosis and multidisciplinary management of abdominal TB.

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CASE REPORT

Novel technique of abdominal wall nerve block for laparoscopic colostomy: Rectus sheath block with transperitoneal approach

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Abstract

A 62-year-old man who had acute rectal obstruction due to a large rectal cancer is presented. He underwent emergency laparoscopic colostomy. We used the laparoscopic puncture needle to inject analgesia with the novel transperitoneal approach. In this procedure, both ultrasound and laparoscopic images assisted with the accurate injection of analgesic to the correct layer. The combination of laparoscopic visualization and ultrasound imaging ensured infiltration of analgesic into the correct layer without causing damage to the bowel. Twenty-four hours postoperatively, the patient's pain intensity as assessed by the numeric rating scale was 0-1 during coughing, and a continuous intravenous analgesic was not needed. Colostomy is often necessary in colon obstruction. Epidural anesthesia for postoperative pain cannot be used in patients with a coagulation disorder. We report the use of a novel laparoscopic rectus sheath block for colostomy. There has been no literature described about the nerve block with transperitoneal approach. The laparoscopic rectus sheath block was performed safely and had enough analgesic efficacy for postoperative pain. This technique

could be considered as an optional anesthetic regimen in acute situations.

Key words: Colorectal cancer; Rectus sheath block; Colon obstruction; Postoperative pain

Core tip: This report demonstrated that transperitoneal rectal sheath block can be performed safely in achieving analgesia in patients undergoing laparoscopic colostomy. This transperitoneal rectal sheath block technique has the potential to become an additional postoperative regimen for various forms of laparoscopic abdominal surgery.

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INTRODUCTION

Colostomy is often necessary in acute colon obstruction. The indications for laparoscopic colostomy for large bowel obstruction caused by benign colorectal disease have been described previously[1]. The laparoscopic approach is associated with a significant reduction in postoperative pain, faster recovery, and shorter hospital day compared with open surgery[2]. However, there is still considerable postoperative pain associated with the laparoscopic procedure as a result of the transabdominal sutures, even in the small incisions.

Strategies for analgesia after laparoscopic colostomy are based on the concepts for the open procedure; epidural analgesia is the standard technique. However, epidural use is sometimes limited because of perio-perative anticoagulant therapy and the potential for undesirable complications such as epidural hematomas and infections. Therefore, recently published guidelines from the United Kingdom no longer recommend epi-dural analgesia as standard pain management after laparoscopic colorectal surgery[3]. Furthermore, patients with acute colorectal obstruction often have a coagulation disorder and higher risks. For patients with obstruction, especially in emergency cases, regional anesthetic techniques such as the ultrasound-guided rectus sheath (RS) block have become increasingly popular as methods to provide analgesia for laparoscopic surgery. The RS block has gained popularity owing to a relatively high success rate[4]. However, even the RS block has potential complications such as RS hematoma if the vessels are damaged, and it is possible to puncture the posterior RS, peritoneum, and/or bowel. In this report, we describe a novel laparoscopic transperitoneal approach and assess its efficacy. This is the first report of laparoscopic colostomy using the transperitoneal approach for the RS block.

CASE REPORT

After approval by the Research Ethics Board of our institution and the patient's informed consent. A 62-year-old man with acute rectal obstruction due to a large rectal cancer underwent laparoscopic colostomy. The procedure was performed as an emergency operation, with the patient placed under general anesthesia with 8% sevoflurane *via* a face mask. Epidural anesthesia was not performed, as the patient had a coagulation disorder.

Laparoscopic colostomy was conducted *via* two incisions; the first incision was made *via* the stoma site (25 mm), and a second navel incision (5 mm) was made. After making the skin incisions, pneumoperitoneum was created with the pressure standardized to 10 mmHg. Intraoperatively, under laparoscopic visualization, a bilateral transperitoneal RS block was performed with ultrasound guidance to reduce unexpected abdominal wall pain. Ultrasound was performed with a linear array probe, 13-6 MHz, SonoSite M-Turbo™ (SonoSite Inc., Bothell, WA, United States). The probe was placed longitudinally on the patient's abdominal wall while the tip of a Peti-needle™ (Hakko Co., Ltd., Adachi-ku, Tokyo, Japan) was inserted through the peritoneum under laparoscopic visualization. A Peti-needle™ was inserted through the 5-mm port at the stoma site, and 20 mL of 0.25% levobupivacaine was injected though the peritoneum (Figure 1): Posterior to the rectus muscle and above the underlying RS block. Infiltration into the correct layer without leakage was checked by both laparoscopic visualization and ultrasound (Figure 2). The technique was repeated on the other site. Surgery was completed successfully and the anesthetic procedure did not affect the operation.

Postoperatively, the patient was brought to the post-anesthesia care unit for continuous monitoring of vital signs. Nurses administered intravenous analgesic as needed. Pain severity was assessed at rest and during coughing using a numeric rating scale (NRS), where no pain = 0, and the worst pain = 10. Three hours postoperatively, the patient's pain intensity as assessed by the NRS was 3 at rest and 4 during coughing. Twenty-four hours postoperatively, the patient's NRS pain intensity was 0-1 during coughing, and an intravenous analgesic was no longer needed. There were no other postoperative problems such as hematoma or severe infection in the muscle.

DISCUSSION

The RS block is a regional anesthetic procedure that was first reported in 1899[5]. It has been used in the treatment of pediatric chronic abdominal wall pain[6].

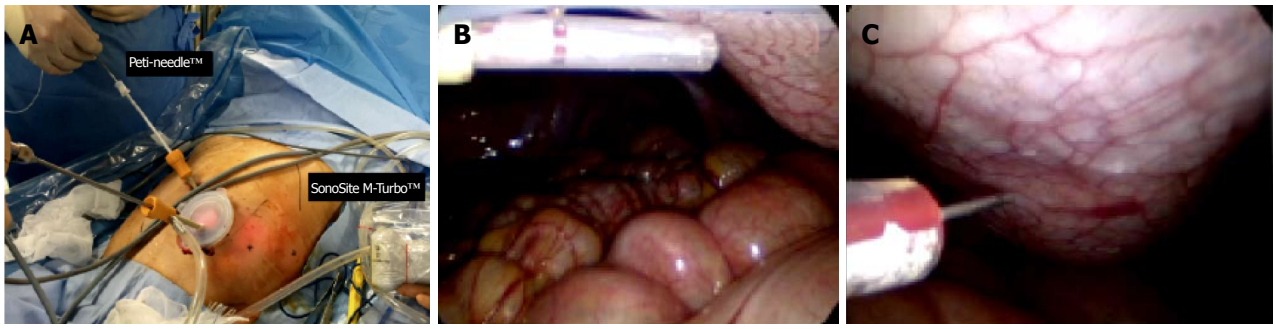

Figure 1 Intraoperative photographs. A: The Peti-needle™ inserted *via* the naval port (5 mm); B: Delivered to the peritoneum; C: The anesthetic agent was then injected through the Peti-needle™ by the transperitoneal approach under laparoscopic visualization.

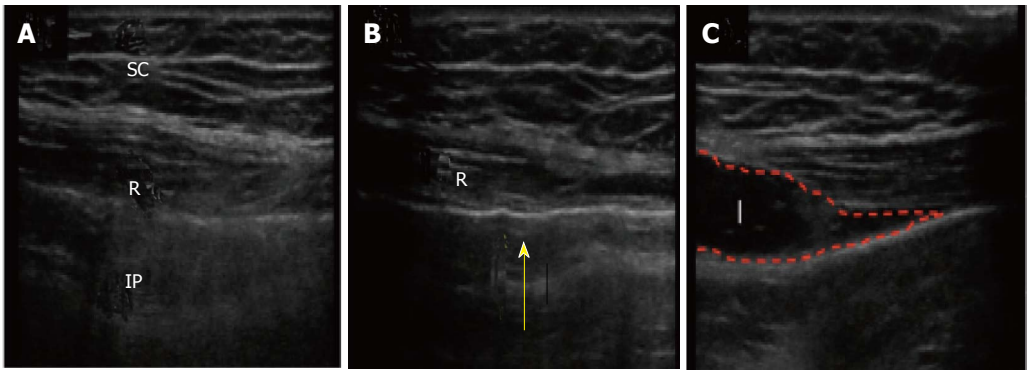

Figure 2 Ultrasound images. A: The muscle layers; B: The Peti-needle™ positioned below the peritoneum, the notch was made by the needle tip (yellow arrow) before the needle was inserted *via* the peritoneum; C: Local analgesic was then administered into the correct layer. R: Rectus muscle; IP: Intraperitoneal space; SC: Subcutaneous tissue; I: Injectate.

Any regional technique carries a risk of introducing infection, causing bleeding, or damaging local structures[7]. Proposed benefits of these regional blocks include the avoidance of neuroaxial techniques such as epidural analgesia and their associated risks, as well as a reported reduction in opioid consumption[8-10].

Laparoscopic-assisted transversus abdominis plane block has been performed for ventral hernia repair[11] and cholecystectomy[12]; however, this procedure was done only with ultrasound guidance, and the needle was inserted transcutaneously. Using the transperitoneal approach *via* laparoscopy and ultrasound guidance, the RS block has been demonstrated to be simpler and safer.

RS block *via* the transperitoneal approach in laparoscopic colostomy provided effective and safe postoperative analgesia in a patient with acute colon obstruction. When compared with the open procedure, laparoscopic colostomy itself carries several advantages including early postoperative recovery, less postoperative pain, and rapid restoration of bowel function[13]. A laparoscopic RS block can be performed by the operating surgeon without perforation of the bowel. This procedure could be performed in high-risk patients who have a coagulation disorder, and also in highly obese patients. Currently, there are no published trials examining the role of the laparoscopically performed RS block *via* the transperitoneal approach for the management of perioperative pain in laparoscopic abdominal surgery. In the present case, the procedure was performed safely and the transperitoneal RS block provided the effective analgesia in abdominal surgery.

Although the RS block, known as a compartment block, is thought to require a large amount of local anesthetic to provide an analgesic effect, our result showed that it was possible to produce sufficient analgesia with a small dosage of local anesthetic with ultrasonic and laparoscopic visualization. The RS block has no hemodynamic effects, and is ideal for patients with hypotension related to sepsis or hypovolemia. Unlike epidurals and continuous intravenous analgesia, the RS block does not require connection to pumps and stands, thereby enabling early patient mobilization. Our novel analgesia technique has potential use as a regimen for postoperative pain of various laparoscopic surgeries. This study had a limitation; the Peti-needle™ costs twice as much as the needle used for the percutaneous approach. Additional prospective studies are required to evaluate the benefits of laparoscopic transperitoneal RS block in other techniques such as local anesthetic wound infiltration, patient-controlled intravenous opioid administration, and the percutaneous approach.

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COMMENTS

Case characteristics

A 62-year-old man who had huge rectal cancer underwent laparoscopic colostomy and a novel nerve block with transperitoneal injection of analgesia.

Clinical diagnosis

A huge rectal tumor of his pelvic space occurred acute colon obstruction.

Differential diagnosis

Gastrointestinal tumor, neuroendocrine tumor.

Laboratory diagnosis

Only carcino-embryonic antigen was arized, other labs were within normal limits.

Imaging diagnosis

A huge rectal tumor of his pelvic space occurred acute colon obstruction.

Pathological diagnosis

Moderately differentiated adenocarcinoma.

Peer-review

This is a case report that is describing a novel rectus sheath block technique for laparoscopic colostomy in an adult. However, the authors would like to point out the following. Generally, the manuscript is good written.

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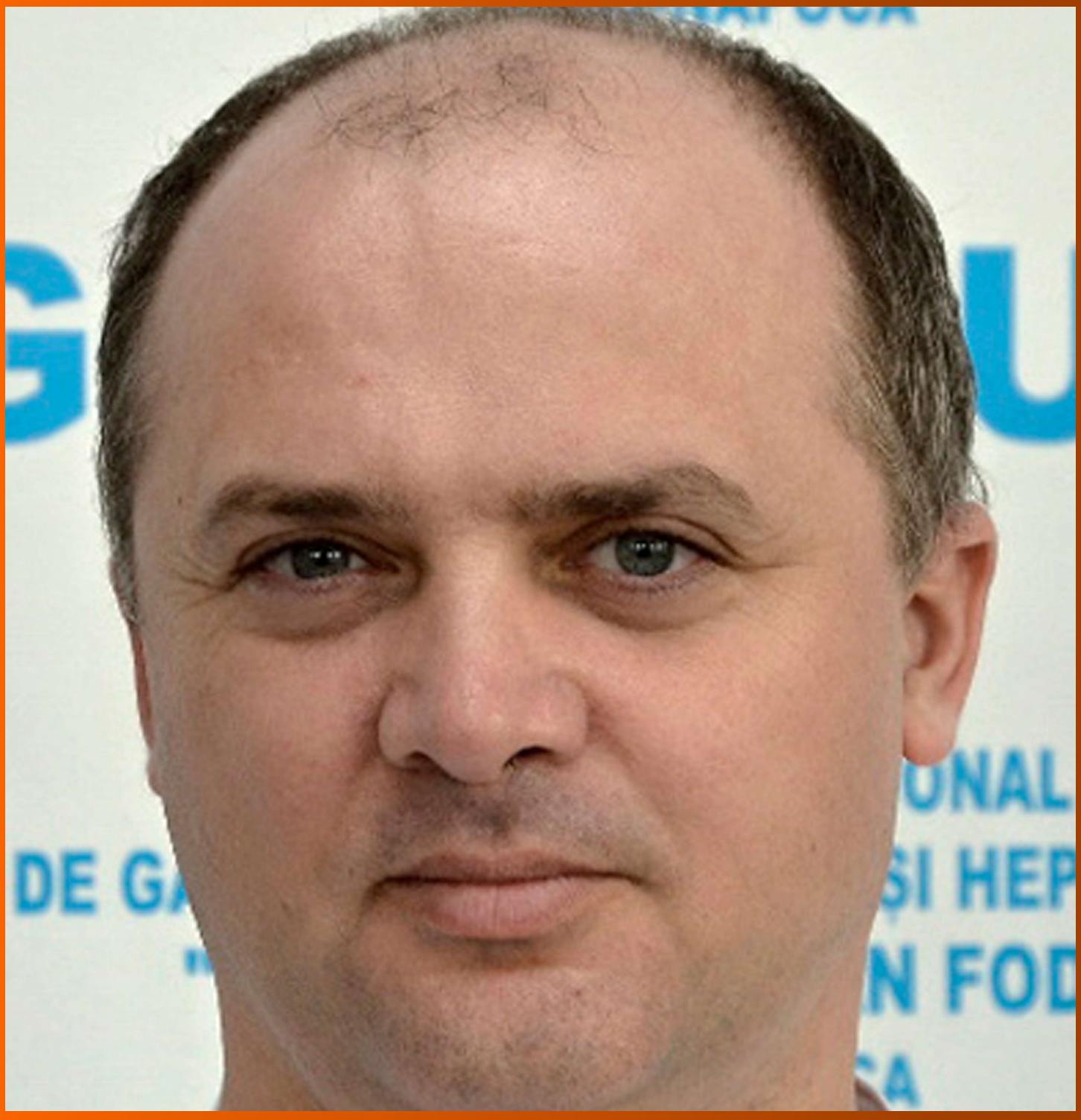

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MINIREVIEWS

Role of "reduced-size" liver/bowel grafts in the "abdominal wall transplantation" era

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Abstract

The evolution of multi-visceral and isolated intestinal transplant techniques over the last 3 decades has highlighted the technical challenges related to the closure of the abdomen at the end of the procedure. Two key factors that contribute to this challenge include: (1) Volume/edema of donor graft; and (2) loss of abdominal domain in the recipient. Not being able to close the abdominal wall leads to a variety of complications and morbidity that range from complex ventral hernias to bowel perforation. At the end of the 90's this challenge was overcome by graft reduction during the donor operation or bench table procedure (especially reducing liver and small intestine), as well as techniques to increase the volume of abdominal cavity by pre-operative expansion devices. Recent reports from a few groups have demonstrated the ability of transplanting a full-thickness, vascularized abdominal wall from the same donor. Thus, a spectrum of techniques have co-evolved with multi-visceral and intestinal transplantation, ranging from graft reduction to enlarging the volume of the abdominal cavity. None of these techniques are free from complications, however in large-volume centers the combinations of both (graft reduction and abdominal widening, sometimes used in the same patient) could decrease the adverse events related to recipient's closure, allowing a faster recovery. The quest for a solution to this unique challenge has led to the proposal and implementation of innovative solutions to enlarge the abdominal cavity.

Key words: Abdominal wall transplant; Reduced-size graft; Combined liver-bowel transplantation

Core tip: Matching donors with recipients to perform liver-bowel transplantation is a challenging task, especially in front of pediatric candidates due to the shortage of suitable donors. Historically, the issue was overcome reducing the size of liver and bowel during donation in order to implant the combined graft in the small abdominal cavity of the recipient. Due to the presence of complications, the procedure has been improved by enlarging the abdominal cavity of the recipients, initially

through conventional techniques used in hernia repair or trauma surgery and later by transplanting the donor abdominal wall into the recipient. Results are encouraging but limited to high experienced centers.

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INTRODUCTION

Experience has shown that intestinal and multi-visceral transplantation (ITx) is a feasible and potentially life-saving procedure. Donor-recipient size discrepancies have however been the Achilles heel, limiting the pool of donor organs especially for pediatric recipients due to donor-to-recipient body weight ratio, ideally between 1.1 and 0.76[1] , and size mismatching makes primary closure of the recipient abdominal wall one of the important technical challenges related to intestinal transplantation, mainly due to two factors: loss of abdominal domain because of sepsis, enteric-cutaneous fistulas or multiple surgeries of the recipient[2]; and volume or post-reperfusion intestinal edema of the graft[3]. Achieving tension-free closure after bowel transplant is of utmost importance to avoid post-operative abdominal compartment syndrome, risking ischemia and necrosis of the graft[4].

Different options have been reported in literature when a fascia closure is impossible, in the case of a donor-recipient size mismatch that has been undertaken due to unavailability of smaller donors.

The two main approaches focus on (1) Volume reduction of the graft[5]; or (2) an enlargement of the recipient abdominal domain[6]. The first approach includes an anatomical reduction of the graft that mainly applies for pediatric transplantation to prevent high waitlist mortality rates, while the second approach focuses on techniques to enlarge the abdominal domain ,mainly used in > 18 years population.

Pre-transplant mortality has gradually decreased for pediatric candidates in United States (less than 3 per 100 waitlist years, while for adult candidates is at 22.1 per 100 waitlist years), but notably it is still higher for intestine-liver transplant candidates[7], especially represented by the pediatric population: The need of total parenteral nutrition puts children at risk for developing liver disease and subsequently life-threatening complications[8].

Since the 90's, the conventional transplant approach has utilized small size donors. But given the shortage of donors that fulfill the ideal characteristics, transplant centers have been increasingly accepting organs with considerable graft mismatch. Reducing the size of transplanted organs, with a reduced-size composite liver-intestinal allograft using split techniques[9], has resulted in utilization of organs from donors up to five times larger than recipients[10].

The development of reduced-size isolated bowel grafts has improved the limited availability of donors for candidates weighing less than 10 kg due to the possibility to overcome donor-recipient size mismatches[11] greater than to 10:1 (body weight).

An alternate method to solve the issue of size mismatch involves abdominal wall reconstruction, enabling substantial expansion of the recipient's abdominal domain, especially when more organs (like liver-bowel) are to be transplanted[12]. However, this is challenging since most recipients are poor candidates for plastic surgery techniques such as tissue advancement or flap closure of the defect because of many previous surgeries.

Few techniques of abdominal wall reconstruction have been reported, many of them already used in difficult abdominal wall hernia repair or trauma surgery. Staged closure of the abdomen has been described by the Birmingham (United Kingdom) group[13], reporting on 23 combined liver and bowel transplants closed using a Silastic® sheet together with a vacuum occlusive dressing.

The skin of the abdominal wall is often more pliable than the underlying tissue, and closure is possible sometimes with the help of tissue expanders[14,15]: Accordingly, twenty cases of inflatable tissue expanders in ITx candidates were reported in international literature. Localization of tissue expanders were: Subcutaneously in 13; intraperitoneally in 4; placed retromuscularly and 1 intraperitoneally; 1 patient had biplanar tissue expander (intraperitoneally placed and extending retromuscularly) and in 1 localization was unreported.

Alternatively, common used techniques include absorbable mesh[16]: Five pediatric liver and intestinal living-donor transplant recipients were treated by Chicago group initially through an absorbable Polygalactin mesh and later , once a granulated tissue was present, by a split-thickness skin graft. Sometimes the use of non-absorbable mesh[17] has also been reported: a prosthetic mesh alone was used in three patients from Bologna series to perform abdominal reconstruction , only in one case followed by a myocutaneous flap.

Apart from traditional reconstructive techniques, alternative methods include bioengineered skin equivalent[18], a-cellular dermal matrix[19,20], frozen human fibroblast-derived dermis[21], non-vascularized rectus muscle fascia[22,23], and vascularized "split-thickness"[24] or "full-thickness" skin grafts[25-31], either with classical[25], microsurgical[32] or remote revascularization technique[33]. These techniques are summarized in Table 1.

The use of either vascularized "partial" (rectus fascia) or "full-thickness" abdominal wall insensate[34] grafts (obtained from the same donor as the intestinal organs) has been successfully done in both, adult[35] as well as pediatric population[25].

Table 1 Techniques of abdominal wall closure after intestinal and multi-visceral transplantation

Ref.	Children/adults with difficult closure	Techniques used for closure	Post-ITx complications related to closure
Nery *et al*[5], 1998	N.a./n.a. tot = 11 (+ 5 graft reduction/ modification)	4 silastic or PTFE mesh 2 skin flap 1 myocutaneous flap 3 mesh + graft reduction 1 skin flap + graft reduction	5 incomplete closure
Alexandrides *et al*[4], 2000	9/6	7 goretex mesh 4 myocutaneous flap 3 silastic mesh 1 abdominal expander	None
Levi *et al*[25], 2003	2/6	8 full-thickness wall graft	2 wall infarction
Charles *et al*[21], 2004	0/1	1 fibroblast-derived dermis	None
Drosou *et al*[18], 2005	0/4	4 bioengineered skin equivalent	None
Asham *et al*[19], 2006	0/1	1 acellular dermal matrix	None
Carlsen *et al*[2], 2007	8/6	7 goretex mesh 4 (+ 2) split-thickness skin graft 2 (+ 2) skin flap 1 (+ 1) fascia	6 incisional hernia
Zanfi *et al*[3], 2008	0/13 (+ 2 graft reduction)	5 skin closure 1 staged closure 4 prosthetic mesh 3 full-thickness wall graft	6 incisional hernia 4 mesh infection 2 fistulas 1 abdominal compartments
Gondolesi *et al*[22], 2009	10/6	16 non-vascularized rectus fascia	7 wall infections
Grevious *et al*[16], 2009	5/0	5 staged closure (meshà split-thickness skin graft)	1 fistula
Sheth *et al*[13], 2012	23/0	23 staged closure	2 abdominal compartment s.
Mangus *et al*[20], 2012	12/25	30 acellular dermal allograft 7 mesh or donor fascia	1 dehiscence 5 incisional hernia 2 fistulas
Vianna *et al*, 2013 (unpublished results)	0/1	1 full-thickness wall graft	N.a.
Weiner *et al*[15],2014	1/0	1 bi-planar tissue expander	None
Vaidya *et al*, 2015 (in Chennai) (unpublished results)	1 n.a.	1 full-thickness wall graft	N.a.
Haveman *et al*[35], 2016	0/1	1 full-thickness wall graft	None
Giele *et al*[24], 2016	0/19	17 full-thickness wall graft 1 partial-thickness vascularized graft 1 partial-Thickness nonvascularized graft	3 wound infection

ITx: Intestinal and multi-visceral transplantation; PTEE: Partial-thickness nonvascularized graft.

The vascularized donor abdominal wall may have an immunological impact as well[36], and it has been proposed as a "sentinel" graft[37-41]. An allograft skin rash may represent a rejection phenomenon occurring earlier than the bowel manifestations, allowing to minimize therapy because treatment of abdominal wall rejection (very often steroid-responsive) may prevent intestinal rejection, which is a much more difficult issue to handle pharmacologically.

It has been hypothesized that the combined skin-intestine allograft from the same donor could present diagnostic and therapeutic advantages to the patient and clinician. Furthermore it has also reported the benefit of the skin, from the vascularized abdominal wall, being used to detect graft versus host disease in recipients of a combined abdominal wall-bowel graft by identifying a body rash in the recipient that spares the skin of the abdominal wall graft[42,43].

DONOR PROCUREMENT IN CASE OF SIZE MISMATCH

Procurement strategies for combined multi-organ and composite tissues for transplantation[44] continue to evolve, from the initial reports back in the early 90' s. In case of donor-recipient size mismatch[5], the surgeon could reduce the graft or conversely retrieve an abdominal wall during donor operation.

Splitting both liver (left lateral segment represented by segments Ⅱ and Ⅲ) and intestine (ileum) during a combined transplantation, with resulting Roux-en-Y loop biliary reconstruction in the recipient, was first reported

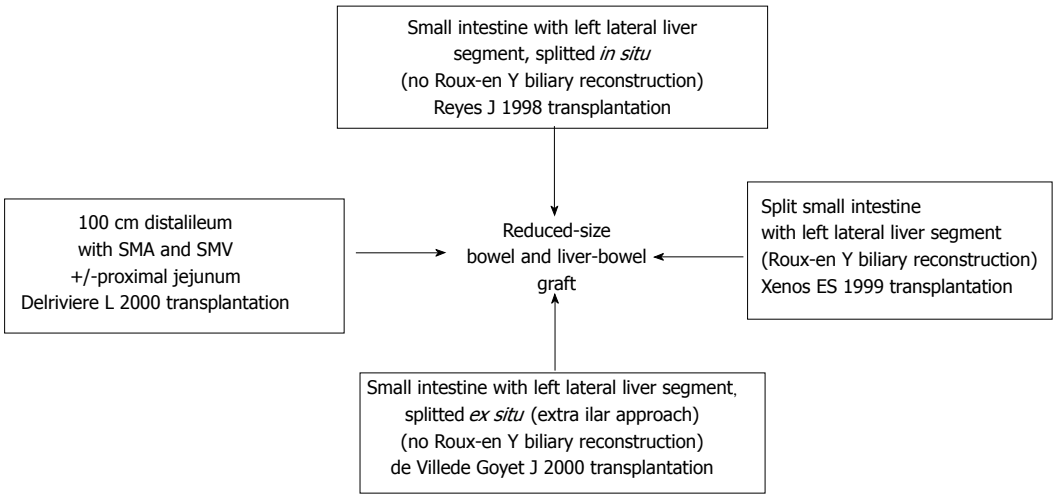

Figure 1 Historical techniques of reduced-size bowel and liver-bowel grafts before intestinal and multi-visceral transplantation.

by Xenos *et al*[45] in 1999.

Another way to reduce the liver-bowel graft during the harvest was described by Reyes *et al*[9] isolating the intestine and removing it en-block with the left lateral liver segment (segment Ⅱ and Ⅲ, previously splitted *in situ*): Eliminating the need of biliary reconstruction reduces most technical complications and avoids the use of the bowel for bilio-digestive anastomosis.

A similar advantage was reported by de Ville de Goyet *et al*[10], where during the bench table surgery the liver was reduced, using an approach that leaves the liver hilum untouched.

Isolated intestinal grafts could be size-modified: Fifteen small bowels were successfully reduced by Delrivière *et al*[11] obtaining a one meter ileal graft vascularized by the superior mesenteric artery and vein. Later, technical modifications allowed the use of two grafts from a single donor, represented by part of ileum and part of jejunum.

These techniques are summarized in Figure 1.

Two popular procedures have been reported in order to harvest an abdominal wall: In the original Miami technique[25] the vessels of the wall graft were represented by donor femoral and iliac vessels, together with a small patch of aorta and inferior vena cava used to implant them into the recipient's common iliac artery and vein. A modified microsurgical procedure was later reported by Cipriani *et al* from Bologna[32], collecting only the donor epigastric vessels with the abdominal wall, so sparing donor femoral-iliac vascular axes by direct anastomosis of the inferior donor-recipient epigastric vessels.

Both the procedures (size reduction and abdominal wall retrieval) are time-consuming in both donor and recipient operations but it is worthwhile to notice that, to date, there have been only insensate abdominal wall graft retrievals without nerve coaptation, a factor that may further impact procurement time if added in the future[46].

REDUCED SIZE LIVER-BOWEL CADAVERIC TRANSPLANTATION

The "golden age" of the reduced size techniques was practiced till the back end of the 90's. In 1998 Reyes *et al*[9] reported the cases of a 3-year-old boy with hepatic-intestinal failure and a 63-year-old man with a central hepatoma and hepatitis C cirrhosis, both transplanted using the same adult cadaveric donor. The donor left lateral hepatic segment (segment Ⅱ and Ⅲ) in continuity with the small intestine was implanted into the child, using a modified *in situ* split technique where biliary reconstruction is unnecessary, while the right side of the donor liver was transplanted into the man. The pediatric recipient was later re-transplanted due to a liver damage related to a native pancreatic fistula, while the adult patient died for rupture of pseudo-aneurysm related to infection of the arterial graft.

In 1999 Xenos *et al*[45] described the use in a child of split liver (left lateral segment represented by segment Ⅱ and Ⅲ) and partial intestine (ileum) from a cadaveric donor during a combined transplantation: The right side went to an adult discharged home without complications. The pediatric recipient underwent a Roux-en-Y loop biliary reconstruction: Later he died for intestinal perforation plus severe rejection.

In 2000, de Ville de Goyet *et al*[10] transplanted two children, weighing 7.6 and 9.8 kg respectively, with a composite graft procured from donors weighing 35 kg (almost five times larger): Both went home on full enteral feeds. The composite graft was obtained during bench table surgery (leaving the hepatic hilum untouched) and was represented by liver segment Ⅱ and Ⅲ and whole small bowel, including duodenum and pancreas head. Also in this case there was no need of biliary reconstruction due to the preservation of the

donor duodenum in continuity with the combined graft.

ABDOMINAL WALL TRANSPLANTATION-TECHNIQUES AND RESULTS

At the beginning of the new millennium, a rather innovative method to overcome the donor-recipient size-mismatching was hypothesized and VCA (vascularized composite allograft) was first reported by Levi *et al*[25] in 2003 in the form of abdominal wall transplantation: Their idea was to cover at the end of an ITx the resulting abdominal wall defect with both donor rectus abdominis muscles plus fascia, subcutaneous tissue and skin. The Miami group transplanted the wall graft like a kidney allograft, using as a blood supply the donor inferior epigastric vessels (left in continuity with the femoral and iliac vessels), and implanting them into the recipient's common iliac artery and vein. The procedure time was about 2 h and this full thickness, vascularized, myocutaneous free flap was finally rotated and positioned according to location of the abdominal wall defect. Doppler ultrasound was used to monitor the blood flow.

The procedure was later modified by the Bologna group[32], using a microsurgical technique with a Zeiss microscope (Oberkochen; Germany): The donor epigastric pedicles were anastomosed end-to-end with the recipient epigastric vessels with no need to collect the donor femoral and iliac vessels. The operative time was similar to the one reported by Miami group.

Giele *et al*[33] from Oxford (United Kingdom) faced a different issue related to abdominal wall transplantation: The storage and subsequent ischemia-reperfusion injury of the wall graft during > 5 h ITx procedures. The ischemic time was minimized by two teams working at the same time on the recipient, one performing the intestinal transplant and the other re-vascularizing the abdominal wall remotely on the recipient forearm vessels. The procedure time lasted 50 min (30-60 min). Later the wall graft was re-vascularized on the abdomen.

Other groups reported, even very recently, few cases of abdominal wall transplantation[35] but the comprehensive picture of the results, related to the use of VCAs to close the abdominal wall after intestinal/multi-visceral transplantation ,were summarized in a recent paper published in 2017[24] where 35 full-thickness vascularized abdominal wall transplants were described (17 in Oxford, 12 in Miami, 3 in Bologna, 1 in Chennai, 1 in Indianapolis, 1 in Groningen).

The reported rate of successful abdominal closure after abdominal wall transplantation is very high, with 88% of flap/graft survival and no related mortality[26]: The overall follow-up is between 6 mo (Oxford, Bologna) and 7 years (Miami).

Moreover, it is worthwhile to notice that the skin component of the abdominal wall may serve as an immune modulator: A recent paper[37] analyzed a small cohort of 29 intestinal/multi-visceral transplants, 14 of them combined with abdominal wall transplants. The advantage to carry a wall graft was represented by lower bowel rejection rate (7% *vs* 27%) and lower rate (14% *vs* 33%) of misdiagnoses (viral infection vs rejection), followed by better intestinal graft survival (79% *vs* 60%).

Despite the good outcome, the procedure is still limited in few transplant centers where the expertise of the transplant team is well integrated with the plastic surgical service: Due to the low the numbers presented also by the 3 main groups (Miami, Oxford and Bologna) it is not possible to make a definitive statement related to the best technique (less morbidity, flap loss, and operative time).

Literature has shown that wall transplantation is feasible and reasonably time-consuming but it is a safe procedure with low morbidity and mortality.

CONCLUSION

The evolution and success of intestinal and multi-visceral transplantation has, in the last 20 years, raised the issue of difficult or even impossible abdominal closure, a topic very rarely encountered in other fields of transplantation.

The number of transplanted organs (volume) and/or graft edema, worsened by a small recipient abdominal cavity due to age or previous surgeries, makes a primary closure technically challenging or even impossible.

Different techniques have been proposed to address this topic and the choice depends upon the transplant team's expertise and/or the availability of a plastic surgical service.

Whatever the approach used, may it be reduction of donor graft size or abdominal wall transplantation, it is important to realize that they may not be mutually exclusive to each other and both approaches can be used as a combination in the same recipient to assure the success of the transplant procedure.

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ORIGINAL ARTICLE

Observational Study

Development of a telehealth monitoring service after colorectal surgery: A feasibility study

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Abstract

AIM

To evaluate the feasibility of a text-messaging system to remotely monitor and support patients after discharge following elective colorectal surgery, within an enhanced recovery protocol.

METHODS

Florence (FLO) is a National Health Service telehealth solution utilised for monitoring chronic health conditions, such as hypertension, using text-messaging. New

algorithms were designed to monitor the well-being, basic physiological observations and any patient-reported symptoms, and provide support messages to patients undergoing colorectal surgery within an enhanced recovery after surgery protocol for 30 d after discharge. All interactions with FLO and physiological readings were recorded and patients were invited to provide feedback.

RESULTS

Over a four-week period, 16 out of 17 patients used the FLO telehealth service at home. These patients did not receive telephone follow-up at three days, as per our standard protocol, unless they reported being unwell or did not make use of the technology. Three patients were readmitted within 30 d, and two of these were identified as being unwell by FLO prior to readmission. No adverse events attributable to the use of the technology were encountered.

CONCLUSION

The utilisation of telehealth in the early follow-up of patients who have undergone major colorectal surgery after discharge is feasible. The use of this technology may assist in the early recognition and management of complications after discharge.

Key words: Telehealth; Remote monitoring; Colorectal surgery; Telephone follow up; Readmission

Core tip: Remote follow-up in the immediate post-discharge period utilising telehealth is feasible, and may help identify patients at risk of developing complications sooner, leading to earlier proactive management.

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INTRODUCTION

Unplanned readmissions to hospital in the United Kingdom increased by 52% between 1992-1999 and 2007-2008[1]. The National Health Service (NHS) faces a predicted disparity between resources and patient need of nearly 30 billion by 2020-2021[2]. Introduced in 2011, the financial penalties (Payment by Results) apportioned to NHS Hospital Trusts for patients readmitted within 30 d of discharge have created concern for health care providers, who face the challenge of balancing timely discharge against the risk of early readmission.

In 2013, a telephone follow-up call was provided to patients between two and four days following discharge for patients undergoing colorectal surgery as part of an enhanced recovery after surgery (ERAS) protocol at Nottingham University Hospitals (NUH)[3]. The telephone call is designed to provide emotional and psychological support to patients following discharge, but also to identify and address any symptoms and to reiterate advice about successful recovery[3].

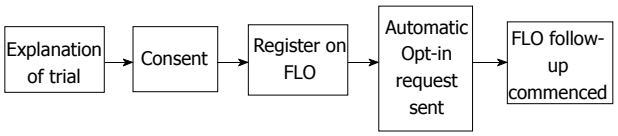

Figure 1 Recruitment on to Florence. FLO: Florence.

A number of telehealth solutions are now available for healthcare providers, including telephone follow up[3], text messaging[4,5], mobile applications[6], video conferencing[7], and automated device transmission[8]. FLO, short for "Florence", is an NHS telehealth solution (in collaboration with Mediaburst Ltd., Manchester, United Kingdom) that has been shown to be effective in helping to manage hypertension[4], and is an acceptable modality of healthcare provision for patients[7]. The aim of this feasibility study was to investigate FLO in the early follow-up of patients who have been discharged from hospital after colorectal surgery within an ERAS protocol, and to assess patients' perceptions of this modality of short-term follow-up.

MATERIALS AND METHODS

Setting

This evaluation was conducted at an 1100-bedded United Kingdom teaching hospital, where around 380 major colorectal procedures are performed each year within an ERAS protocol. Target lengths of stay for patients on ERAS pathways for laparoscopic and open procedures are 3 and 5 d, respectively[9].

Design

This service evaluation was conducted over a four-week period. Patients were identified at their pre-operative assessment, and provided with a brief explanation and an information leaflet about the trial. Following surgery, patients were approached 24-48 h prior to their predicted discharge date, by either the ERAS nurse or ERAS fellow, and a more detailed explanation of the service was offered (Figure 1). Those who opted in to use FLO were followed-up remotely by FLO every day for 30 d after discharge.

At any stage during the follow-up period, the patient would be able to text in the word "stop" and the service would terminate. Patients who declined to participate, and those who were ineligible, or failed to opt-in or utilise the telehealth service having opted in, received a telephone call from the ERAS nurse practitioner between 2 and 4 d following discharge, as per the usual care[3]. Telephone follow-up was not performed if patients had

Table 1 Symptoms recognised by Florence

Symptoms		
Nausea and vomiting	Stoma - constipation	Fever
Urinary	Emptying stoma bag	Generally unwell
Wound appearance	Bowels - loose stools	Tired
Painful wound	Bowels - constipated	Swollen leg
Stoma - loose motion	Pain	Shortness of breath/chest pain

Table 2 List of diagnoses and care team responsible

Colorectal team	Emergency department	General practitioner
Small bowel obstruction, postoperative ileus, retention of urine, hernia, surgical site infection, stoma problems, high output stoma, SIRS, fever, DVT, hypotension	Breathlessness, chest pain	Analgesia review, urinary tract infection

SIRS: Systemic inflammatory response syndrome; DVT: Deep vein thrombosis.

reported being well to FLO for 4 d, but subsequently opted out of the service prior to completing 30 days' follow-up.

Patient population

Eligible participants were those who had undergone a colorectal procedure as part of an ERAS protocol, had mental capacity, were willing to participate, possessed a mobile phone and had experience with sending and receiving text messages. Patients who required reoperation or who were admitted to the intensive care or high dependency units were not invited to participate.

Ethics and consent

The Nottingham ethics committee deemed this study to be a service evaluation, and formal ethical committee review was not warranted. Informed, written consent was obtained from all patients.

Development

The algorithms were designed utilising FLO editing software. These were based on the telephone algorithms currently used by the ERAS nurse practitioner, and were categorised as well-being checks, support messages, physiological observations and self-reported symptoms. For the purposes of this evaluation, the algorithms were designed to provide automated advice.

A trial run of the algorithms was performed by clinical staff; feedback from this process allowed us to modify and streamline the algorithms. A workshop day was organised through the NHS patient and public involvement, and volunteers provided feedback on the equipment, information packs and text-messaging. Despite some of the volunteers having never sent a text message before, they could communicate proficiently with FLO after a brief tutorial.

The well-being checks followed an algorithm, outlined in Figure 2. If patients reported feeling unwell, FLO would proceed to ask the patients for more specific information, limited to the symptoms set out in Table 1. An alert would also be highlighted on the clinicians' FLO dashboard (Figure 3) for patients reporting feeling unwell, any complications, or abnormal physiological readings. Patients who developed an alert on the FLO dashboard were telephoned by the ERAS nurse practitioner within office hours. FLO has the capability to email or text the health care professional when an alert has been triggered. For this evaluation, alert forwarding to the ERAS team was not utilised.

Algorithms were programmed to respond to symptoms that patients could text in to obtain advice. Each symptom required a separate algorithm to be constructed. The list of symptoms was provided as part of an information booklet that patients received, including a brief explanation of each symptom.

Upon receipt of a symptom, FLO proceeds to ask the patient clinical questions to identify a diagnosis. If the symptoms aligned with expected self-limiting problems, reassurance was provided, otherwise, advice was sent and an alert would be created on the clinician's FLO dashboard.

As an example, for symptoms related to bowel movements, the patients would be asked to provide Bristol Stool Scale ratings. These are plotted on the FLO online dashboard, and management options are automatically sent to patients, for example, reduce opioid intake, contact the stoma nurses or increase fluid intake.

During the first 10 d after discharge, several reminder messages were sent to patients, including the timing of removal of surgical skin clips, the importance of regular mobilisation, dietary advice, and the nature of erratic bowel movement after colonic resections. It is also possible to remind patients to take medications at specific times, for example, extended venous thromboembolism prophylaxis.

Lead clinicians in local primary care and in the emergency department were consulted as to the nature of the service being evaluated. It was agreed that certain "trigger" conditions should inform the patient to present either to the colorectal department, the emergency department or to the patient's general practitioner (Table 2).

Implementation and information gathering

Patients were given packs consisting of: (1) Consent form; (2) generic FLO information leaflet; (3) colorectal ERAS FLO information booklet; (4) blood pressure cuff (providing blood pressure and pulse rate); (5) thermometer; and (6) evaluation forms (Likert 5-point

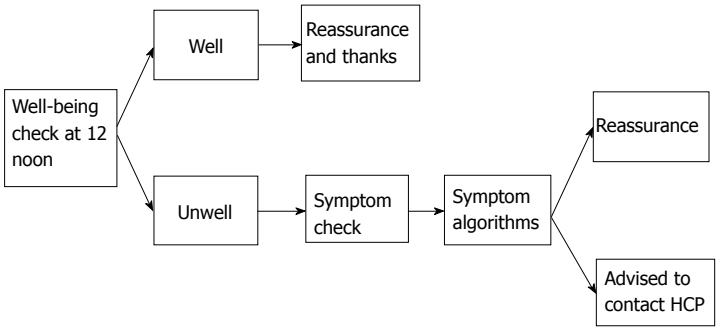

Figure 2 Overview of algorithm. HCP: Health care practitioner.

Figure 3 Example of heart rate dashboard.

scale[10]) included the statements: I feel comfortable using a mobile phone with FLO; I feel confident that sending my symptoms and readings to FLO makes a difference; Regular contact with FLO means I need to visit my GP less often; Using computers and text-messages to follow-up patients following discharge from hospital is beneficial; I would recommend FLO to a friend or family member; FLO is easy to use; FLO is helping me manage my own recovery better.

Patients and/or patient's carers involved in the evaluation were shown how to perform and upload temperature, heart rate and blood pressure measurements to FLO and were asked to provide at least one reading per day. If they forgot to provide a reading, a text-message reminder was automatically sent by FLO to ask for this. Certain symptoms, for example, "generally unwell", would also trigger FLO to request basic physiological readings from the patient. If readings were outside a predetermined range (which can be customised), a request was sent by FLO to repeat the readings. Depending on the readings received, advice was provided, and an alert would be created on the FLO dashboard. All communications between FLO and the patient are stored. If a patient texted in a message that was not understood by FLO, these can be seen and reviewed. This helped us to refine communications. It was also possible to send customised messages to patients and read any responses through the clinician's dashboard.

Statistical analysis

The FLO dashboard is a web-based interface utilising 256-bit encryption. The dashboard (Figure 3) displays a list of all active patients (*i.e.*, those who are still within their 30-d participation), and also those who have been "discharged" from the service, or had opted out. The dashboard has several tabs which display patients' readings including: Well-being checks; basic observations; alerts generated; all support messages and any symptoms or free-text that the patient has sent.

RESULTS

Use of FLO

During the 4-wk trial period, 24 patients were approached. Twenty patients were eligible to use the service. Two patients were eligible but declined to participate. Eighteen patients agreed to trial the service, but 1 did not opt in via text message and did not participate any further. Out of the 17 who opted in, 16 reliably interacted with the service at home. The patient who did not use the service after opting in was readmitted within 24 h of discharge. At any time after 4 d, patients could opt out of the service with no further ERAS follow up.

Well-being, basic observations and symptoms

We subdivided the data into patients readmitted *vs* those not readmitted in Table 3. The mean follow up period is based on the number of days patients remained under FLO follow up before opting out. Patients were asked by FLO at noon daily whether they felt well or unwell. Whilst patients were opted in, the overall response rate to the well-being check was 83%, and the number of days patients were unwell in each category is demonstrated in Table 3. Abnormal observations of blood pressure, heart rate and temperature were defined according to the National Early Warning Score (NEWS)[11]. All symptoms reported by patients were recorded, including those not recognised by FLO (*e.g.*, "anxiety shakes"). The number of symptoms reported are somewhat skewed in the readmitted group as one patient uploaded 50 symptoms (mainly due to pre-existing health conditions).

The numbers observed in this study are too small to draw any firm conclusions of any impact this technology could have. We did note that in the patients who were readmitted, more had uploaded abnormal observations

Table 3 Well-being, observations and symptoms: Readmitted *vs* non-readmitted

	No. of Patients	Total follow-up period (d)	Mean follow-up (d)	No. of days unwell (%)	Abnormal observations, *n* (%)	Symptoms reported, *n* (*n*/d)
Not readmitted	14	390	27.9	9 (3)	21 (5)	37 (0.09)
	3	34	11.3	14 (54)	12 (18)	55 (1.62)

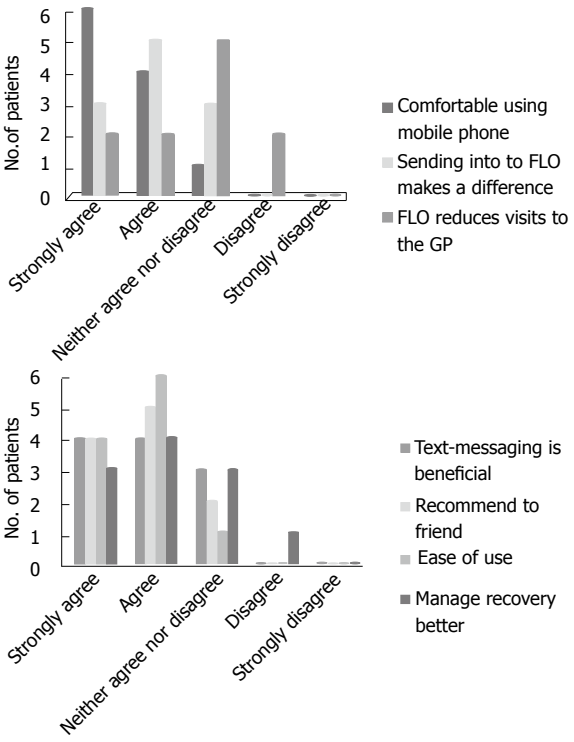

Figure 4 Patient feedback. FLO: Florence; GP: General practitioner.

(18% *vs* 5%), and reported being unwell on more of the days they were followed up for (54% *vs* 3%).

Patient feedback

Most patients felt that the text-messaging service was acceptable to them and patient feedback about the service is summarised in Figure 4.

DISCUSSION

This investigation has demonstrated that it is feasible to develop an acceptable method of remotely monitoring patients who have undergone colorectal surgery after discharge. Using a basic telehealth solution, we designed advanced algorithms to monitor the daily well-being of patients, their physiological observations, and provided a method to respond and triage common postoperative symptoms and diagnoses. We also provided support messages for common postoperative problems. The method was feasible and acceptable to patients and reduced the number of telephone follow-up consultations required as part of our usual care.

Following discharge from hospital, patients' care is effectively "handed back" to primary care services. However, despite the limited number of complications which can be dealt with in primary care (Table 2), there is a lack of incentive for secondary care teams to provide assistance for patients after discharge from hospital[12]. Patients discharged from hospital could thus be considered to be in "no-man's land". Advances in perioperative practice include strategies to reduce the magnitude and impact of surgical trauma, for example, by reducing inappropriate sympathetic response by thoracic epidural analgesia usage[13], and pre-loading patients with carbohydrate drinks to reduce postoperative insulin resistance[14]. Reducing the physiological burden that surgery places on patients permits a quicker recovery[15], reduced length of stay[16] and cost savings[17]. Although readmission to hospital may be viewed as a quality marker, the notion that patients are discharged prior to full recovery[1] more likely reflects advancements in treatment, as seen in ERAS programmes, where patients can be fit for discharge in as little as 23-48 h following major abdominal surgery[15,18].

Although no differences in readmission rates have been reported utilising ERAS pathways[19], the more serious complications, such as anastomotic leak, are reported to be diagnosed, on average, 12.7 d after surgery[20], and mortality resulting from this complication approaches 22%[21]. It is, therefore, important that signs of complications are recognised early, especially after discharge, to prevent patients from being readmitted in extremis.

When serious complications, such as anastomotic leaks, occur when patients are at home, treatment can be delayed. The use of the technology described in this trial may assist in identifying and treating complications sooner. At NUH, we have recently introduced "surgical hot clinics", where appointments can be made by clinicians to review patients on a "very urgent" outpatient basis. Although the numbers in this feasibility trial were small, we have demonstrated that remote monitoring of patients after major abdominal surgery is possible, in what could be viewed as a "virtual ward". Utilising a telehealth service may permit a more integrated and supportive discharge from secondary care, and could help to bridge the gap to a full primary care hand-back.

Prolonging hospital stay for patients who have apparently recovered would inevitably reduce readmissions, but this approach does not make financial sense, and exposes patients to additional risks associated with prolonged stay. Although epidemiologists have evaluated methods of predicting patients at higher risk for readmission[22], the scoring systems have not been widely adopted in United Kingdom surgical practice.

Limitations

The algorithms in the current study were designed to be automated, but we felt the system was too complex

given the limitations of the technology being utilised. For example, FLO can identify key words such as "bleeding" or "blood", and an algorithm could be created to ask specific questions about where the bleeding is coming from, how much there is, and whether it's mixed with anything else. The FLO "brain" has limited intelligence. It is not possible to program a "yes" or "no" response for individual symptom algorithms, as FLO cannot discriminate "yes" or "no" from other symptom algorithms. If bleeding was the symptom, FLO would have to ask: (1) Where the bleeding is coming from. Responses would have to be programmed and built in to the response sent to the patient (*i.e.,* per rectal bleeding, per stomal bleeding, wound bleeding); (2) responses then must be carefully phrased in lay language, but are limited to 144 characters; and (3) for FLO to understand the reply, only specific phrases are understood, such as "B1" for rectal bleeding, "B2" for Stoma bleeding, or "B3" for Wound bleeding, which can be confusing, particularly if patients use phones where the previous messages are not on the same screen when they type their response.

FLO in its current guise requires patients to be precise in their responses; there is no "fuzzy matching". For example, a patient may text in "lose bowls", meaning loose bowels. FLO would respond to this with a generic "I didn't understand that" or "that reading is too low". It is possible to add additional keywords to individual algorithms to pick up potential misspellings or abbreviations, but this was not done during this short trial.

Finally, using FLO in an automated manner is not feasible. We felt that to comprehensively monitor patients remotely in this manner, a clinician is required to oversee the dashboard to ensure patients were not running into problems. Conversely, we did not have to make routine telephone calls to 13 of the 17 patients who utilised the service, which usually take approximately 20 min to complete. It is possible to provide shared cross-speciality access to the FLO dashboard, but since this was a small, short-term trial, we did not provide FLO access to individual GPs or the emergency department.

FLO could be used in other surgical practice including patients being sent home with drains - for example those with biliary or pancreatic fistulas, or after breast surgery in those with seromas.

The use of a modern technology was evaluated to remotely monitor patients who have undergone major abdominal surgery after discharge from hospital. The technology as it currently exists has limitations, and is not suitable for every patient. However, its use appears to be acceptable to those who did use it, and requires further evaluation as a method to bridge the gap between primary and secondary care services.

COMMENTS

Background

Patients can be fit for discharge in as little as 23-48 h following major abdominal surgery. However, serious complications, such as anastomotic leak, are reported to be diagnosed, on average, 12.7 d after surgery. It is therefore important that signs of complications are recognised early, to prevent patients from being readmitted in extremis. The aim of this telehealth evaluation was to monitor patients in the early follow up period after discharge.

Research frontiers

Traditional follow-up after surgery included a telephone call from a nurse between 2-4 d following discharge to patients at home. This method is fairly resource-intense and does not include basic physiological parameters.

Innovations and breakthroughs

Although this evaluation was not powered to detect changes in the ability to pick up postoperative changes earlier, we have demonstrated that this method of follow-up is acceptable to patients and may form the basis of a larger study, which may incorporate newer technologies, such as the internet of things (IoT).

Applications

The evaluation of this technology demonstrates that use of telehealth in the immediate postoperative period is feasible and may help identify postoperative complications sooner. Methods arising from this evaluation may assist in future medical applications, such as devices in the IoT.

Terminology

Telehealth is the provision of healthcare remotely by means of telecommunications technology.

Peer-review

This is a very well written article reporting an innovative approach for following patients after discharge.

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ORIGINAL ARTICLE

Retrospective Study

Mortality and morbidity in necrotizing pancreatitis managed on principles of step-up approach: 7 years experience from a single surgical unit

Deshpande Aparna, Sunil Kumar, Shukla Kamalkumar

Deshpande Aparna, Sunil Kumar, Shukla Kamalkumar, Department of Surgery, Seth G.S.Medical College and K.E.M. Hospital, Parel, Mumbai 400012, India

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Abstract

AIM

To determine percentage of patients of necrotizing pancreatitis (NP) requiring intervention and the types of interventions performed. Outcomes of patients of step up necrosectomy to those of direct necrosectomy were compared. Operative mortality, overall mortality, morbidity and overall length of stay were determined.

METHODS

After institutional ethics committee clearance and waiver of consent, records of patients of pancreatitis were reviewed. After excluding patients as per criteria, epidemiologic and clinical data of patients of NP was noted. Treatment protocol was reviewed. Data of patients in whom step-up approach was used was compared to those in whom it was not used.

RESULTS

A total of 41 interventions were required in 39% patients. About 60% interventions targeted the pancreatic necrosis while the rest were required to deal with the complications of the necrosis. Image guided percutaneous catheter drainage was done in 9 patients for infected necrosis all of whom required further necrosectomy and in 3 patients with sterile necrosis. Direct retroperitoneal or anterior necrosectomy was performed in 15 patients. The average time to first intervention was 19.6 d in the non step-up group (range 11-36) *vs* 18.22 d in the Step-up group

(range 13-25). The average hospital stay in non step-up group was 33.3 d *vs* 38 d in step up group. The mortality in the step-up group was 0% (0/9) *vs* 13% (2/15) in the non step up group. Overall mortality was 10.3% while post-operative mortality was 8.3%. Average hospital stay was 22.25 d.

CONCLUSION

Early conservative management plays an important role in management of NP. In patients who require intervention, the approach used and the timing of intervention should be based upon the clinical condition and local expertise available. Delaying intervention and use of minimal invasive means when intervention is necessary is desirable. The step-up approach should be used whenever possible. Even when the classical retroperitoneal catheter drainage is not feasible, there should be an attempt to follow principles of step-up technique to buy time. The outcome of patients in the step-up group compared to the non step-up group is comparable in our series. Interventions for bowel diversion, bypass and hemorrhage control should be done at the appropriate times.

Key words: Necrotizing pancreatitis; Nerosectomy; Morbidity and mortality in necrotizing pancreatitis; Step-up approach

Core tip: Necrotizing pancreatitis is a clinical challenge which requires aggressive conservative management in the early part of the attack. About 60% patients respond to conservative management. Patients who develop infection in the necrosis may require intervention. Delay, drain and debride if required, are the principles of step-up approach. Percutaneous drainage should be performed to be followed later by a step-up necrosectomy if required. If percutaneous drainage is not available or is technically unfeasible, surgical necrosectomy can yield equally good results when performed after an appropriate delay at least of 2 wk. With advent of minimally invasive modalities, infected as well as symptomatic sterile necrosis can be treated variably with radiological, surgical or endoscopic means. The modality selected depends upon the local morphology of the inflamed pancreas and availability of expertise.

Aparna D, Kumar S, Kamalkumar S. Mortality and morbidity in necrotizing pancreatitis managed on principles of step-up approach: 7 years experience from a single surgical unit. *World J Gastrointest Surg* 2017; 9(10): 200-208 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i10/200.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i10.200

INTRODUCTION

Necrotizing pancreatitis (NP) evolves in 15% to 25% of cases of acute pancreatitis[1-3]. It is a challenging clinical problem and despite great advances in the understanding of pathophysiology and management, the mortality rates in pancreatitis especially those with infected necrosis (IN) remain high[4-6]. Traditionally, open necrosectomy was the only tool available for surgical treatment of pancreatic necrosis. This was found to be associated with high mortality rates up to 40%[7]. With the understanding of the biphasic nature of the illness, the treatment of pancreatitis has undergone a paradigm change from early operative intervention to aggressive conservative management with avoidance of intervention as much as possible. The landmark paper by Besselink *et al*[8] in 2006 laid out the principles of "step up "approach to pancreatic necrosis. "Delay" the intervention, "drain" where possible by minimally invasive means and "debride" only when necessary became the pillars of management[9]. A multidisciplinary approach is now becoming the key to managing these patients[10]. These patients have long hospital stay and are a drain on the economic resources of the hospital as well as family. Morbidity can be extreme and happens in various forms.

On the background of the changes that have happened in the management of NP over the last decade we planned to review our prospective database to evaluate management of patients of NP. The aim was to determine percentage of patients in whom intervention was performed and the types of interventions they underwent. We attempted to identify the overall success rate of percutaneous catheter drainage (PCD) and to compare the outcomes of patients of step up necrosectomy to those of direct necrosectomy. Operative mortality, overall mortality, various forms of morbidity and treatment offered for the same, and overall length of stay was determined.

MATERIALS AND METHODS

After taking clearance from the institutional review board with a waiver of consent, a retrospective review of a prospective database of patients diagnosed to have acute pancreatitis admitted over a 7 years period between 2008 to 2014 was carried out. All patients having pancreatic necrosis were included in the study. Patients who had non-necrotizing acute pancreatitis, pancreatic pseudocysts, acute-on-chronic pancreatitis, those who took discharge against medical advice and in whom the data was incomplete, were excluded. We also excluded the patients who were referred late in the course of their illness from other hospitals after multiple interventions.

Epidemiological details regarding age, sex, etiology, interval between onset of attack and hospitalization, were noted. The APACHE Ⅱ scores and the percentage of necrosis was noted. The severity of the episode was categorized as per the revised Atlanta guidelines into moderately severe or severe[11]. The computed tomography severity index (CTSI) was noted[12].

The management of patients was reviewed. Patie-

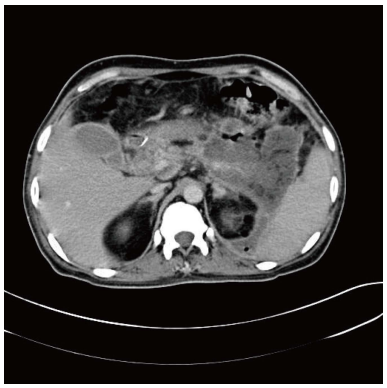

Figure 1 Air in pancreatic necrosis.

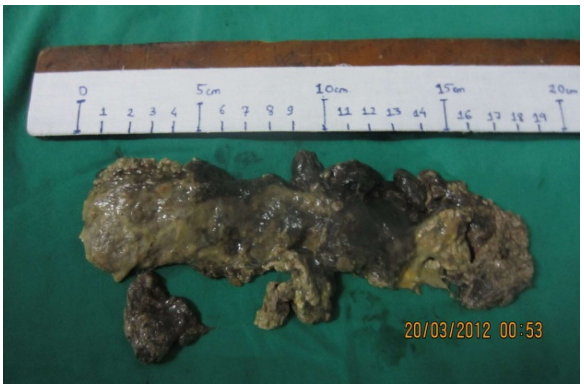

Figure 2 Cast of pancreatic necrosis.

nts responding to conservative management with no further admissions were identified. In the rest, total interventions performed and indications for the interventions were noted. Intervention for abdominal compartment syndrome and endoscopic retrograde cholangiography with sphincterotomy and stenting if any was excluded. Interventions were categorized as those directed to pancreatic and perpancreatic necrosis and those performed for complications associated with necrosis or treatment. Timing of the primary intervention for the necrosis from the onset of illness was recorded. Patients undergoing necrosectomy were categorized into those with step-up necrosectomy and those with direct retroperitoneal or anterior necrosectomy. These two categories were compared for timing of intervention, mortality and hospital stay. Mortality in operated patients and the overall mortality was studied. Cause of death and timing of death in relation to onset of the attack was noted. The morbidity was recorded in terms of bowel fistulation, bowel obstruction and hemorrhage. The interventions required for the same were noted. Total duration of hospital stay was noted.

Treatment protocol

Intensive early management is instituted in all patients suspected to have severe acute pancreatitis. Adequate fluid resuscitation, oxygenation, electrolyte maintenance, pain relief are given. Great emphasis is placed on caloric support and early naso-jejunal feeding is instituted as soon as possible. In addition, chest physiotherapy and supplemental tapping of pleural fluid when necessary are used as measures to keep the oxygen saturation above 97%-98%. Ventilatory support is used whenever necessary.

Interventions for the pancreatic necrosis are avoided in the early period. Release of abdominal compartment is performed in the early phase when indicated, but there is no attempt to open the lesser sac at this stage. If patients respond to conservative management, no further intervention is planned. They are discharged once they are hemodynamically stable and enteral nutrition is established.

If there is suggestion of IN in the form of rising white cell count, febrile episodes not related to other sources (central venous catheters or pulmonary consolidation), tachycardia, tachypnea, sicker patient with weight loss, or evidence of gas in the area of necrosis on contrast enhanced computed tomography (CECT) scan (Figure 1), then intervention is planned based upon the principles of step-up approach. The approach to IN in order of preference is: (1) Image guided catheter through the flank directly into the retroperitoneum with step-up to retroperitoneal necrosectomy, if required; (2) direct retroperitoneal necrosectomy (video 1); (3) image guided catheter through anterior abdominal wall followed by focused anterior necrosectomy, if required (4) direct anterior laparotomy with necrosectomy and closed lavage of lesser sac. Open Abdomen approach is used in extreme cases. Irrespective of the approach, we try to enter the necrosis through minimal dissection. During necrosectomy, the loose necrotic tissue is removed and sharp dissection is avoided. The necrotic tissue sometimes is delivered as a cast (Figure 2) or piecemeal (Figure 3). The cavity is flushed with copious amount of warm saline which removes as much nonviable tissue as possible. This is followed by placement of an indigenously created irrigation system where a 12 Fr Ryle's tube is inserted into a 32 Fr abdominal tube drain through a side cut near its outer end. The number of drains depends upon the space available. The necrotic cavity can be irrigated through the Ryles' tube and the fluid is allowed to return through the tube drain. Because the drain is placed deep within the cavity, general peritoneal contamination is avoided even in anterior necrosectomy. Any overflow of fluid into the peritoneal cavity is removed by another drain placed in the pelvic cavity. Postoperatively, the intra-cavitary Ryles' tube is used to lavage the cavity till all the solid necrotic elements are removed with further liquefaction. The lavage is performed either continuously or at intervals. The irrigation is discontinued when the drain stops showing pieces of solid debris or purulent fluid.

When patients with presumed sterile walled off necrosis (WON) have symptoms like gastric outlet obstruction, failure to thrive or pain, depending upon the thickness of the wall of the necrotic sac, percutaneous

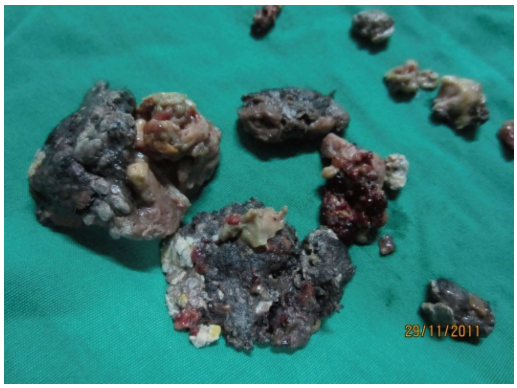

Figure 3 Piecemeal pancreatic necrosis.

drainage by catheters or trans-gastric debridement with cysto-gastrostomy for internal drainage is performed. In some cases, intervention is required due to obstruction of the bowel or suspected bowel fistulation. Bypass of the obstructed bowel and proximal diverting enterostomy is performed accordingly. Hemorrhage within the necrotic area is another indication for intervention. Trans-catheter embolization is used as the first choice of treatment for such cases.

RESULTS

During the 7 year period amongst all patients of acute pancreatitis (n = 276), 84 were identified as NP. Seven patients were excluded as per the exclusion criteria. The baseline characteristics of the patients included in the study (n = 77) are given in Table 1.

Forty-seven patients (61%) responded to conservative management and required no further intervention during that admission or later.

A total of 41 interventions were carried out in 30 (39%) patients. The details of intervention are given in Table 2. Of these 41 interventions, 32 interventions targeted the pancreatic necrosis while 9 were required for dealing with the complications of the necrosis.

Indications for intervention were infection (n = 30), bowel obstruction (n = 1), bowel fistulization (n = 6), hemorrhage (n = 2), persistent organ failure (n = 1), pain, failure to thrive (n = 4). The interventions were chiefly surgical and radiological. Image guided PCD and embolization were the radiologic interventions.

PCD was performed in 9 patients for IN based upon the inclusion criteria. In all these patients a step-up necrosectomy was required. In 3 patients PCD was performed for indication other than infection where a 100% result was achieved and no other intervention was required. Thus the overall success rate for PCD was 25% (3/12).

Direct retroperitoneal necrosectomy (n = 3) or anterior necrosectomy (n = 12) was performed in 15 patients. Thus necrosectomy was required in 24 patients in all, 9 following PCD (step-up) and 15 without prior catheter drainage (Non step-up). All these were

Table 1 Epidemiologic and Radiologic characteristics of patients *n* (%)

Total patients	77
Age range	15-65
Average age	35.65
M:F	6:01
Etiology	
Alcohol	55 (71.5)
Gall stones	16 (20.8)
Ascariasis	1 (1.2)
Idiopathic	5 (6.5)
Severity	
Moderately severe	59 (76.6)
Severe	18 (23.4)
Extent of involvement	
> 90%	27 (35.06)
50%-90%	38 (49.35)
30%-50%	9 (11.68)
Peripancreatic necrosis	3 (3.89)
APACHE Ⅱ score range	8-19
Average APACHE score	12.4
CTSI range	6-10
CTSI average	8

CTSI: Computed tomography severity index. M: Male; F: Female.

cases of IN. On comparing these two groups, the average time to first intervention was 19.6 d in the non step-up group (range 11-36) *vs* 18.22 d in the step-up group (range 13-25). The average hospital stay in non step-up group was 33.3 d *vs* 38 d in step up group. The difference between the two groups using the *T*-test was non significant for both these parameters. The mortality in the step-up group was 0% (0/9) *vs* 13% (2/15) in the non step up group. Using the fischer's exact test, the difference was statistically not significant (P = 0.5). In all, 6 interventions were performed in first 2 wk compared to 18 in over 2 wk. Both the operative deaths occurred in patients undergoing direct necrosectomy within the first 2 wk though the difference was not statistically significant. In all patients after necrosectomy, closed lavage of the lesser sac was performed for an average duration of 16.5 d with a range of 12 to 32 d.

In 5 patients intervention was required for large persistent symptomatic WON without evidence of infection. Depending on the wall maturity they underwent either trans-gastric debridement and internal drainage of the necrosis in the form of cysto-gastrostomy (n = 2, 1 laparoscopic) or PCD (n = 3) (Figure 2) under image guidance. The average time for intervention in these patients was 60 d with a range of 42-90 d. These patients had an average post- intervention stay of 7.4 d.

Morbidity was seen in the form of bowel obstruction in 3 patients. In 2 cases, transient colonic obstruction occurred with air fluid levels on X-ray Abdomen. In both cases, it resolved with extended conservative management. One patient of duodenal obstruction required a duodenojejunostomy.

Bowel fistulation was apparent in 4 patients spontaneously and in 2 patients after a necrosectomy (one

Table 2 Details of interventions done in 30 patients

Name of procedure	No. of patients
Percutaneous catheter drainage	12
Step-up retroperitoneal necrosectomy	3
Direct retroperitoneal necrosectomy	3
Direct anterior necrosectomy	12
Transgastric debridement with internal drainage (Cystogastrostomy)	2
Diverting stoma	6
Duodenojejunal bypass	1
Embolisation for bleeding pseudoaneurysms	2

each from the retroperitoneal and anterior necrosectomy group). A proximal diversion was carried out in all these patients. The diverting stoma was closed in all patients 5-6 mo later without any further morbidity. Hemorrhage of visceral artery pseudoaneurysm occurred in 2 patients which was treated by radiologic embolization.

Overall mortality 10.38%. Five patients succumbed within first 4 d due to fulminant respiratory failure (n = 4) and sudden severe hemorrhage within pancreatic necrosis (n = 1). In the remaining 3 patients, the cause of death was new onset respiratory failure in the second week (n = 1) and sepsis with multi-organ failure (n = 2). The timing of death in these patients was 14th, 18th and 32nd day respectively. Excluding the early deaths, the mortality was 4.1%. Two out of these 3 patients were subjected to operative necrosectomy. Mortality in all patients undergoing necrosectomy (step-up or non step-up) was 2/24, *i.e.*, 8.3%.

The average duration of stay was 22.25 d with a range of 7 to 110 d. The patients who responded to conservative management required an average 11.26 d of hospitalization. In the patients requiring intervention, the average hospital stay increased to 31.76 d.

DISCUSSION

Gallstones and alcohol are the commonest causes of pancreatitis worldwide, with gallstones having a larger role in the western population[13]. In Indian population alcohol is a more common etiological factor as seen in previous studies[14]. The revised Atlanta guideline of 2012 stratifies patients in three categories: Mild, moderately severe and severe depending upon the presence or absence of necrosis and transient or persistent organ failure. Moderately severe pancreatitis was proposed by Vege *et al*[15] who identified the large group of such patients in their patient population. We find similar distribution in our patients, with a nearly 77% of patients in the moderately severe category.

At the onset of the attack, it is difficult to determine the subgroup of patients likely to develop significant pancreatic necrosis. Since pancreatic necrosis increases mortality significantly, diagnosing it is imperative in management. CECT is the gold standard for diagnosing NP and is especially helpful if done after the 4th to 5th day of onset[13]. Studies have demonstrated that AP patients with a CTSI higher than 5 had 8 times higher mortality, 17 times more likelihood of a prolonged hospital course and were 10 times more likely to require necrosectomy than those with CTSI score < 5[16]. In our study group, more than 50% of pancreatic necrosis was seen in 38 patients and in additional 27 patients it was near total necrosis. This is also indicated by the high CTSI (average 8) in our patients. Clinically, this can lead to more local complications. Exclusively Peri-pancreatic necrosis was seen in 3 of our cases.

Due to better understanding of the initial systemic inflammatory response phase, the focus of initial management has shifted to an aggressive conservative one. Standard protocol for management should be established for all suspected cases of acute pancreatitis even before stratifying the patients. A significant number of patients respond to this management. In our series, 61% patients completely settled with conservative treatment and did not need any intervention either in the same admission or later. The role of intervention in NP is becoming more refined. With studies showing that early surgery is associated with higher mortality and that a large number of patients will respond to conservative management[1,17], the current recommendation is to delay the intervention to as late as possible.

Early intervention is required most often for IN. The mortality increases from 5%-25% in patients with sterile necrosis to 15%-28% when infection occurs[13]. Issues in managing IN are threefold. First issue is establishing the diagnosis of infection. A definite diagnosis requires Fine needle aspiration from the necrosis with gram staining. However with many studies showing recovery of some patients of IN with conservative management, the role of FNA is increasingly limited[18]. We have never used FNA to detect infection in the necrosis. Clinical signs can raise suspicion of infection and the CT scan may sometimes reveal air inside the necrotic area.

The second issue is the timing of intervention. IAP guidelines of 2002 recommended avoiding intervention till 14 d for better outcomes[19]. Subsequent studies have recommended further delaying this to the 28th or 29th day[20]. This is highly desirable as by this time the systemic inflammatory response subsides and patients are in a better condition to withstand interventions. The risk of iatrogenic injuries and hemorrhage becomes less as the necrosis is well separated from viable tissue[21]. The definition of delay varies between studies[19,22]. However, prolonging intervention beyond a certain time may entail overuse of antibiotics, increased incidence of resistant organisms as well as fungal superinfections[23,24]. In our patients, the average time to first intervention for IN whether radiological or surgical was 19.21 d, with the earliest intervention being the 12th day. Balancing this decision to intervene at the right time before the patient becomes too ill for any recovery is a clinical challenge. Though we have not found statistically significant difference between the mortality when intervention was performed below 2 wk and over 2 wk, it is still important to note that both the operative deaths occurred when

procedure was performed in the first 2 wk.

The third issue in managing IN is the approach. IN till recently was considered as an indication for a traditional necrosectomy. However, this approach also has the reputation of being very morbid with a high mortality rate upto 40%[7]. Newer minimally invasive modalities have evolved over the last few years with an aim to reduce this morbidity and mortality. The step-up approach described by Santvoort *et al*[25], has changed the management of IN. Image guided PCD either through the retroperitoneal or transabdominal route now plays an important role as the first line drainage in IN. The success rate of PCD in IN varies and ranges from 0% to 78%[25,26]. In a meta-analysis, including 384 patients from 11 studies of PCD as a primary treatment for NP, surgical necrosectomy could be avoided in 56% of the patients and the overall mortality rate was 17%[27]. The incidence of IN in this group was 71%. Thus, PCD either causes sepsis reversal or allows complete recovery avoiding surgical intervention[23]. In 9 patients with clinically suspected IN we used PCD as the first line of management. In all these patients, a step-up necrosectomy was later required. So, our success rate for complete drainage was 0% in IN. However sepsis control was achieved and it allowed delay of surgery. The catheter tracts were used to perform focused necrosectomies. This allowed smaller incisions and prevented contamination of the general peritoneal cavity. The average time to insertion of PCD in the 9 patients with IN was 18.22 d.

Though it is desirable to use step-up approach in all patients of IN, it is sometimes not feasible to do so due to the morphology of the local area or lack of expertise. In such an event direct necrosectomy (retroperitoneal or anterior) may sometimes be necessary. We had to perform a direct necrosectomy in 15 patients. We prefer the retroperitoneal route to access the necrosis through the lienorenal ligament. The video assisted (VARD) or minimal access (MARPN) retroperitoneal necrosectomy is widely described mode for retroperitoneal necrosectomy. We have used the direct retroperitoneal access *via* a flank incision. This is possible when the inflammatory fluid tracks along the lienorenal ligament. This approach has the advantage of avoiding incisions on the abdominal wall thus reducing the chances of later wound dehiscence, hernia and pulmonary complications[28]. A retrospective analysis of 394 patients undergoing minimal access retroperitoneal necrosectomy compared with open necrosectomy showed MARPN to be superior in terms of postoperative complications and outcome[29]. Both MARPN and VARD have been shown at times to need open necrosectomy for better drainage. We have performed retroperitoneal necrosectomy in 3 patients as a step-up procedure and in 3 patients primarily and there was no further need for traditional necrosectomy in any of these patients. This approach should be used whenever feasible.

When the retroperitoneal route is not possible, anterior necrosectomy is performed. Historically traditional necrosectomy is associated with high morbidity and mortality rates. However, this needs to be reviewed in view of newer concepts of delaying intervention to at least 3rd week[27]. The average timing from onset to direct necrosectomy (both retroperitoneal and anterior) in our group of patients was 19.67 d.

Direct Endoscopic trans-gastric necrosectomy (DEN) is now performed across various centres to treat infected WON[30]. Using DEN, a stoma is created endoscopically between the enteric lumen and the necrotic collection, which allows for an endoscopic necrosectomy. There is no clarity in literature about the patients selected for this intervention. Current literature suggests that DEN is a less invasive and less risky alternative to open surgical necrosectomy for managing infected WON and infected pseudocyst with solid debris[31]. Two randomized trials have resulted in a high success rate at the beginning[32,33].

We have not used endoscopy as a modality in any of our cases. We are skeptical about transgressing the gastric lumen to enter into an area of IN with inadequate demarcation and increased vascularity. There are other limitations of endoscopic procedure as well, namely inadequate drainage and closure of the communication.

Our results with direct necrosectomy with postoperative lavage have been very good. We have performed anterior necrosectomy in 12 patients with no prior PCD with a mortality of 16.66%. The overall mortality in all patients undergoing necrosectomy with or without prior catheter drainage is 8.3%. This shows that inspite of newer minimal invasive modalities, there is still a role for traditional surgical intervention as also voiced by Gou *et al*[34].

The best sub-group of patients is those who respond to conservative management and then follow-up later after a period of 2-3 mo with a persistent symptomatic WON. In this group, a trans-gastric necrosectomy with internal drainage by cysto-gastrostomy offers a perfect single step cure if the wall is mature. This internal drainage can be performed by standard open technique, laparoscopically or by endoscopic route depending upon the local expertise available[35,36]. The results from any of these modalities are comparable[36]. We had the opportunity to perform this procedure for WON only in 2 of our 77 patients. In one of them, it was performed laparoscopically. In the same subset, when the wall of WON is not mature and the content is more fluid, PCD can effectively drain most of the necrotic fluid. In three of our patients, we used this approach. Whether such cases with intermediate characteristics can be treated with endoscopic cysto-gastrostomy is question which may need randomized controlled trials to establish the answers[1]. In sterile necrosis, the mortality has been shown to be time dependent after intervention and nearing 0% by the stage of sterile WON[35].

The mortality of NP has a bimodal pattern[37]. Early deaths (within the first week) occur due to severe systemic inflammatory response leading to organ failure. In our series there were 4 early deaths related to uncontrolled respiratory failure. One death occurred due to sudden severe hemorrhage in the pancreatic necrosis

on day 6 of admission. Late mortality (occurs after 2 to 3 wk) is secondary to sepsis related organ failure. Three of our patients succumbed to multi-organ failure secondary to sepsis late in the course of illness.

In one patient there was a new onset respiratory failure on day 12 which led to death. This new onset organ failure led us to intervene in this patient with a traditional necrosectomy, which was probably avoidable. All the patients who died were severe pancreatitis. The overall mortality rate is 10.38% in our patient group. Patients of NP have high morbidity. This exists in terms of bowel obstruction, fistulation, hemorrhage, extended hospitalization. Colonic complications associated with pancreatitis occur infrequently (< 1% of cases). These can vary from reactive ileus to severe obstruction, necrosis or perforation[10]. Two of our patients had colonic obstruction with air fluid levels and both these patients responded to conservative management. Duodenal obstruction was encountered in one patient which persisted even after necrosectomy and required duodeno-jejunal bypass.

Bowel fistulation was seen in 6 patients requiring diversion stoma. Fistulation into the bowel can happen spontaneously due to severe inflammation or can be iatrogenic after extensive debridement. It is imperative that the necrosectomy is done with utmost care to prevent iatrogenic injury to bowel. Sharp dissection should be avoided and only loose nonviable tissue should be removed. Hydro-dissection is a good way to improve scope of necrosectomy compared to sharp dissection. High index of suspicion is required for the possibility of bowel fistulation. Early decision for proximal diversion helps reduce the morbidity.

Gastroduodenal or pancreaticoduodenal artery pseudo-aneurysms occur after significant inflammation of the pancreas and can lead to hemorrhage, which has been reported in 2.4% to 10% of cases[38]. Embolization is the treatment of choice. This was seen in two patients and radiologic embolization was successful in both. Patients of NP pose a significant financial burden on the healthcare systems. Multiple interventions may be required and this increases the hospital stay significantly.

In management of NP, early conservative management plays an important role. Having a standard management protocol is essential. In about 60% cases, conservative management is successful. In the rest, multidisciplinary management is required for the best outcome. Approach used, timing of intervention is based upon the clinical condition and local expertise available. Delayed intervention using minimally invasive techniques is desirable. The step-up approach should be used whenever possible. Using image guided PCD to reduce the sepsis followed by necrosectomy is desirable. The outcome of step up approach and direct surgical approach is comparable if intervention is delayed. Interventions for bowel diversion, bypass and hemorrhage control should be done at the appropriate times. An overall mortality of 10.38% is achieved by following all the above principles which is a very low figure. Good outcome of the patient is the primary objective.

COMMENTS

Background

Necrotizing pancreatitis is a challenging clinical condition. At present, avoiding surgical intervention whenever possible and using various minimally invasive modalities if intervention is absolutely necessary are the chief practice guidelines. Different centres have their own protocol for treating these patients and the modality that a particular centre will follow depends upon the expertise available. The outcome of the patient is most important. It is essential to have published data from various centres in order to know the different modalities followed.

Research frontiers

Currently, minimal invasive retroperitoneal necrosectomy and endoscopic approach to pancreatic necrosis are being researched widely. Also, the subgroup of patients with infected necrosis who can be treated without intervention is also an area of research. There are papers evaluating outcomes with operative necrosectomy and comparing them with minimal invasive necrosectomy.

Innovations and breakthroughs

Most of the techniques are standard techniques described in literature. One essential modification the development of an indigenous sump drain system whereby small ryles' tube is inserted into the larger drain which is then used as a continuous irrigation system. Also, the focused abdominal necrosectomy, which uses the previously placed pigtail catheter is used to enter the area of necrosis is an important advance to keep the procedure less invasive.

Applications

Every patient of pancreatitis needs to be approached with a tailored management. Initial conservative management should be standardized. Whenever intervention is required, one should apply the various minimally invasive modalities whenever feasible. Operative necrosectomy should not be withheld in case such expertise is not available. Principles of appropriate delay should be followed strictly. If local conditions are not conducive for minimal invasive procedures, in such cases also operative necrosectomy may be offered. Comparative studies between minimal invasive necrosectomy and operative necrosectomy may be planned as multicenter studies.

Terminology

All terms used in the paper are standard terms well known to physicians dealing in patients of acute pancreatitis.

Peer-review

This manuscript shows the valuable experience of a tertiary referral center on severe acute pancreatitis.

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CASE REPORT

Mesenteric vein thrombosis following impregnation *via in vitro* fertilization-embryo transfer

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Abstract

Pregnancy is an acquired hypercoagulable state. Most patients with thrombosis that develops during pregnancy present with deep vein leg thrombosis and/or pulmonary embolism, whereas the development of mesenteric vein thrombosis (MVT) in pregnant patients is rare. We report a case of MVT in a 34-year-old woman who had achieved pregnancy *via in vitro* fertilization-embryo transfer (IVF-ET). At 7 wk of gestation, the patient was referred to us due to abdominal pain accompanied by vomiting and hematochezia, and she was diagnosed with superior MVT. Following resection of the gangrenous portion of the small intestine, anticoagulation therapy with unfractionated heparin and thrombolysis therapy via a catheter placed in the superior mesenteric artery were performed, and the patient underwent an artificial abortion. Oral estrogen had been administered for hormone replacement as part of the IVF-ET procedure, and additional precipitating factors related to thrombosis were not found. Pregnancy itself, in addition to the administered estrogen, may have caused MVT in this case. We believe that MVT should be included in the differential diagnosis of a pregnant patient who presents with an acute abdomen.

Key words: Mesenteric vein thrombosis; Pregnancy; *In vitro* fertilization-embryo transfer; Oral estrogen

Core tip: Pregnancy is a hypercoagulable state that

can lead to mesenteric vein thrombosis (MVT). Those symptoms are often nonspecific. Certain signs of MVT can be interpreted as normal changes during the progression of pregnancy; therefore, it is important to recognize the possibility of the development of MVT in the differential diagnosis of a pregnant patient with an acute abdomen. Estrogen can also cause thrombosis and is often administered for hormone replacement as part of an assisted reproductive technology (ART) procedure, particularly *in vitro* fertilization-embryo transfer. With further development of ART, the number of women taking oral estrogen during pregnancy may increase.

Hirata M, Yano H, Taji T, Shirakata Y. Mesenteric vein thrombosis following impregnation *via in vitro* fertilization-embryo transfer. *World J Gastrointest Surg* 2017; 9(10): 209-213 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i10/209.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i10.209

INTRODUCTION

It is well known that pregnancy and estrogen are risk factors for thrombosis. The development of thrombosis during pregnancy is multifactorial, occurring due to physiological changes associated with pregnancy and the additional impact of inherited or acquired thrombophilia[1]. Deep vein leg thrombosis and/or pulmonary embolism are the presentations of most events in affected patients. However, mesenteric vein thrombosis (MVT) that develops during pregnancy is rare; only 10 known cases involving this condition have previously been reported.

We present here a case of MVT in a 34-year-old pregnant woman at 7 wk of gestation. Pregnancy had been achieved *via in vitro* fertilization-embryo transfer (IVF-ET), and oral estrogen had been administered for hormone replacement as part of that procedure. This is the first report of MVT that developed after impregnation achieved *via* IVF-ET.

CASE REPORT

At 7 wk of gestation, a 34-year-old Japanese woman, gravida 0, para 0, was referred to our emergency department from a reproductive clinic for abdominal pain that had lasted for 12 h and was accompanied by vomiting and hematochezia. Nausea had appeared 4 d prior and was treated as hyperemesis gravidarum. The patient had a history of infertility related to endometriosis, and pregnancy was achieved after her first IVF procedure with frozen-thawed embryo transfer. As part of that procedure, oral conjugated equine estrogen (3.75 mg/d) was administered for hormone replacement for 49 d; the patient also received intramuscular injections of progesterone (50 mg/4 d) and a vaginal progesterone suppository (800 mg/d). She was a nonsmoker and had no prior history suggestive of thrombosis. She had no family history of coagulopathies or thromboembolic events. The patient underwent a laparoscopic ovarian cystectomy for endometriosis 4 years prior to her presentation at our hospital. Her body mass index was 24 kg/m^2.

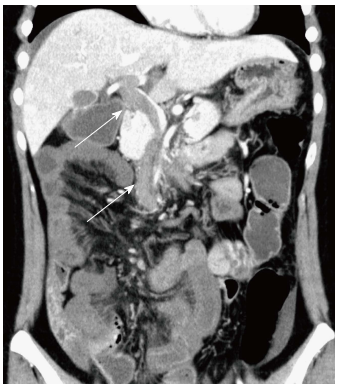

Figure 1 Abdominal computed tomography image obtained at the initial examination. Acute mesenteric vein thrombosis extending into the portal vein (arrow) was demonstrated.

Upon arrival, the patient exhibited the following vital signs: A temperature of 36.8 ℃, a heart rate of 119 beats/min, a blood pressure of 89/76 mmHg, a respiratory rate of 28/min, and oxygen saturation of 97% in room air. A physical examination showed tenderness without guarding, rigidity or rebound tenderness throughout the entire abdomen, and a hematologic examination revealed leukocytosis with a left shift (white blood cell count, 21000/μL; segmented neutrophils, 94.9%). The platelet count was 142000/μL. The patient had a C-reactive protein level of 5.13 mg/dL, aspartate aminotransferase level of 23 U/L (normal, 13-30 U/L), alanine aminotransferase level of 29 U/L (normal, 7-23 U/L), serum creatinine level of 0.58 mg/dL, and blood urea nitrogen level of 14.3 mg/dL. Her D-dimer level was elevated (46.8 μg/mL; normal, < 1.0 μg/mL), the prothrombin time was 13.4 s (normal, 10.2-13.6 s), and the activated partial thromboplastin time was 24.1 s (normal, 23.0-36.0 s). The findings of a hypercoagulability workup, including results for protein S, protein C, and antithrombin, were within normal limits. Anticardiolipin antibodies, antiphospholipid antibodies, and lupus anticoagulant were not detected. She refused screens of the FV Leiden mutation and FII G20210A mutations, which are not found in Japanese people. JAK2 V617F mutation was also not screened because hemoglobin and platelets were in the normal range.

Obstetric ultrasound indicated that the embryo had a normal appearance compatible with its gestational age. Computed tomography (CT) scanning demonstrated thrombosis in the superior mesenteric vein (SMV) extending into the portal vein (Figure 1). A moderate amount of ascites was observed, and the affected small bowel had an edematous and thickened wall with decreased enhancement, which suggested bowel ischemia.

Emergency surgical exploration was performed; this exploration found hemorrhagic fluid and a gangrenous portion of the small intestine extending from 80 cm

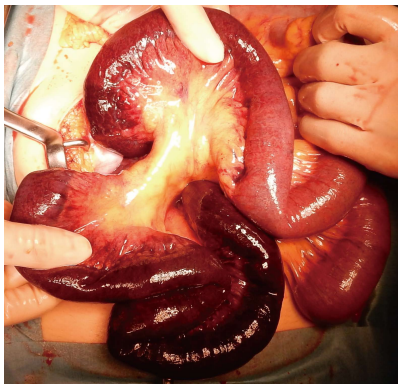

Figure 2 Gangrenous portion of the small intestine. A gangrenous portion of the small intestine extending from 80 cm distal to the ligament of Treitz to 160 cm proximal to the ileocecal valve was found.

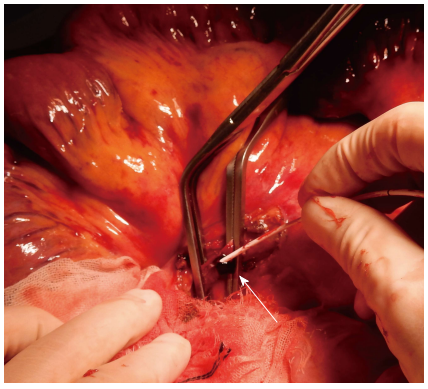

Figure 3 Surgical removal of superior mesenteric vein thrombi with a Fogarty catheter. A Fogarty catheter was inserted from superior mesenteric vein proximal to the ileocolic vein (arrow). The thrombus was removed and blood flow was confirmed.

distal to the ligament of Treitz to 160 cm proximal to the ileocecal valve (Figure 2). After the surgical removal of SMV thrombi (Figure 3), the necrotic portion of the small bowel, which was approximately 170 cm in length, was resected, and end-to-end anastomosis was performed. Following surgery, the patient was transferred to the intensive care unit, and anticoagulation therapy with unfractionated heparin was started immediately. We confirmed cardiac activity in the embryo by ultrasonography.

The subsequent postoperative course was not favorable. CT scanning on postoperative day 4 demonstrated re-occlusion of the SMV and portal vein and no improvement in small bowel congestion. Thrombolysis therapy *via* a catheter placed in the superior mesenteric artery (SMA) was performed by continuously administering unfractionated heparin with urokinase *via* the SMA at a dose of 240000 units/d for 5 d. In addition to thrombolysis therapy, we discussed artificial abortion with the patient; after obtaining consent, we performed this procedure due to the early pregnancy stage and the recurrence of thrombosis despite heparin administration. Following the artificial abortion, the patient's condition improved, and she was discharged on postoperative day 18 with bridging to warfarin from unfractionated heparin.

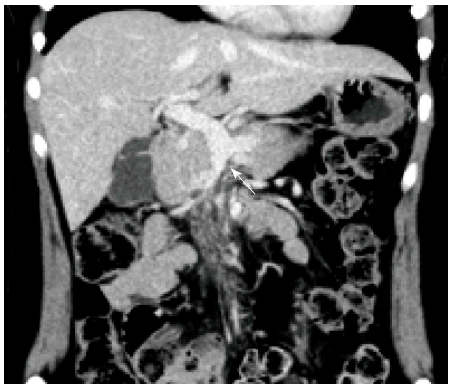

Figure 4 Abdominal computed tomography image obtained four months after surgery. The portal vein recanalized completely, and the superior mesenteric vein was completely occluded from the distal to the first jejunal branches (arrow).

Four months later, the patient continued to receive anticoagulation therapy uneventfully, and a follow-up CT scan revealed complete recanalization of the portal vein, and the SMV was completely occluded from the distal to the first jejunal branches (Figure 4). The first jejunal vein was expanding and functioning as a collateral pathway. The follow-up laboratory data were as follows: Platelet count, 260000/μL; aspartate aminotransferase level, 19 U/L (normal, 13-30 U/L); alanine aminotransferase level, 17 U/L (normal, 7-23 U/L); serum creatinine level, 0.54 mg/dL; blood urea nitrogen level, 11.1 mg/dL; D-dimer level, 0.5 μg/mL (normal, < 1.0 μg/mL); prothrombin time on warfarin, 19.3 s (normal, 10.2-13.6 s); and activated partial thromboplastin time, 31.5 s (normal, 23.0-36.0 s). She had normal liver function, no symptoms of portal hypertension, and had no ascites. We plan to continue anticoagulation therapy for one year.

DISCUSSION

This article provides the first description of MVT that developed following impregnation achieved *via* IVF-ET. We could not identify factors related to inherited or acquired thrombophilia in this case. We believe that the relative hypercoagulability induced by pregnancy, in addition to the administration of oral estrogen during hormone replacement as part of the IVF-ET procedure, may have caused MVT in this patient, who lacked other precipitating factors.

The overall rate of venous thromboembolic events during pregnancy is 200 per 100000 deliveries[2]. Deep vein leg thrombosis and pulmonary embolism have been recognized as related events, whereas MVT is rare, with only 10 previously documented cases of MVT occurring in pregnant patients.

MVT is a life-threatening form of bowel ischemia, with an estimated mortality rate ranging from 20%-50%[3]. Symptoms of MVT are often nonspecific and include colic, progressive abdominal pain, anorexia, and abdominal distention. In pregnant patients, signs related to MVT are

Table 1 Clinical features of mesenteric vein thrombosis during pregnancy

Case	Ref.	Year	Age	Gestation (wk)	Additional risk	Intestinal resection	Pregnancy outcome
1	Van Way *et al*[7]	1970	33	12	-	Yes	ND
2	Graubard *et al*[8]	1987	30	14	Oral contraceptives by mistake	Yes	ND
3	Engelhardt *et al*[9]	1989	32	ND	-	Yes	Live birth
4	Foo *et al*[10]	1996	27	6	-	–	Artificial abortion
5	Sönmezer *et al*[11]	2004	32	27	Factor V Leiden mutation	–	Live birth
6	Terzhumanov *et al*[12]	2005	33	ND	Hemoglobinopathy	Yes	Miscarriage
7	Atakan *et al*[13]	2009	35	20	Protein S deficiency	Yes	Maternal death
8	Lin *et al*[14]	2011	31	34	-	Yes	Live birth
9	García-Botella *et al*[15]	2016	29	7	Antithrombin deficiency	Yes	Live birth
10	Reiber *et al*[16]	2016	30	ND	-	Yes	Live birth
11	Present case	2017	34	7	Oral estrogen associated with IVF-ET	Yes	Artificial abortion

ND: Not described; IVF-ET: *In vitro* fertilization-embryo transfer.

most likely interpreted as normal changes associated with the progression of pregnancy; as a result, MVT is difficult to accurately diagnose. In the present case, nausea appeared 4 d prior to the development of abdominal pain and, might have been a prodromal symptom rather than an indication of hyperemesis gravidarum. For accurate diagnosis, careful observation is necessary with MVT in mind, and abdominal enhanced CT scanning is recommended[3]. A delay in diagnosis may lead to unfavorable results for both the mother and the fetus. Once a diagnosis of MVT is established, immediate treatment with anticoagulation therapy and/or surgical exploration is necessary if an ischemic bowel is suspected. Thrombolysis therapy *via* a catheter placed in the SMA may be managed if thrombosis worsens despite anticoagulation therapy with heparin, although urokinase carries the risk of fetal hemorrhagic complications. Thrombosis due to underlying prothrombotic states, including pregnancy, begins in small vessels and progresses to involve larger vessels. Considering this pathogenesis, thrombolysis therapy at the SMA may be recommended.

In this case, we also selected artificial abortion for the following three reasons. First, screens for inherited thrombotic disorders were negative, and pregnancy itself may have caused the thrombosis. Second, thrombosis may have recurred during pregnancy because of the diagnosis during early pregnancy. Third, the health of the mother is given priority.

Life-long anticoagulation is warranted in patients with inherited thrombophilia, whereas anticoagulation therapy for at least 6 mo to one year is recommended for patients with reversible predisposing causes, including pregnancy[3]. Therefore we planned to continue anti-coagulation therapy for one year.

The development of MVT during pregnancy is multi-factorial, occurring due to physiological changes related to pregnancy and the additional impact of inherited or acquired thrombophilia. Clinical features noted in the 10 previously reported cases and the present case of MVT in a pregnant patient are shown in Table 1. Causes of the development of MVT in these cases were pregnancy itself in 5 patients, hypercoagulopathy in 3 patients, and hemoglobinopathy in 1 patient. Oral estrogen was administered during pregnancy in 2 cases, including the present case.

MVT development in our patient was associated with pregnancy achieved *via* IVF-ET, which is the most common assisted reproductive technology (ART) procedure used for infertility. In this case, IVF and frozen-thawed embryo transfer were performed; during this process, exogenous steroids (estrogen and progesterone) are often administered to prepare the endometrium to receive the thawed embryos and to ensure that the timing of endometrial preparation and embryo development coincide. Among steroids, oral contraceptives (OC) are known to be a risk factor for MVT[3], and OC accounts for 9%-18% of episodes of MVT in young women[4,5]. It is difficult to compare the effects of conjugated equine estrogen with those of OC because of differences in dosage and biological effects. However, in the present case, the administration of conjugated equine estrogen, in addition to pregnancy itself, might have caused similar MVT-related effects to those observed for OC. With the development of ART, the number of pregnant women taking estrogen during pregnancy may increase, which could lead to the more frequent development of thrombosis, including MVT.

Antepartum thrombo-prophylaxis is generally recommended for pregnant women with prior thrombosis[6]. However, findings regarding the risk of thrombosis in women with prior thrombosis who undergo ART are lacking, and dosage and thrombo-prophylaxis duration after ART have not been well investigated. For the present patient, another pregnancy may be difficult to achieve because infertility treatment without estrogen will be necessary.

In conclusion, pregnancy can increase the risk of MVT, which should be considered in the differential diagnosis of a pregnant patient with an acute abdomen. In cases of pregnancy achieved *via* IVF-ET, particularly frozen-thawed embryo transfer, the risk of thrombosis, including MVT, may be further increased due to the administration of estrogen for hormone replacement.

COMMENTS

Case characteristics

A 34-year-old woman was referred to the authors' hospital because of abdominal pain accompanied by vomiting and hematochezia.

Clinical diagnosis
The patient was diagnosed with acute mesenteric ischemia.

Differential diagnosis
The different diagnosis was hyperemesis gravidarum.

Laboratory diagnosis
An elevated D-dimer level suggested thrombosis.

Imaging diagnosis
Computed tomography scanning demonstrated thrombosis in the superior mesenteric vein extending into the portal vein.

Pathological diagnosis
Ischemic changes, including necrosis of the small bowel, were observed.

Treatment
The administered treatment was resection of the necrotic portion of the small bowel, anticoagulant therapy with unfractionated heparin, and urokinase continuously administered *via* the superior mesenteric artery.

Related reports
Mesenteric vein thrombosis (MVT) that develops during pregnancy is rare; only 10 known cases of this condition have previously been reported. This article provides the first report of MVT that developed following impregnation achieved *via in vitro* fertilization-embryo transfer.

Experiences and lessons
MVT should be included in the differential diagnosis of a pregnant patient who presents with an acute abdomen.

Peer-review
This is an interesting case highlighting the potential for a serious albeit infrequent complication of ART.

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In this article, the name of the third author, Dr. Di Saverio was spelled incorrectly. The correct name should be Salomone Di Saverio. We apologize for the error.

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ORIGINAL ARTICLE

Clinical Trials Study

Laparoscopic complete mesocolic excisions for colonic cancer in the last decade: Five-year survival in a single centre

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Author contributions: Storli KE designed the study, drafted the manuscript, collected the data and performed the statistical analysis; Lygre KB assisted in data collection and read and revised the manuscript; Iversen KB and Decap M operated several of the patients of the study and read the manuscript; Eide GE approved the statistical analysis and the manuscript text and content.

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Abstract

AIM

To analyse clinical and long-term oncologic results after laparoscopic complete mesocolic excision (CME) for colonic cancer over a 10-year period.

METHODS

Consecutive patients who received laparoscopic CME at our hospital from 2007 to 2017 were prospectively registered and retrospectively analysed. In total, 341

patients were included with tumour-nodal-metastasis (TNM) stages 0-III.

RESULTS

The mean age of the patients was 71.9 years. The median length of stay was 5 d. The mean lymph node harvest was 17.8. The mortality rate was 1.2%. Fifteen patients were reoperated on for anastomotic leaks. The local recurrence rate was 2.3%. Five-year TTR and cancer-specific survival CSS were 83.1% and 90.3%. The location of the tumour was not a significant variable for survival in unadjusted and adjusted survival analysis. TNM stage and anastomotic leaks were significant variables with respect to survival.

CONCLUSION

Laparoscopic CME results in acceptable complication rates and long-term oncologic results. It is important to avoid anastomotic leaks because of their negative effect on survival.

Key words: Complete mesocolic excision; Central vascular ligature; Colonic cancer; Laparoscopic surgery; Time to recurrence; Cancer specific survival

Core tip: This study presents a large cohort of patients operated on with laparoscopic complete mesocolic excisions (CME) for colonic cancer. Five-year survival data are presented. For the first time in a study on laparoscopic CME, it is shown that reoperation for an anastomotic leak has a negative impact on both unadjusted and adjusted survival analysis. The location of the tumour does not impact long-term survival.

Storli KE, Lygre KB, Iversen KB, Decap M, Eide GE. Laparoscopic complete mesocolic excisions for colonic cancer in the last decade: Five-year survival in a single centre. *World J Gastrointest Surg* 2017; 9(11): 215-223 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i11/215.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i11.215

INTRODUCTION

Colonic cancer is an important challenge for specialists in gastrointestinal surgery. Complete mesocolic eccision (CME) has been put forward as a method of standardizing the surgical aspect of colon cancer with acceptable survival results. Dr. Hohenberger introduced this principle and has published impressive outcome data[1,2]. Extended lymphadenectomy or D3 excision is popular in eastern countries and is the standard for T3/T4 tumours in Japan. This technique is comparable to CME and has demonstrated excellent survival results[3]. The completeness of the specimen after CME with central vascular ligature (CVL) and D3 excision has been proven to be of the same quality as CME alone in another paper[4]. The basis of the CME technique has been published in several papers[5,6]. A recent consensus article suggests that CME with CVL should be "the gold standard" for surgery in colonic cancer[5]. The minimal invasive/laparoscopic technique for treating colonic cancer has been evolving in the last decade. CME can also be performed with the laparoscopic approach[7-9]. Laparoscopic CME for transverse colonic cancer has also been shown to be feasible with acceptable morbidity and survival results[10].

In our hospital we converted the surgery for colon cancer into CME from 2007. The goal of the present study is to analyse the last ten years with laparoscopic CME for colonic cancer and present the short-term results as well as long- term oncologic results. Five-year survival data are presented. The data are prospectively recorded and retrospectively analysed. For the first time this paper demonstrates that postoperative complications have an important role in colonic cancer survival after radical laparoscopic CME.

MATERIALS AND METHODS

Patient selection

Consecutive patients were enrolled in a prospective study from January 2007 through December 2017. Survival data were analysed and collected in April 2017. All patients had a computed tomography (CT) scan of the chest and abdomen before surgery. The Union for International Cancer Control (UICC) tumour-nodal-metastasis (TNM) system was used for staging (7th edition)[11]. Patients were excluded if they had a radiological T4 tumour on preoperative CT scan of the chest and abdomen. If some part of the CME-principles was disregarded or the surgeons were not accredited to perform CME, these procedures were excluded (n = 5). All operative reports were read in detail.

Patient eligibility

Patients were included if they had a colonic cancer detected on colonoscopy and histologically proven to be an adenocarcinoma. The patients who were operated on according to the CME principles with the laparoscopic access were included. If the surgery was converted to an open procedure within 15 min from the start of the procedure, the patient was excluded from the study. Patients were included regardless of an earlier history of malignancy. Body mass index (BMI) was not considered. Robotic surgery was not implemented in our hospital for colonic cancer.

Patient evaluation and follow-up

Patients were operated in a single hospital and they were scheduled for a follow-up visit every 6 mo after blood tests and CT scan of the chest and abdomen. The patients were followed for five years. Colonoscopy was performed after one- and four-years after surgery.

Surgery

All the patients were operated with laparoscopic CME according to the principles of CME. The specimen was extracted from a small incision in the umbilicus. In the right sided resection the anastomosis was performed extra-corporally. Between March 2009 and 2017, approximately 80% of the resections were performed by lap CME. Less than 5% of the resections were converted from laparoscopic CME to open CME in this period.

Study design

This study was a cohort study on laparoscopic CME with data extracted from 2007 through December 2017. Patients converted to open surgery within the first 15 min of the laparoscopic procedure were excluded from the study. The survival data was analysed according to the actual treatment.

Treatment outcome

Treatment outcome was extracted after 5 years according to Punt *et al*[12]. TTR and CSS were used as the survival endpoints. Regarding oncologic results the patients were analysed as treated, meaning that only patients that were operated on laparoscopically from start to end were included.

Statistical analysis

We used the χ^2 test to compare proportions between groups. Gosset's *t*-test[13] or the Wilcoxon-Mann-Whitney test[14] were used to compare means. Regarding survival the log-rank test and Kaplan-Meier[15] plots were used. Multiple prognostic factors were analysed with the Cox proportional hazards model[16]. A significance level of $P \leq 0.05$ was applied. SPSS version 24 was used for statistical calculations.

RESULTS

Four hundred and seventy-five patients with TNM stages 0-IV colonic cancer operated on with laparoscopic CME were prospectively registered from May 2007 through December 2017. Patients operated on by surgeons not familiar with the CME principle were excluded (n = 5). Resections other than segmental resections were excluded, including single access procedures (n = 44). For the survival analysis only the patients with more than 12 mo of potential follow-up were included (2007-2015) (n = 375).

The aim of the study was to analyse the patients with TNM stages 0-Ⅲ and this left 341 patients for inclusion. These patients had a colonic cancer in all the different locations of the colon, including the transverse colon. Rectal cancer was defined as a tumour situated less than 15 cm from the anal verge defined on rectal examination or with MRI. These patients were excluded and treated in a different hospital.

Pathology

The patients had a mean age of 71.9 years. The mean BMI was 25.8 kg/m^2. One hundred and forty patients (41.1%) were operated on with a right hemicolectomy. Forty-nine patients (14.4%) were operated on with a right extended hemicolectomy for tumours in the right colonic flexure and the right transverse colon. Twenty-six patients (7.6%) were operated on with a left extended hemicolectomy for colonic tumours in the left of the mid-transverse colon, in the left flexure, and in the descending colon. One-hundred and twenty-six patients (37%) had an anterior resection. The cohort also included TNM stage 0 patients, patients with resection of a segment of the colon after R1 endoscopic resection of a malignant polyp. The resected specimen did not harbour malignancy locally or lymph nodes with metastasis. One-hundred and seventy patients were staged as TNM stage II (49.9%) and 102 patients were TNM stage III (29.9%). The patients had a mean lymph node count of 17.8 (range: 0-69). For the TNM stages 0-Ⅲ patients the mean number of positive lymph nodes was 3.2 (Table 1).

Morbidity and mortality

The median length of stay was 5 d. The mean length of stay was 6.7 d. Two hundred and sixty-seven patients (78.8%) had no complications or mortality. Four patients died in the first 30 d after surgery resulting in a mortality rate of 1.2%.

Fifteen patients had anastomotic leaks and were treated with surgery (4.4%). Six patients with a right-sided hemicolectomy had anastomotic leaks (4.3%). Seven patients (5.6%) with an anterior resection had anastomotic leask. Seventeen patients (5.0%) were treated for paralytic ileus (Table 2).

Oncologic outcome

The local recurrence rate was 2.3%. For right CME hemi-colectomy the local recurrence rate was 2.1% and 2.3% for anterior resection (n. s.). Twenty-two patients (6.5%) developed liver-metastasis, 5 patients (1.5%) a lung metastasis, and 19 patients (5.6%) combined metastasis. In the TNM stage Ⅲ group, 14 patients (13.7%) had combined metastasis and 9 patients (8.8%) had a liver-metastasis.

Five-year time to recurrence (TTR) and cancer specific survival (CSS) was 83.1% and 90.3%. TTR was 87.3% for TNM stage II and 69.5% for TNM stage Ⅲ. CSS was 94.4% for TNM stage Ⅱ and 77.0% for TNM stage III (Table 3). For TTR and CSS, operative procedure (or tumour-location) did not show a significant survival difference in univariate analysis (Figures 1 and 2). Whether the patient developed an anastomotic leak or not revealed a significant difference in survival both in TTR and CSS (Figures 3-5). With respect to TTR the patients with anastomotic leaks had significantly worse survival (P = 0.037)

Table 1 Characteristics of 341 tumour-nodal-metastasis stages 0-III patients with colonic cancer, operated on with laparascopic complete mesocolic excision resection in a community teaching hospital in Norway in 2007-2015

Variable category	Laparoscopic CME resection, *n* = 341 (%)
Age in years, mean, (range)	71.9 (28-94)
BMI in kg/m^2, mean (range)	25.8 (15-42)
Surgical procedure	
Right hemicolectomy	140 (41.1)
Extended right hemicolectomy	49 (14.4)
Left extended hemicolectomy	26 (7.6)
Sigmoid resection	126 (37.0)
TNM stage	
Stage 0	8 (2.3)
Stage I	61 (17.9)
Stage II	170 (49.9)
Stage III	102 (29.9)
No. of lymph nodes, mean (range)	17.8 (0-69)
No. of positive lymph nodes, TNM st III, mean (range)	1.2 (0-19)
Length of stay, d, mean (range)	6.7 (2-57)

TNM: Tumour-nodal-metastasis; CME: Complete mesocolic excision; BMI: Body mass index.

Table 2 Operative morbidity and mortality in 341 patients with colonic cancer (tumour-nodal-metastasis stage 0-III) operated on with laparoscopic complete mesocolic excision in a community teaching hospital in Norway in 2007-2015 *n* (%)

Variables Category	Laparoscopic CME colectomy (*n* = 341)
Morbidity	
No morbidity	267 (78.8)
Paralytic ileus	17 (5.0)
Wound infection	4 (1.2)
Wound dehiscence	8 (2.3)
Deep (IAA) infection	5 (1.5)
Anastomotic leakage	15 (4.4)
Cardiac/respiratory distress	11 (3.2)
Ileus reoperation	2 (0.6)
Other (bladder infection, iatrogenic perf small intestine)	6 (1.8)
Mortality	4 (1.2)

TNM: Tumour-nodal-metastasis; CME: Complete mesocolic excision; IAA: Intra-abdominal abscess.

Table 3 Five-year survival figures given as time to recurrence and cancer-specific survival according to tumour-nodal-metastases stages 0-III in 341 colon cancer patients that were operated on with laparoscopic complete mesocolic excision during 2007-2015 in one community teaching hospitals in Norway

Survival type TNM	5-yr survival (%)	*P* value[1]
TTR	83.1	< 0.001
Stage 0	100	
Stage I	91.9	
Stage II	87.3	
Stage III	69.5	
CSS	90.3	< 0.001
Stage 0	100	
Stage 1	100	
Stage 2	94.4	
Stage 3	77	

[1]Adjusted for TNM stage with the log rank test. TNM: Tumour-nodal-metastases; CME: Complete mesocolic excision; TTR: Time to recurrence; CSS: Cancer-specific survival.

than those without a leak. This is also shown in a Cox regression analysis according to operative procedure (Figure 3). With respect to CSS the difference was also significant (P = 0.023). In multiple Cox regression for TTR, TNM stage and an anastomotic leak were significant factors for survival (Table 4).

DISCUSSION

The interest in proper radical surgery for colonic

Table 4 Uni- and multi-variate analysis of 5-year time to recurrence for 341 patients operated for tumour-nodal-metastases stage 0-III colonic cancer in a Norwegian community teaching hospital

	Unadjusted HR (95%CI)	LR test *P* value	Adjusted HR (95%CI)	LR test *P* value
Age		0.665		0.673
< 70 yr	1 (reference)		1 (reference)	
> 70 yr	0.89 (0.51, 1.54)		1.15 (0.60, 2.20)	
BMI	1.01 (0.94, 1.08)	0.777	1.01 (0.94, 1.08)	0.855
Operative procedure		0.696		0.367
Right hemicolectomy	1 (reference)		1 (reference)	
Extended right hemicol	0.70 (0.37, 1.30)		1.96 (0.76, 5.08)	
Extended left hemicol	0.97 (0.43, 2.17)		1.63 (0.51, 5.23)	
Anterior resection	0.87 (0.30, 2.52)		1.85 (0.88, 3.88)	
Lymph nodes	1.02 (0.98, 1.05)	0.356	1.00 (0.97, 1.05)	0.652
Positive lymph nodes	1.16 (1.09, 1.23)	< 0.001	1.21 (1.13, 1.29)	< 0.001
Anastomotic leakage		0.045		0.019
No leak	1 (reference)		1 (reference)	
Leak, reoperated	2.57 (1.02, 6.47)		3.13 (1.21, 8.10)	

BMI: Body mass index; LR: Likelihood ratio.

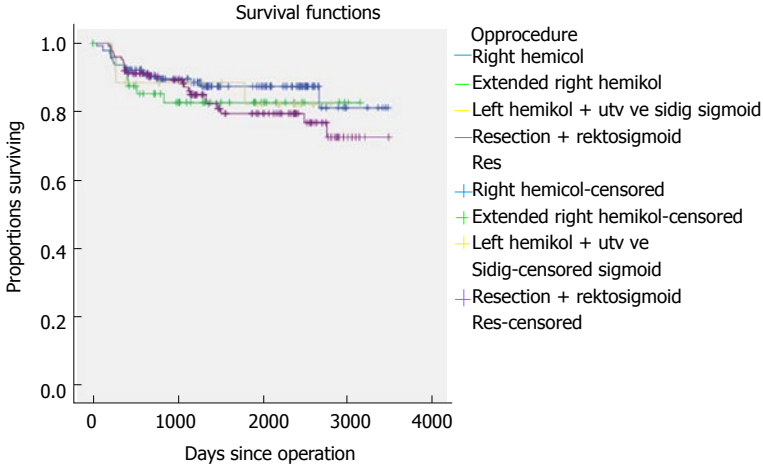

Figure 1 Time to recurrence shown according to resection type for 341 patients with colonic cancer operated on with laparoscopic complete mesocolic excision in a Norwegian community teaching hospital during 2007-2017 (*P* = NS).

cancer has increased in the last decade since the first publications on CME from Dr. Hohenberger. Opponents of this technique argue that this is nothing new[17].

Another interesting discussion is whether removing the apical lymph nodes in extended lymphadenectomy or in CME with CVL in patients with TNM stage III disease matters. Many argue that these patients have a systemic disease and might develop distant metastasis regardless of the CME with CVL. Many of these patients also receive chemotherapy, which influences survival[18]. Bertelsen *et al*[19] demonstrated better disease-free survival in patients with TNM stage Ⅰ and Ⅱ colonic cancer treated with CME versus conventional surgery. Our group has also demonstrated this in patients with TNM stage I and Ⅱ disease[20]. Survival for the TNM stage III patients was improved in the paper by Bertelsen *et al*[19] but it was not significant. If the surgeon removes the apical lymph nodes in CME surgery with cancer cells, there could be an upstaging of the disease from TNM stage Ⅱ to TNM stage Ⅲ. This will also require treatment with chemotherapy. There is evidence indicating that this upstaging might not be the case. In a paper from our group we compared two patient cohorts in two time periods in three hospitals with increasing lymph node harvest from a mean figure of 10 lymph nodes to 16 lymph nodes. We could not show any stage migration[21].

In the recent years, there has been an increasing focus on the nature of the tumours in the right and transverse colon. Papers have focused mostly on CME for right-sided colonic cancer[8,22,23]. The complex anatomy of the right colon makes open and laparoscopic CME procedures more difficult than the conventional right hemicolectomy. The vascular anatomy can be different from patient to patient[24]. In this trial we could not show any significant difference in survival according to the operative procedure or location of the tumour. We followed 75 patients with a tumour in the transverse colon and in the flexures

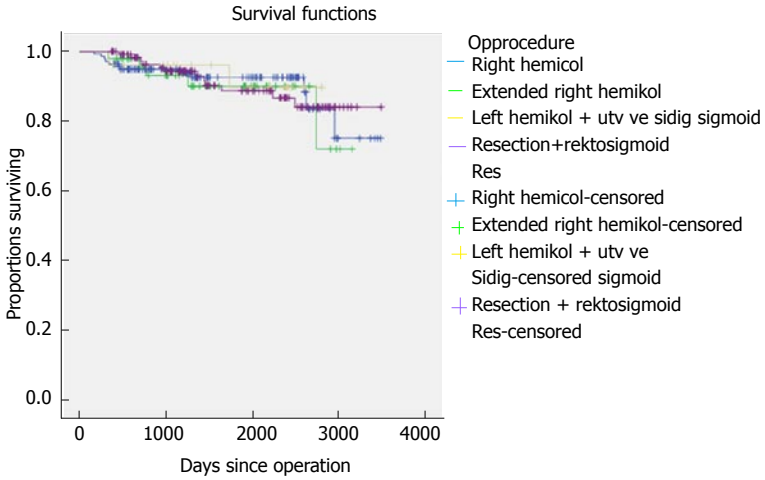

Figure 2 Cancer-specific survival shown according to resection type for 341 patients with colonic cancer operated on with laparoscopic complete mesocolic excision in a Norwegian community teaching hospital during 2007-2017 (*P* = NS).

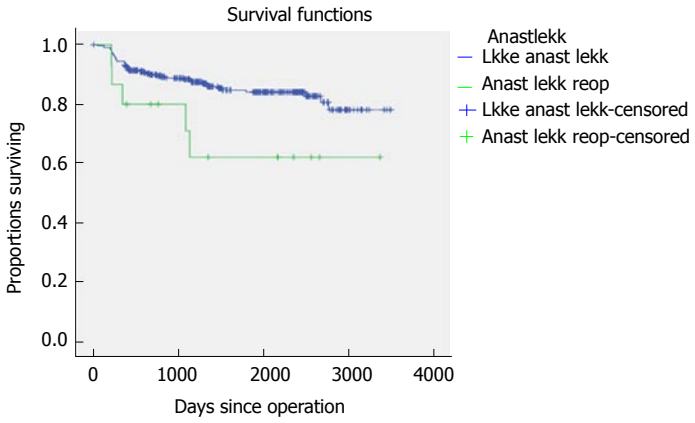

Figure 3 Time to recurrence shown according to reoperation for anastomotic leak for 341 patients with colonic cancer operated on with laparoscopic complete mesocolic excision in a Norwegian community teaching hospital during 2007-2017 (*P* = 0.037).

and 140 patients with a tumour in the right colon. Tumours located between the flexures are even more complex in anatomy and demands a technically skilled surgeon to perform laparoscopic CME. In the literature, there is very little evidence for CME surgery as a treatment for transverse colonic cancer. There is only one study from our group comparing laparoscopic CME and open CME[10]. This study shows decent survival results and no difference in survival between open and laparoscopic CME.

Morbidity is another important issue with CME surgery. With CVL of the superior mesenteric vein and artery, there is of course the possibility of vessel injury. Bertelsen *et al*[25] demonstrated in their study a small increase in vessel damage with CME compared to conventional surgery. The mean age of the patients in this study was 71.9 years. The mortality was 1.2%. The anastomotic leak rate was 4.4%, and these patients required reoperation. Almost 80% of the patients had no complications. Whether the surgeons should pursue even more radical surgical approaches for colonic cancer or not should be questioned.

Robotic surgery for colonic cancer and with CME has been performed. Spinoglio *et al*[26] demonstrated the feasibility of this procedure and also showed quite acceptable survival data. The advantage of robotic surgery is of a more technical nature. The more natural flexion and "wrist" like instruments make it easier to perform surgery and an intra-corporal anastomosis. An experienced laparoscopic surgeon might not perform better using the robot. The increased cost of the robotic platform makes it difficult to implement when the evidence of the "real" advantages does not exist. It was published in two CME-review articles in 2017. Emmanuel *et al*[27] concluded that there is a reasonable basis for the technique, but that there are no randomized trials from which to draw conclusions. There is no high quality evidence to recommend CME as the gold standard in colonic cancer surgery[27]. Gouvas *et al*[28] found evidence for a better surgical specimen after CME surgery. There are more lymph nodes and more tissue excised, which is important for a better surgical outcome. They admit, however, that there is limited evidence for an improved survival

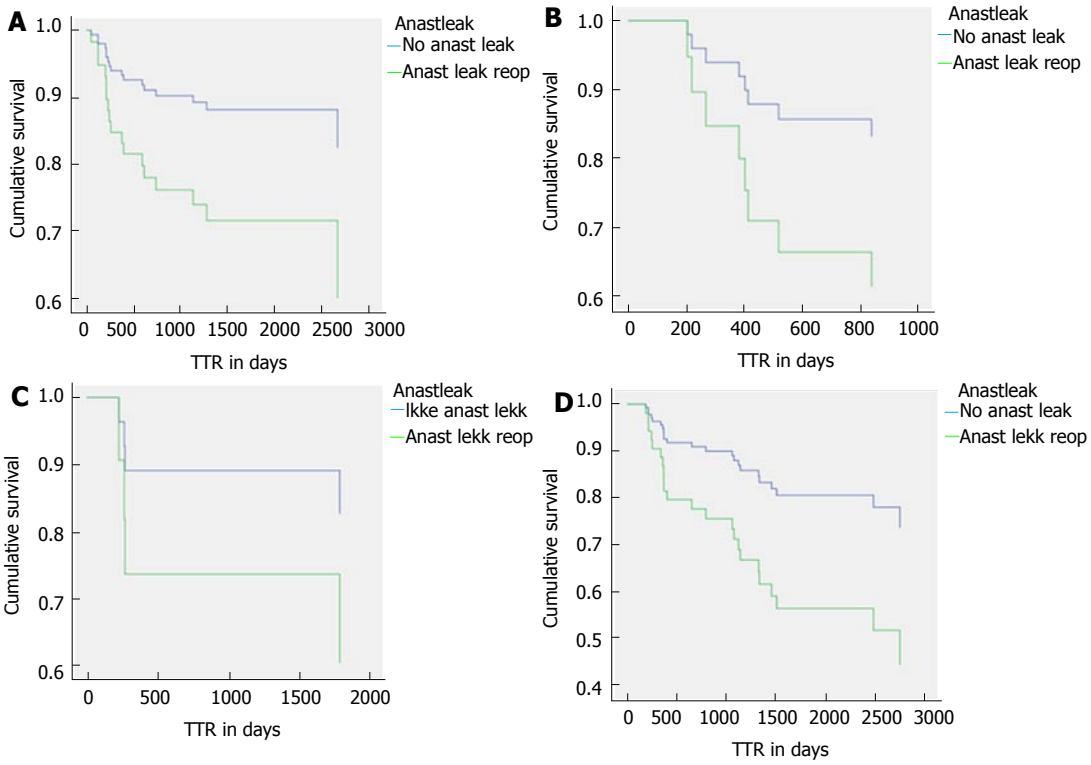

Figure 4 Time to recurrence and anastomotic leakage. A: Survival curves for time to recurrence (TTR) from a Cox regression model for patients with right colonic cancer operated on with laparoscopic complete mesocolic excision (CME) in a Norwegian community teaching hospital during 2007-2015 with or without an anastomotic leak (P = 0.037); B: TTR shown as Cox regression curves for patients with right flexure or right proximal transverse colonic cancer operated on with laparoscopic CME in a Norwegian community teaching hospital during 2007-2015 with or without an anastomotic leak (P = 0.037); C: TTR shown as Cox regression curves for patients with left transverse, left flexure or descending colon cancer operated on with laparoscopic CME in a Norwegian community teaching hospital during 2007-2015 with or without an anastomotic leak (P = 0.037); D: TTR shown as Cox regression curves for patients with sigmoid or recto-sigmoid colon cancer operated on with laparoscopic CME in a Norwegian community teaching hospital during 2007-2015 with or without an anastomotic leak (P = 0.037).

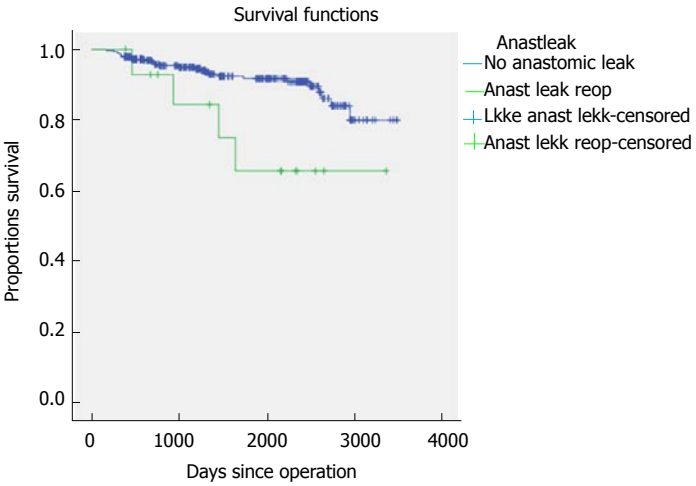

Figure 5 Cancer-specific survival shown according to reoperation for anastomotic leak for 341 patients with colonic cancer operated on with laparoscopic complete mesocolic excision in a Norwegian community teaching hospital during 2007-2017 (P = 0.023).

outcome after CME[28]. There might be a problem with a randomised trial of CME. What will be the other group? There is hope for a standardisation of the surgical technique in colonic cancer. This can also result in improvement of the survival of colonic cancer globally.

In this paper, we presented data on the long-term survival outcome of patients with colonic cancer operated on by laparoscopic CME. The 5-year TTR was 83.1% in TNM stage Ⅰ-Ⅲ patients. For TNM stage Ⅱ and Ⅲ, it was 87.3% and 69.5% respectively. The 5-year cancer specific survival (CSS) was 90.3%. For TNM stage Ⅱ and Ⅲ, it was 94.4% and 77% respectively. In both unadjusted and adjusted

survival analysis, anastomotic leak was a significant variable together with TNM stage. To the best of our knowledge, this is the first paper to show an inferior survival with anastomotic leaks in laparoscopic CME surgery for colonic cancer. The limitations of this study are the sample size, the confounding factor of the selection process of patients to the laparoscopic procedure and the lack of analysis of the patients after the intention to treat principle.

It is important to perform optimal radical surgery with avoidance of anastomotic leaks in patients with colon cancer. It is also important to avoid an anastomotic leak in the patients with colonic cancer. Laparoscopic mesocolic excision (CME) is feasible and shows acceptable long-term oncological outcomes.

COMMENTS

Background

Surgery in colonic cancer has improved over the last decade. There has been an increased interest in more standardized and more extensive or radical surgery. The Japanese surgeons have standardized their resections according to the depth of tumour growth. T3 and T4 tumours are treated with D3 excision in the central area and complete mesocolic excision (CME) around the tumour and mesocolon. T1 and T2 tumours are treated less radical with a D2 excision. The CT scan is the basis for staging preoperatively and for the extent of resection. Laparoscopic surgery for colonic cancer has been proven to be not inferior to open surgery. The most important issue is the oncologic technique and the standardisation of this technique and not the open or laparoscopic approach. The benefit of laparoscopc surgery in the short term is proven in many papers and population studies. If the surgeon has the laparoscopic skills, the preferred approach for colonic cancer is by laparoscopy. The CME technique is a promising approach for colonic cancer. The evidence is building up but there are no randomised trials comparing CME + central vascular ligature (CVL) and other techniques. The problem is which procedure is less radical or more "ordinary" than CME? Is it possible to conduct a randomised trial?

Research frontiers

The authors hope for population based studies in the future comparing CME with some other technique or no standardised colonic cancer surgery. The authors have initiated a randomised trial together with Haukeland University Hospital, comparing laparoscopic CME + CVL and extended D3 excision with open surgery. The authors hope that this trail will show the extent of radical surgery needed to perform a safe and proper oncological resection for colonic cancer. What is enough? Open surgery and extended D3 excision can potentially be harmful to the patients. The authors need to evaluate this issue over the next years.

Innovations and breakthroughs

Robotic surgery is already implemented in many hospitals and more and more resections are being performed for colonic cancer. Robotic surgery is only an alternative approach in minimal invasive surgery but proponents claim that patients can have even better short term effects with the robot. There is still no evidence showing improvement in any regard with the use of the robot compared to laparoscopic surgery for colonic cancer. There is an increasing focus on mapping the vasculature around the right colon and this improves the planning before the surgery. The surgeon is delivered more knowledge about the vessels but also the tumour and lymph nodes based on improved radiological services. For the more advanced tumours of the colon (T3 and T4) there is promising studies around using neoadjuvant chemotherapy. This treatment can downstage these tumours and make surgery possible without resection of other organs. Some patients who is node positive before surgery can be node negative after treatment and then they do not need chemotherapy treatment after surgery.

Applications

This is a quite big cohort of patients operated with laparoscopic CME and CVL. The survival results show a decent 5-year survival. The short-term effect is quite good with a low mortality and few complications. These results are building up the evidence in favour of laparoscopic CME + CVL as the new "gold" standard for colonic cancer surgery.

Terminology

CME is a surgical method which focuses on doing surgery in embryological planes without tearing the planes. The standardisation of the surgery is important. CVL and D3 surgery in the central area are almost the same.

Peer-review

Well written paper on a topic of interest.

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ORIGINAL ARTICLE

Clinical Trials Study

Colorectal surgeon consensus with diverticulitis clinical practice guidelines

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Institutional review board statement: The study was reviewed and approved by the Human and Research Ethics Committee, The University of Sydney and the Colorectal Surgical Society of Australia and New-Zealand for distribution to members.

Informed consent statement: Submission of the completed survey was an indication of the surgeon's consent to participate in the study. This was mentioned in the participant information sheet (attached) to all members of the Colorectal Surgical Society of Australia and New Zealand.

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Abstract

AIM

To determine the application of clinical practice guidelines for the current management of diverticulitis and colorectal surgeon specialist consensus in Australia and New Zealand.

METHODS

A survey was distributed to 205 colorectal surgeons in Australia and New Zealand, using 22 hypothetical clinical scenarios.

RESULTS

The response rate was 102 (50%). For 19 guideline-based scenarios, only 11 (58%) reached consensus (defined as > 70% majority opinion) and agreed with guidelines; while 3 (16%) reached consensus and did not agree with guidelines. The remaining 5 (26%) scenarios showed community equipoise (defined as less than/equal to 70% majority opinion). These included diagnostic imaging where CT scan was contraindicated, management options in the failure

of conservative therapy for complicated diverticulitis, surgical management of Hinchey grade 3, proximal extent of resection in sigmoid diverticulitis and use of oral mechanical bowel preparation and antibiotics for an elective colectomy. The consensus areas not agreeing with guidelines were management of simple diverticulitis, management following the failure of conservative therapy in uncomplicated diverticulitis and follow-up after an episode of complicated diverticulitis. Fifty-percent of rural/regional based surgeons would perform an urgent sigmoid colectomy in failed conservative therapy of diverticulitis compared to only 8% of surgeons city-based (Fisher's exact test $P = 0.016$). In right-sided complicated diverticulitis, a greater number of those in practice for more than ten years would perform an ileocecal resection and ileocolic anastomosis (79% *vs* 41%, $P < 0.0001$).

CONCLUSION

While there are areas of consensus in diverticulitis management, there are areas of community equipoise for future research, potentially in the form of RCTs.

Key words: Diverticulitis; Clinical practice guidelines; Consensus

Core tip: This study illustrates colorectal surgeon specialist consensus with clinical practice guidelines for diverticulitis. While consensus occurred with the majority of guideline recommendations, areas with lack of consensus and even consensus that disagrees with guidelines focuses where future research efforts should be placed.

Siddiqui J, Zahid A, Hong J, Young CJ. Colorectal surgeon consensus with diverticulitis clinical practice guidelines. *World J Gastrointest Surg* 2017; 9(11): 224-232 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i11/224.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i11.224

INTRODUCTION

Sigmoid diverticulitis is a common affliction of the Western world, and recently, due to migration, there has been an increase in the incidence of right-sided diverticulitis[1]. Diverticulitis can be divided into the simple and complicated disease. Complicated disease includes perforation, obstruction, abscesses, fistula and stricture formation. With greater understanding of the pathophysiology of diverticulitis and the advancement of technology, the management of diverticulitis has been evolving in recent times. There is a greater push towards the outpatient management of simple diverticulitis and less aggressive initial management for complicated cases. There is also a change in surgical management options including laparoscopic *vs* open approach and primary anastomosis *vs* Hartmann's procedure for Hinchey Grades 3 and 4. An attempt has been made by several societies to condense some of this into guidelines and practice parameters based on level of evidence[2-4].

Previous surveys[5-9] have assessed correlation in their community with these guidelines. However, no surveys have been conducted in Australasia that evaluates correlation with guidelines for both the current medical and surgical management of diverticulitis, as well as giving consideration to right-sided diverticulitis.

The aim of our survey was to assess consensus of current colorectal specialist practice within Australia and New Zealand with the clinical practice guidelines for the management of simple and complicated diverticulitis (mainly practice parameters published by the Standards Task Force of The American Society of Colon and Rectal Surgeons[2] as there are no Australasian guidelines on this subject). We also aimed to highlight areas of community equipoise, to identify areas that will benefit from future research.

MATERIALS AND METHODS

All members of the Colorectal Surgical Society of Australia and New Zealand (CSSANZ) were mailed out an anonymous survey consisting of 22 clinical scenarios with multiple choice options (Appendix 1). One reminder mail was sent out after six weeks to non-respondents. The University of Sydney Human Ethics department granted ethical approval and the CSSANZ approved the distribution of the questionnaires.

Surgeon demographics were collected including age range, gender, years practicing, the location of training and current practice, as well as the presence of interventional radiology and an Acute Surgical Unit (ASU) at the place of practice.

The survey was based on clinical scenarios to evaluate the medical and surgical management of uncomplicated and complicated diverticulitis. Nineteen questions were derived from the recently published guidelines[2,4] containing an option of 3 to 4 multiple choices, one of which matched the guideline recommendations. The remaining three scenarios were not directly related to the guidelines but were developed to examine surgeon preferences in additional controversies in diverticulitis management not included in the guidelines. The areas covered included initial diagnostic imaging, diagnostic imaging when CT is contraindicated, management of differing size and location of abscesses, management in a medically complex patient, management upon failure of conservative therapy, follow-up options following simple and complicated diverticulitis, surgical management options for different Hinchey grades, as well as operative considerations and management of right-sided diverticulitis. The American Society of Anesthesiologists

Table 1 Surgeon demographics

Characteristic	*n* (%)
Age range (yr)	
30-39	10 (10)
40-49	37 (37)
50-59	40 (40)
Over 60	14 (14)
Gender	
Male	90 (89)
Female	11 (11)
Location of current practice	
City (tertiary/quaternary referral center)	79 (78)
City (secondary referral)	16 (16)
Rural	6 (6)
Location of subspecialty training[1]	
Australia/New Zealand	66 (65)
Europe	28 (28)
North America	15 (15)
Country of current practice	
Australia	84 (83)
New Zealand	17 (17)
ASU present in current practice location	57 (56)
Interventional radiology available	99 (98)
Average years in practice (years ± SD)	14 ± 8.5

[1]Total > 100% due to > 1 location of training.

(ASA) grade was provided for reference. Completion of the survey by other colorectal specialists in the department tested for accuracy and validity before dissemination to other members of CSSANZ.

Statistical analysis

Statistical analyses were conducted using IBM SPSS Statistics Version 22. Demographics were tabulated and descriptive statistics (proportion and mean ± SD) were calculated. Two groups were formed - the first compared those that agreed with guideline recommended options and the second compared those that chose the most popular option among the choices provided (*i.e.*, the greatest number of respondents choosing this option). All demographic data were tested for their association with these two groups. Univariate analysis was carried out using the χ^2 test or Fisher's exact test where appropriate. Multivariate logistic regression analysis was used to assess associations between covariates. A *P*-value of less than 0.05 was considered significant.

The proportion of surgeons that agreed with the guideline-recommended option for each scenario was calculated, as well as the proportion forming a majority for an option. Evidence suggests[10,11] community equipoise is low when more than 70% of respondents favored one treatment option. Thus, community equipoise was then assessed by classifying the survey scenarios into one of four categories based on the proportion of responses: (1) Consensus/Disagree: scenarios with > 70% of surgeons choosing an option that disagrees with guideline recommendation; (2) Equipoise/Disagree: scenarios with ≤ 70% of surgeons choosing an option that disagrees with guideline recommendation; (3) Equipoise/Agree: scenarios with ≤ 70% of surgeons choosing an option that agrees with guideline recommendation; and (4) Consensus/Agree: scenarios with > 70% surgeons choosing an option that agrees with guideline recommendations.

RESULTS

Of 205 members of the CSSANZ, 102 (50%) responded by returning the survey, of which one was incomplete and excluded from analysis. Surgeon demographics are summarized in Table 1. The mean number of years in practice was 14, with 53% of surgeons aged more than 50 years. Sixty-five percent underwent the majority of their sub-specialty colorectal surgery training in Australia or New Zealand, and 82% are currently practicing in Australia.

From the 19 guideline based scenarios in the survey, 14 (74%) reached consensus. Of these 14, 3 (21%) scenarios disagreed with guideline recommendation. Five (26%) scenarios showed community equipoise, out of which 2 (40%) disagreed with guideline recommendation and 3 (60%) agreed with guidelines (Figure 1).

Consensus and disagree with guideline recommendations

There were three scenarios that reached consensus but disagreed with guideline recommendations. These were: (1) Initial management of diverticulitis: The consensus being admitting for bowel rest and intravenous antibiotics (76%) as opposed to guideline recommendation of outpatient management on oral antibiotics (18%). Four percent would provide

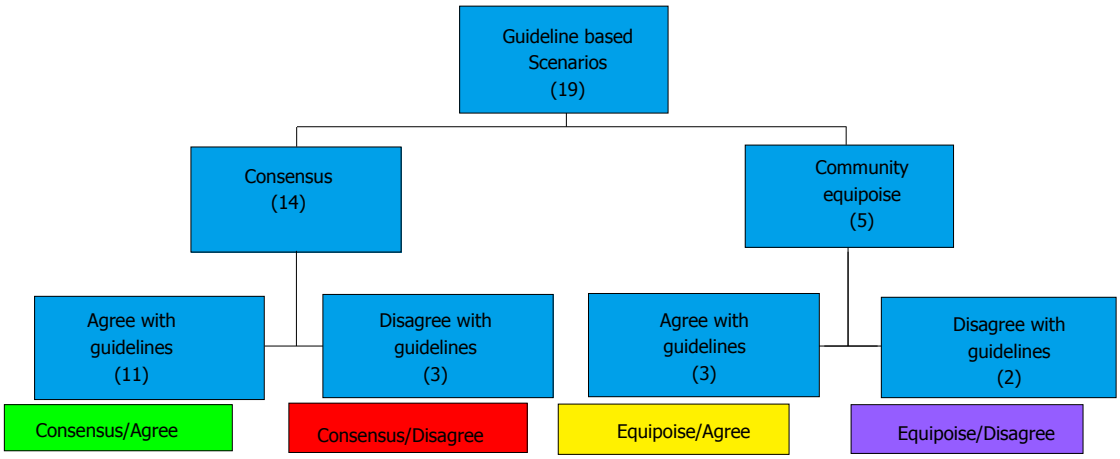

Figure 1 Summary of survey responses forming the four categories.

supportive care without the use of antibiotics; (2) Failure of conservative management for uncomplicated sigmoid diverticulitis: The consensus being to repeat CT scan of abdomen (71%, shown by multivariate analysis to be more likely if practicing for greater than 10 years - 80% *vs* 59%, $P = 0.043$) as opposed to organizing an emergency sigmoid colectomy (11%, more likely if working in a rural/regional center - 50% *vs* 8%, Fisher's exact test $P = 0.016$); and (3) Management following recovery from an episode of complicated diverticulitis: The consensus being no operative management (92%) as opposed to resection (7%).

Community equipoise

Equipoise and disagree with guidelines recommendations: There were two scenarios with equipoise and disagreed with guideline recommendation. These were: (1) Imaging modality when CT contraindicated. The majority opinion was to perform a CT scan (57%), with some stating without contrast. Only 21% agreed to the alternative of US or MRI. 71 percent of surgeons practicing less than 10 years *vs* 48% practicing for more than 10 years would choose CT scan when CT was contraindicated ($P = 0.03$). Choosing US or MRI was more likely if the surgeon was aged over 50 years old (30% *vs* 11%, Fisher's exact test $P = 0.017$); (2) Use of bowel preparation and antibiotics prior to elective colectomy. The majority (57%) of respondents would use oral, mechanical bowel preparation prior to the procedure and Ⅳ antibiotics on induction of general anesthesia. This was more likely to be the case if the surgeon was aged over 50 years old (67% *vs* 47%, $P = 0.04$).

Equipoise and agree with guideline recommendations: There were three scenarios with equipoise but agreed with guideline recommendations. These were: (1) Failed conservative management for complicated diverticulitis. Sixty-three percent of respondents agreed to image guided percutaneous drainage for a 3 cm mesocolic abscess not responding to conservative management. Univariate analyses demonstrated that a significantly greater number of those practicing in a rural/regional or a secondary referral center compared with those in a tertiary or quaternary referral center (91% *vs* 56%, $P = 0.002$), and those practicing for more than 10 years (71% *vs* 50%, $P = 0.047$) was associated with this; (2) Hinchey Grade 3 management. Fifty-six percent would do a Hartmann's procedure as opposed to 3% choosing resection with primary anastomosis and diverting colostomy and 34% choosing on table colonic lavage and colorectal anastomosis with diverting loop ileostomy. A greater proportion of North American sub-specialty trained surgeons (87% *vs* 51%, Fisher's exact test $P = 0.009$) and non-Australasian trained surgeons (77% *vs* 46%, $P = 0.002$) would perform a Hartmann's procedure in this case, as well those practicing for more than 10 years (67% *vs* 32%, $P = 0.001$) and surgeons aged over 50 years old (70% *vs* 40%, $P = 0.002$); and (3) Proximal extent of resection. The majority (57%) would remove colon where there is thickened, inflamed and hypertrophic tissue and resect the whole sigmoid colon (62% of Australian based *vs* 35% of New Zealand based surgeons, $P = 0.04$), whereas 14% would only do the former and 24% would only do the latter.

Consensus and agree with guideline recommendations

There were eleven scenarios that reached consensus and agreed with guideline recommendations. These are summarized in Table 2.

The remaining three scenario-based questions that did not relate to guidelines were based on surgical management options. In a patient undergoing resection of the diseased segment in sigmoid diverticulitis, 42% would complete the operation *via* a colorectal anastomosis with diverting loop ileostomy ± on-table colonic lavage, 31% would complete it with a colorectal anastomosis ± on-table colonic lavage without diversion and 18% with an end colostomy construction. For Hinchey Grade 2, where only surgical management

Table 2 Topics that reached consensus and agree with guideline recommendations

Guideline recommendation	In agreement (%)	*P*-value
CT scan as initial diagnostic modality	77	
Surgeon North American trained	100 *vs* 73	0.015[1]
Surgeon practicing in Australia	81 *vs* 59	0.047
Right-sided diverticulitis - CT initial imaging	93	
Surgeon age < 50 years old	100 *vs* 89	0.02[1]
Right-sided diverticulitis - Initial management oral/IV antibiotics and bowel rest	95	
Surgeon practicing in Australia	98 *vs* 82	0.033[1]
Small diverticular abscess management with antibiotics/bowel rest	77	
Surgeon North American trained	100 *vs* 73	0.015[1]
Large left-sided diverticular abscess management with percutaneous drainage	81	
Large right-sided diverticular abscess - percutaneous drainage	83	
Absence of ASU at surgeons place of practice	93 *vs* 75	0.016[1]
Hinchey Grade 4 - Hartmann's procedure	81	
Surgeon age > 50 years old	89 *vs* 72	0.034
Routine elective resection in young patient (< 50 years) NOT recommended	99	
For elective anterior resection - extend distal margin to proximal rectum	94	
Surgeon Non-European trained	99 *vs* 82	0.006[1]
Follow-up for high risk patient with uncomplicated diverticulitis	99	
Endoscopic evaluation following acute episode	83	

[1]Fisher's exact test *P*-value. ASU: Acute surgical unit.

options were provided, 48% would resect with primary anastomosis, 20% chose Hartmann's operation and 18% chose laparoscopic lavage, with 14% not choosing an option and some stating they would not operate and treat conservatively. Multivariate analysis demonstrated that those practicing in a city setting were more likely to choose resection with primary anastomosis (55% *vs* 27%, $P = 0.035$). In a patient with right-sided diverticulitis with confirmed perforation and a 5 cm abscess formation, 66% would perform an ileocecal resection and ileocolic anastomosis. This was more likely if a surgeon was in practice for more than 10 years (78% *vs* 41%, $P < 0.0001$) or based in Australia compared to New Zealand (71% *vs* 41%, $P = 0.016$). By multivariate analysis, practicing for more than 10 years was found to be significant for performing an ileocecal resection and ileocolic anastomosis ($P = 0.001$) (Figure 2).

The responses to the 19 guideline-based scenario questions are summarized in Figure 3 according to the sixteen clinically based diverticulitis management topics that they fit into. This is due to the eleven scenarios that reached consensus and agree scenarios in Table 2 being able to coalesce into eight topics.

DISCUSSION

Our survey is the first to evaluate both medical and surgical management decisions of simple and complicated diverticulitis within Australasia. It shows there remain areas of community equipoise, approximately in a third of the guideline related topics in our survey, and where consensus does exist, it is not always in agreement with accepted guidelines. Some management decisions were found to be dependent on duration of practice.

Individual equipoise measures clinical uncertainty and occurs when an individual clinician is completely undecided. Community equipoise applies when there are differing views among the profession as a whole[10]. There were three topics with moderate quality evidence in guideline recommendations; however, our survey respondents disagreed with these. These were in the areas of management following failed conservative therapy for uncomplicated diverticulitis, recovery from an episode of complicated diverticulitis and use of bowel preparation and antibiotics for elective resection.

The ASCRS practice parameters[2] recommends an urgent sigmoid colectomy for those in whom non-operative management of acute diverticulitis fails. This includes those who have continued abdominal pain or cannot tolerate enteral nutrition secondary to a bowel obstruction or ileus. In our survey, 71% opted for a repeat CT scan instead. This may be a reasonable option in order to exclude possible abscess formation avoiding the need for surgery. The urgency to operate should be assessed on a case by case basis depending on patient factors.

Despite the recommendation of an elective colectomy following recovery from an acute episode of complicated diverticulitis, only 7% of respondents in our survey chose this for an ASA grade 2 patient. The ASCRS[2], The Netherland[12], WGO[4] and German guidelines[13] recommend elective colectomy following recovery from an episode of complicated diverticulitis. However, there is still a need for further research in terms of resection criteria for this group of patients, which may explain why Australasian colorectal specialists are still acting conservatively. In contrast, the Danish guidelines[14] do not recommend elective resection unless it is for patients with fistula or stenosis. Vennix *et al*[3] concluded in their systematic review of guidelines that surgery

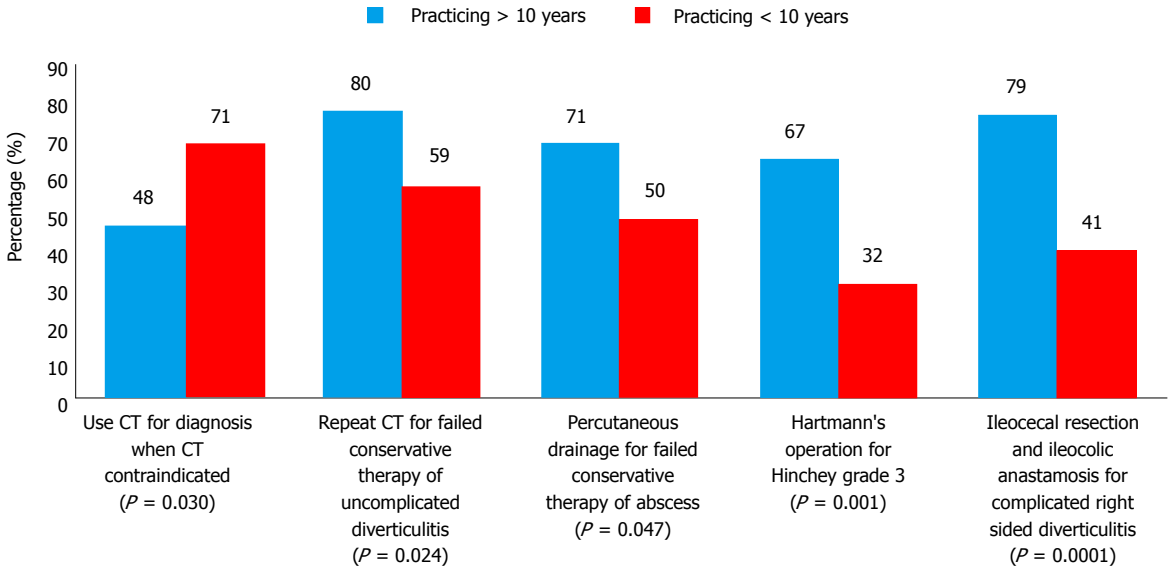

Figure 2 Areas of significance when considering duration of colorectal surgeons practice. All *P* values are from χ^2 test.

is not required in the case of conservatively treated abscess, however, if it is a pelvic abscess then this can be justified. Recently, a population-based analysis[15] also showed a decline in elective colectomy following an episode of diverticulitis. This was most pronounced in those younger than 50 years old (17% to 5%) and with complicated disease states (21% to 8%, $P < 0.0001$).

The ASCRS practice parameters[2] state that for elective colon resection, oral mechanical bowel preparation is not required; however, oral antibiotics given pre-operatively may reduce surgical site infections. Recently the use of oral, mechanical bowel preparation has been questioned prior to elective colectomy and the ASCRS guidelines recommend the use of oral antibiotics to reduce surgical site infections (SSI). A large systematic review found no statistically significant evidence that patients undergoing colonic surgery benefit from mechanical bowel preparation. Guenaga *et al*[16] conducted a meta-analysis showing there was no benefit of mechanical bowel preparation in terms of reduced rates of wound infection or anastomotic failure. Bellows's *et al*[17] meta-analysis showed that use of oral and IV antibiotics reduced risk of surgical wound infection (RR 0.57, 95%CI: 0.43-0.76, $P = 0.0002$), but had no effect on organ space infections or risk of anastomotic leak. There is still lack of high-grade research looking specifically at diverticulitis and colonic surgery. Our survey showed that surgeons aged over 50 years old were more likely to use oral, mechanical bowel preparation and IV antibiotics on GA induction compared to those under 50 years.

There were two topics with low quality evidence in guideline recommendations that our survey respondents disagreed with. This included initial management of uncomplicated diverticulitis and initial diagnostic modality when CT contraindicated.

For management of simple, uncomplicated diverticulitis in patients with no systemic manifestations of infection, recent studies[18-21] have pushed towards the outpatient management of simple diverticulitis utilizing oral antibiotics. The recommendation is based on the belief that the body's host defense mechanisms can manage the inflammation without antibiotics if the patient is otherwise well and immunocompetent. Chabok *et al*[22] conducted a randomized control trial (RCT) that showed that treatment with antibiotics did not accelerate recovery nor prevent complications or recurrence when compared to treatment without antibiotics. Similar results were reported in a recent Cochrane review of 3 RCTs[23]. Many of the more recent guidelines have moved towards advising outpatient treatment for those with minimal comorbidities and otherwise well. Jackson *et al*[24] published a systematic review on this showing that 97% of patients were successfully treated in an outpatient type setting. The DIVER trial[25] also demonstrated this, where patients received a dose of Ⅳ antibiotics in the emergency department and then were randomized to being hospitalized or discharged for management. The Delphi study[8] demonstrated international acceptance of this as well as other survey studies[5,6]. Contrary to this, the majority (76%) of respondents in our study elected to admit for bowel rest and Ⅳ antibiotics. Whether this view may change with a high-quality study being conducted in Australasia needs to be seen.

In keeping with other survey studies[5-8] and with current guidelines[2], the majority (77%) of surgeons opted for CT scan as initial diagnostic modality. However, only 21% would utilize an US or MRI where CT was contraindicated, with some stating they would perform a CT without contrast. This is despite the fact that US has been shown to have a comparable diagnostic accuracy to CT[2,26]. Nevertheless, US does have its limitations and is inferior when considering diagnosis of alternative diseases[27].

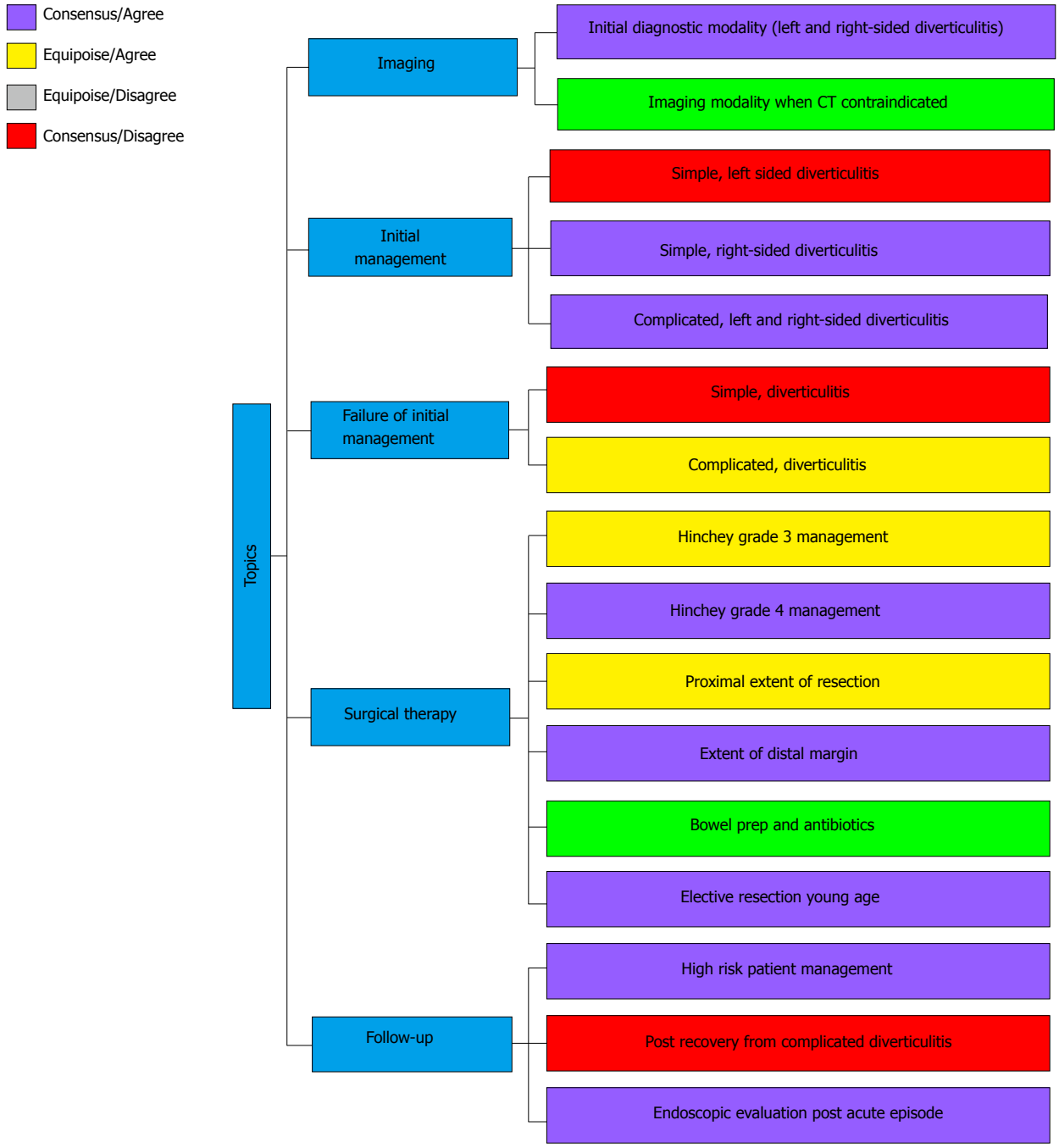

Figure 3 Summary by topic (responses agree/disagree with guidelines, consensus or equipoise).

Controversy remains regarding the best surgical option for Hinchey Grades 3 and 4 diverticulitis. Like previous surveys[6,8], the majority opted for Hartmann's procedure for Hinchey Grade 4. However, there remains a divide between Hartmann's and primary anastomosis with diverting loop ileostomy for Hinchey Grade 3. A systematic review[28] showed that patients undergoing primary anastomosis had lower mortality; however, the studies included were low quality with selection bias. A recent multi-center RCT[29] concluded that primary anastomosis with diverting ileostomy is favored over Hartmann's procedure. However, a number of limitations were identified following publication. Binda *et al*[30] brought to attention a number of issues with the trial, including selection bias, surgeons refusing to randomize certain patients, the inclusion of patients with perforation not secondary to diverticulitis and failure to base conclusions on the pre-planned endpoint. The LOLA arm (laparoscopic lavage with sigmoidectomy)[31] of the LADIES trial[32] was prematurely terminated following increased adverse events post laparoscopic lavage compared with sigmoidectomy. However, we

still await the results of the DIVA arm comparing Hartmann's procedure with sigmoidectomy plus primary anastomosis. This will provide randomized, controlled evidence for this controversial issue.

We did not use previous surveys that are already published and then compare our responses to them. This is because previous surveys did not cover as many aspects of diverticulitis management and did not focus as much, if at all, on surgical management. Also, previously published surveys are heterogeneous in terms of areas covered when compared to each other.

Weaknesses in our study include a suboptimal response rate. This may be due in part to the length of the survey, which was necessary to explore the topic. Also, we do not have data on the non-responders and whether they differed markedly from responders. Furthermore, only subspecialty colorectal surgeons were invited to complete this survey in an effort to maximize the response rate. We acknowledge that many general surgeons also treat diverticulitis. These factors limit the generalizability of the results. Furthermore, responses to clinical scenarios may be constrained by the multiple choice options, which may have varied from the respondents' true preference. Never-the-less, the survey results are still useful in highlighting current practices and areas of equipoise.

In conclusion, this survey has identified areas of community equipoise and areas of clinical practice that disagree with guideline recommendations in the management of diverticulitis. It has also demonstrated that despite the availability of guidelines, some areas in clinical practice reach consensus contrary to these recommendations. In order for guidelines to become more widely acceptable, further higher quality research is necessary in these areas.

COMMENTS

Background

Diverticular disease carries a significant disease burden. It ranges from presence of diverticula to simple inflammation to more complex disease processes. There are established guidelines with regards to initial investigations and management options for varying severity of disease. It is unclear whether current clinical practice in Australia and New Zealand is in consensus to established guidelines. The aim of this study was to determine the application of clinical practice guidelines for the current management of diverticulitis and colorectal surgeon specialist consensus in Australia and New Zealand.

Research frontiers

There remains disagreement in areas of diverticulitis management including the move to outpatient management and treatment without antibiotics for simple diverticulitis; and operative strategies for Hinchey grade 3 and 4 diverticulitis. This, together with low quality evidence for some guideline recommendations, means that guidelines need to be reviewed and revised with more recent studies.

Innovations and breakthroughs

The achievement of this study is in highlighting areas of equipoise and consensus, albeit not with guideline recommendations, to be areas of future research to provide better quality evidence so that guidelines may be adopted.

Applications

Areas of further research identified include initial management of simple diverticulitis, failure of conservative management for diverticulitis, whether recovery following complicated diverticulitis requires operative intervention, use of bowel preparation and proximal extent of resection for elective resection and surgical management of Hinchey Grade 3 diverticulitis. Higher quality evidence to back up recommendations for these will result in better outcomes for patients and given the increasing disease burden, will also help reduce the future financial burden on health care organizations dealing with this.

Terminology

Evidence suggests community equipoise is low when more than 70% of respondents favor one treatment option. Thus, community equipoise was assessed by classifying the survey scenarios into one of four categories based on the proportion of responses: (1) Consensus/Disagree: scenarios with > 70% of surgeons choosing an option that disagrees with guideline recommendation; (2) Equipoise/Disagree: scenarios with ≤ 70% of surgeons choosing an option that disagrees with guideline recommendation; (3) Equipoise/Agree: scenarios with ≤ 70% of surgeons choosing an option that agrees with guideline recommendation; and (4) Consensus/Agree: scenarios with > 70% surgeons choosing an option that agrees with guideline recommendations.

Peer-review

It is an interesting piece to read and publish. It provides very good overview of Australian surgeons' opinions on diverticulitis guidelines.

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REVIEW

Advances and challenges in laparoscopic surgery in the management of hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma is the fifth most common malignancy and the third most common cause of cancer-related mortality worldwide. From the wide variety of treatment options, surgical resection and liver transplantation are the only therapeutic ones. However, due to shortage of liver grafts, surgical resection is the most common therapeutic modality implemented. Owing to rapid technological development, minimally invasive approaches have been incorporated in liver surgery. Liver laparoscopic resection has been evaluated in comparison to the open technique and has been shown to be superior because of the reported decrease in surgical incision length and trauma, blood loss, operating theatre time, postsurgical pain and complications, R0 resection, length of stay, time to recovery and oral intake. It has been reported that laparoscopic excision is a safe and feasible approach with near zero mortality and oncologic outcomes similar to open resection. Nevertheless, current indications include solid tumors in the periphery < 5 cm, especially in segments Ⅱ through Ⅵ, while according to the consensus laparoscopic major hepatectomy should only be performed by surgeons with high expertise in laparoscopic and hepatobiliary surgery in tertiary centers. It is necessary for a surgeon to surpass the 60-cases learning curve observed in order to accomplish the desirable outcomes and preserve patient safety. In this review, our aim is to thoroughly describe the general principles and current status of laparoscopic liver resection for hepatocellular carcinoma, as well as future prospects.

Key words: Hepatocellular carcinoma; Laparoscopic liver resection; Minimally invasive surgery; Laparoscopic hepatectomy; Liver malignant disease; Surgical excision

Core tip: Hepatocellular carcinoma is the most common primary malignant tumor of the liver and fifth most common malignancy worldwide. Surgical resection is the therapeutic treatment of choice and its laparoscopic version has come into play since 1992. Several matched comparative studies reported its superiority over open

resection regarding operating theatre time and hospital stay, blood loss, need for transfusion and postsurgical opioid analgesics, postoperative pain, morbidity, R0 resection, time to recuperation, time to oral intake and stress response. The high costs of the procedure are offset by the decrease in the length of the operation and hospital stay, while in experienced hands conversion rates and morbidity are even more diminished. Laparoscopic and robotic liver resection is a continuously evolving field of minimally invasive liver surgery with a very promising future.

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INTRODUCTION

Although research in oncology and surgery has achieved some major milestones, hepatocellular carcinoma (HCC) still represents the fifth most common malignant tumor and the third most common cause of mortality related to cancer in the world[1]. In comparison with other malignant cancers, there is a wide variety of treatments in the armamentarium of surgeons, oncologists and radiologists, such as surgical resection, liver transplantation, chemoembolization, microwave and radiofrequency ablation, or even chemotherapy with sorafenib. However, before deciding on which method to choose from, clinicians ought to first define the clinical stage of the patient's HCC, which also defines the prognosis.

Especially for HCC, the three important factors determining the patient's survival are the tumor's characteristics (size, invasion of the vessels, number of nodules), the patient's physiologic reserve (for instance, Eastern Cooperative Oncology Group performance status) and the ability of the liver to function properly (Child-Pugh score)[2-4]. In addition, the issue still remains that there is lack of a common language in terms of HCC staging. Histopathology should also be taken into consideration when it comes to staging a type of cancer, and thus a variety of HCC staging systems, such as the Japanese Integrated Staging score, have adopted the American Joint Committee on Cancer TNM staging system[5]. One significant limitation of this system is the fact that it cannot incorporate the unresectable HCCs, because when relying primarily on the pathological characteristics of the tumor, it is a prerequisite that a surgical specimen is needed. Moreover, it does not include two of the three major survival factors mentioned above: physiologic reserve and liver function.

The staging system that seems to be the most inclusive, as well as the most widely verified, is the Barcelona Clinic Liver Cancer (commonly known as BCLC) staging system[6]. Based on this system, HCC patients are classified into subgroups based on their malignancy's characteristics, the function of the liver and their health in general, and each subgroup is allocated to a different treatment modality according to the treatment algorithm (Figure 1)[7]. On the other hand, a study ranking the different staging systems as to their prognostic value and patient survival, reported the superiority of the Cancer of the Liver Italian Program (commonly known as CLIP) classification and the Chinese University Prognostic Index (commonly known as CUPI)[8]. Although these staging systems differ to a great extent, mostly due to the geographical variation and etiologies of the different HCCs, the EASL-EORTC guidelines suggest that the BCLC classification should be followed when it comes to the management of HCC[9].

In this review, our aim is to thoroughly present the current knowledge around laparoscopic hepatectomy, with a special interest on the indications, general principles and technique, as well as its envisioned future.

Indications for surgical resection for HCC

The fact that HCC arises mostly in a cirrhotic liver, means that any type of treatment of the tumor has to account for factors related to hepatic quality and function. Regarding the liver-related factors, both quantity and quality of the future liver remnant (FLR) should be taken into consideration before performing an excision. One way to achieve hepatic hypertrophy, to ensure adequate liver mass posthepatectomy, is portal vein embolization (PVE), which improves the FLR of the side not embolized[10]. Another important factor is the preoperative liver function status, which can be evaluated by the Child-Pugh classification system (class A patients are suitable for hepatectomy, while class B or C patients are more prone to major complications after surgery due to liver dysfunction)[11]. Nevertheless, a significant contraindication to hepatectomy is high grade portal hypertension, which could be assessed either invasively by measuring hepatic venous pressure gradient (HVPG)[12,13] or noninvasively by measuring the platelet count[14].

The mostly studied tumor-related issues that determine the indications for liver surgical resection are tumor size, number of tumors and vascular invasion. Size alone is not a determining factor for patient survival after surgery, as it has been shown that excision of tumors larger than 10 cm may exhibit equal survival to those smaller than 10 cm, provided that the FLR is sufficient and there is insignificant vascular invasion[15]. Additionally, the management of multinodular HCC is still under discussion, with tumors arising in the cirrhotic liver due to the "field effect" showing improved survival posthepatectomy, in contrast to intrahepatic metastases, which usually present as a sizeable lesion encircled by satellite minor tumor masses[16,17]. Last but not least, it is generally accepted that significant invasion of major vessels remains an important contraindication to surgical

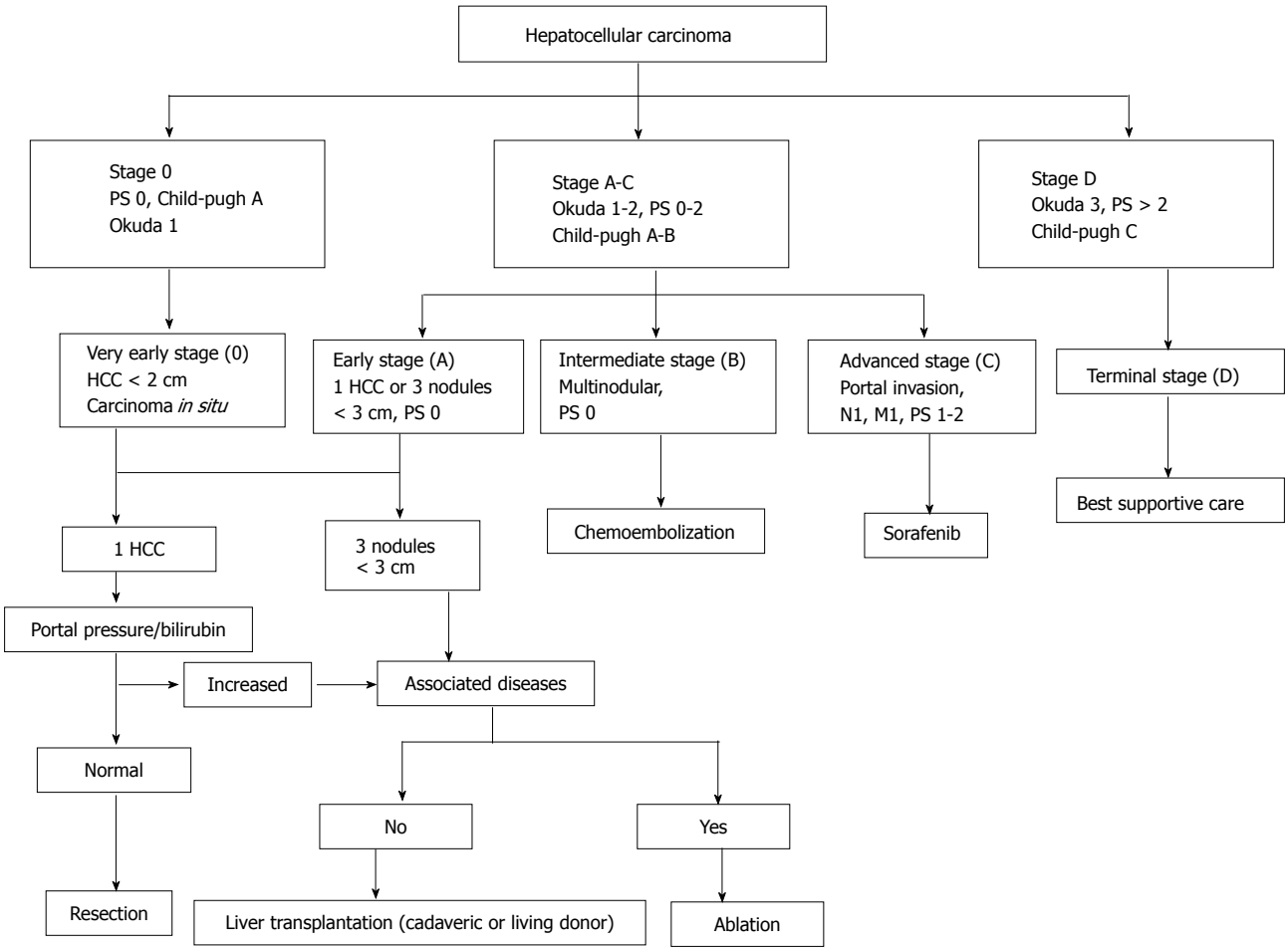

Figure 1 Barcelona Clinic Liver Cancer staging system and treatment algorithm. M: Metastases; N: Nodules; PS: Performance status; HCC: Hepatocellular carcinoma.

resection owing to worse prognosis and early disease recurrence[18].

Laparoscopic liver resection in general

To begin with, there are some challenges in the wider application of laparoscopic surgery. The first one is the loss of tactile sense, such as the margins and staging, but this could be helped by the use of laparoscopic ultrasound and hand-assisted techniques. Another obstacle is that of limited access and instrumentation, which could be solved by hand-assisted maneuvers and improved retractors. The question of bleeding control, while always a significant threat with the liver, can be addressed with devices such as the harmonic scalpel, the vascular stapler and the LigaSure device. In addition, other issues to be addressed include time and money, port side metastases and gas embolism.

Although many studies that compare laparoscopic liver resection (LLR) to open liver resection (OLR) have been carried out to date[19], only one of them was a randomized controlled trial[20]. Despite that, there has been an effort to progress over time from benign to malignant lesions, from smaller to bigger and from normal liver over to the cirrhotic one, by carefully selecting suitable candidates.

Currently, peripheral tumors (segments Ⅱ, Ⅲ, Ⅳb, Ⅴ and Ⅵ) are easier to resect laparoscopically[21]. Regarding larger and deeper located tumors, or those located superiorly or posteriorly, which are more difficult to excise, despite the fact that LLR can be implemented[22-24], it is advisable that hand-assisted or a hybrid technique (laparoscopic-assisted open) are performed[25]. On the whole, LLR is currently indicated, especially for solitary HCCs, 5 cm or less, located in the periphery of the liver, especially in segments Ⅱ through Ⅵ, that allow a wedge excision or a segmentectomy[19,26].

Current status of laparoscopic liver resection for HCC

According to Nguyen and Geller from 1992, when the first LLR was performed till 2009, about 2804 LLRs have been carried out. Half of them involved malignant lesions, while 45% were benign and about 1.7% live donor hepatectomies, with the remaining being undetermined[26]. Regarding the technique used 75% were completely laparoscopic, 17% were hand-assisted and about 2% were hybrid, while as it pertains to the resected specimen 45% of them were wedge or segment resections, 20% were anatomic left lateral sectionectomies and 9% were right and 7% were left hepatectomies[26].

Significantly, only a small percentage of the laparoscopic procedures were converted to open (4.1%) and to

hand-assisted (0.7%).

Safety

LLR is generally thought of as a safe and feasible operation[27,28]. A previously published world review[26] reported a clearly low rate of mortality (0.3%), without any deaths occurring during the procedure. The most common causes of death were liver dysfunction, multiple organ failure, delirium tremens and hemorrhage. Morbidity, on the other hand, was 10.5%, with postoperative bile leak being the most common complication (1.5%), followed by transient liver failure and liver abscess, as well as bleeding, surgical site infection and collection of fluid inside the abdominal cavity. These low rates could possibly be attributed to several factors, though.

It is clear that careful patient selection and high surgical expertise play important roles. Apart from that, the utilization of the hand-assisted method may decrease bleeding more quickly through direct pressure, while laparoscopic sutures could be more safely executed, thus rendering more difficult cases feasible[29]. Moreover, although keeping a low pressure pneumoperitoneum reduces the incidence of air embolism, if it is increased it can be efficacious in reducing venous leakage[29].

The positive effects of pneumoperitoneum do not stop there, as it is helpful in achieving optimal visualization and as a result bloodless parenchymal transection, which decreases the risk of major hemorrhage and the requirements of blood transfusion, therefore also avoiding the unspecified immunosuppression which increases morbidity and cancer recurrence[30]. In addition, a recent meta-analysis reported lower loss of blood and decreased need for transfusion, rapid recovery and significantly decreased postoperative pain[31]. Finally, data suggest that complications are going to decrease more as the surgeon becomes more experienced.

Operative time

In general, operating time, just as blood loss, is quite challenging to calculate due to the high heterogeneity among the wide range of procedures being performed. Despite this, the world review reported that the operating time may vary from 99 min to 331 min[26], while Soubrane *et al*[30] estimated a median operating time of 3 h. Similarly, Cannon *et al*[29] found that for their first 100 patients, the operative time was also 3 h, but as surgeons gained more experience, the time went down to around 2 h for their most recent 100 patients. On the contrary, a meta-analysis of 26 studies showed a significantly increased procedure time as to the open approach[32].

As a matter of fact, OLR involves a larger incision, which needs extra time to be closed; hence, when surgeons become even more expert in this field of hepatobiliary surgery, LLR is not going to be that much more time-consuming. Another meta-analysis found out no difference between LLR and OLR regarding the operative time[28], suggesting that only a minor variance exists. Obviously, the critical factor regarding operative time is the learning curve, something which will also change again in the future as these procedures become more established and they move from the level of the attending to the level of the fellow, and potentially even to the senior resident.

Length of hospital stay

As expected, laparoscopic procedures show a remarkable decrease not only in blood loss and postoperative pain, but also in the length of hospital stay. Specifically, the estimated time for hospital stay is around 2.9 d[29], which is obviously lower than that of the OLR; interestingly, Simillis *et al*[28] reported a decrease of about 2.6 d in patients treated with LLR compared to those undergoing OLR. The world review[26] exhibited a range between 1.2 d to 15.3 d for LLR, which again was proven to be lower than that of OLR. This variance, though, may be due to nuances among the healthcare providers and cultural habits, as well as due to the fact that some studies included liver cyst excisions, while others did not. This kind of cultural bias tends to play a key role in determining the length of the hospital stay as it ranges only between 1.9 d to 4 d in the United States, while in Europe it is about 3.5 d to 10 d and in Asia 4 d to 20 d for LLR; even so, a constant decrease of about 50% was observed in LLR when compared to OLR[33].

Efficiency

At first, there was great concern regarding LLR and the risk of positive margins, potential tumor seeding and port-site metastasis, which impeded its wide implementation. The results reported by Nguyen *et al*[26] state categorically that there is no reason for not adopting LLR, as resection with tumor-free margins can be accomplished, and neither significant tumor seeding nor port-site cancer recurrence have ever been reported. The only exception is a patient whose renal cell carcinoma ruptured before the operation, which clearly had nothing to do with the LLR[34]. Moreover, both approaches are equal in terms of oncological survival outcomes[26].

Many studies including patients with HCC or colorectal metastases reported promising survival rates; and, specifically the 5-year survival for colorectal metastases to the liver ranged between 50%-64%, while R0 excision percentages were about the same as those of OLR[21,35]. As to HCC, a study showed that 1-, 3- and 5-year survival rates were 95.4%, 67.5% and 56.2%, respectively, after LLR *vs* 100%, 73.8% and 53.8% after OLR[36]. Soubrane *et al*[30] also published a LLR study, in which they achieved R0 marginal resection in 92% of their patients, while 1-, 3- and 5-year overall survival was 90.3%, 70.1% and 65.9%, respectively, and 1-, 3- and 5-year progression-free survival was 85.2%, 55.9% and 40.4%, respectively. In this study, they also proved that LLR fulfills the criteria established by the EASL-EORTC guidelines; hence, it should be used widely for the resection of HCC.

Conversion

Laparoscopic liver resection can be converted to laparotomy if the anatomy is not clear or so as not to endanger patient safety. Although some studies report a high rate of conversion of 13%-17%[30,37], generally rates tend to be as low as about 4%-7%[26,38-40]. Excessive bleeding is the most common cause of conversion, while adhesions, gas embolism, poor visualization and anatomic disorientation or nearby large vessels are some other common causes[26,37,39,40]. Resection of postero-superior segments was found to be an independent factor for conversion, as indicated by a multivariate analysis; major hepatectomy was another significant factor for conversion *vs* minor hepatectomy[39]. It would be wrong not to mention the relationship between conversion and learning curve. The considerable learning curve indicates that less experienced surgeons may not be able to deal with the numerous difficulties a LLR involves; hence, it has been observed that only after performing about 60 LLRs will the risk of converting LLR to OLR decrease[41].

It is obvious that when a laparoscopic procedure is converted to open, every advantage of the laparoscopic technique is immediately lost. This does not mean, though, that the surgeon should exceed his/her level of competency in order to avoid a conversion, because if it is delayed in some challenging cases, length of hospital stay may increase and complications may be more numerous and devastating[42]. As a result, the hepatobiliary surgeon must first become competent enough in performing LLR, so as to know when to convert or not.

The main reason for conversion, as mentioned previously, has been bleeding. In order to laparoscopically deal with major hemorrhage, the surgeon can intermittently use the Pringle maneuver, compress with gauzes, use clips or staplers or even the hand-assisted approach[43,44]. It is generally advisable that in case of acute bleeding, laparoscopic sutures should be placed after snatching the vessel, which can lead to less blood loss during conversion, and then saline solution should be used in the abdominal cavity when the converting incision is made[39]. The hand-assisted technique is an "in-between" technique used when there is an urgent need to stop bleeding and the decision to convert or not has not yet been made. The other important cause of conversion, gas embolism, can be managed by shifting the operating table into the Trendelenburg position, which increases central venous pressure in case of a damaged vessel[45]. Finally, when resecting a lesion in a postero-superior segment, which represents a higher risk of conversion, robotic-assisted resection is suggested to decrease the risk of conversion[39]; however, a systematic review reported a 6.6% rate of conversion for the robotic procedure[46] and, thus, more research is necessary.

Comparison with the open technique

When comparing techniques, it is important to ensure patient similarity between the different groups. Aiming to prove the advantages of a laparoscopic approach, Ito *et al*[47] matched 65 patients that received LLR to 65 OLR patients from their archive and then compared them. The results, especially for the short-term, were significantly in favor of the laparoscopic approach, showing a decrease in bleeding, need for transfusion, frequency of the Pringle maneuver, postoperative complications, time to recuperation, length of stay in the hospital and cases of surgical site herniation. As far as the oncologic outcomes are concerned, free-marginal resection and lack of surgical site recurrence were accomplished in both groups, while cancer recurrence rates were also similar. Also, the first study comparing the two techniques for a major liver excision showed that they are equal regarding operative time and postoperative complications, but blood loss, length of hospital stay and general morbidity were significantly reduced in the case of LLR[48].

A meta-analysis comparing the two methods, particularly comparing small resections for solitary tumors in the left lateral lobe or right peripheral subcapsular area, reported that LLR is superior to OLR in short-term outcomes (*i.e.,* loss of blood and postsurgical morbidity), while long-term outcomes (*i.e.,* severity of complications) were similar between the two approaches[49]. Besides, a comparative study reviewing 12 primary studies observed similar mortality rates between the laparoscopic (0.3%) and the open (0.4%) techniques, while liver failure was the most common cause of death in both groups[50].

Other major advantages of the laparoscopic method have to do with improved patient satisfaction and comfort. It is well known that a laparoscopic technique causes less surgical stress than an open one, and this can lead to decreased postsurgical pain, cosmetic advantages (almost no scar) and shorter length of stay in the hospital[51]. Also, time to oral intake and need for opioid analgesics may be reduced[52], the patient may recover faster and get back to his previous activities[53].

A meta-analysis published in 2017 also compared LLR to OLR in terms of short- and long-term outcomes[31]. To elaborate this, the open method showed increased rates of blood loss, requirements for blood transfusion and length of hospital stay, while the only insignificant difference was observed regarding the operating time. Free-marginal resection and width of marginal resection were found to be increased in LLR generally. This study also highlighted the decrease in postsurgical morbidity and in 30-d mortality, in favor of the laparoscopic operation.

Concerning long-term outcomes, although 1-year overall survival was significantly increased in LLR, there was no noticeable difference between the two groups in the 3- and 5-year overall survival. Disease-free survivals after 1, 3 and 5 years, as well as cancer recurrence rates, were also similar for the two methods. Unfortunately, except for one randomized controlled trial from China[20], all the studies included in the meta-analysis are non-randomized comparative studies, which are also

characterized as "methodologically adequate". Although since meta-analysis may over-estimate the effect of sizes in comparison to a meta-analysis of randomized controlled trials[54], the big picture emerges despite the lack of high-quality evidence-based research in LLR. Even though there is a large heterogeneity among the studies regarding surgical expertise, patient selection and tumor-related parameters, this helpful meta-analysis emphasizes the superiority of LLR over OLR for small HCCs.

Cost

Although at first glance one would expect the LLR to be more expensive, given the use of the laparoscopic instruments, this is not necessarily the case. When addressing the issue of cost analysis, the clinical aspect should be taken into consideration and "cost-effectiveness" should be the key concept. Specifically, although using an endoscopic stapler for liver resection is significantly more expensive than the "finger fracture" technique used in an open procedure, the operating room time saved could potentially make up for the difference. Even though, a study reported that the costs of trocars and staplers did not differ between the two groups[55], another from the United Kingdom showed that the devices and disposables utilized in the LLR group were more costly indeed than those in the OLR group[56].

A Canadian study reported no difference in the operative time between the laparoscopic and the open group, which was around 140 min, but an overall theatre time of more than 200 min was documented and the nonsurgical time was occasionally higher than the operative one[55]. Besides, it has been proposed that the theatre usage time is a better indicator of the cost-effectiveness of a procedure than the operative time. This nonsurgical time, though, was similar for the two techniques and was not a result of placing an epidural catheter in the OLR group. However, the aforementioned United Kingdom study[56] showed that although the placement of an epidural anesthesia is beneficial to patients receiving the open operation, it does increase the cost of the procedure compared to the laparoscopic one. As a result, if we add the shorter time of anesthesia and the reduced need for a high-dependency unit admission to the faster recovery time, ambulation time and reduced surgical ward stay observed in the laparoscopic group, it can be seen how the cost of LLR could be lower than that of OLR[56,57]. Additionally, the patient can return to his previous activities quicker, with reduced morbidity, and go to work sooner[58].

In contrast, this financial benefit is not observed in more complex and difficult cases. Specifically, Cannon *et al*[59] reported that although laparoscopy in general is less expensive than the OLR, when performing a right hepatectomy, which is clearly characterized by higher complexity, the cost-effectiveness of LLR is lost. Nevertheless, segmentectomy and bisegmentectomy clearly emphasize the cost-effectiveness of the laparoscopic approach, as the total hospital cost was lower by around £2.571 (~$3.800) compared to the open approach[56]. Similarly, Koffron *et al*[38] compared carefully selected and matched patients that received partial and right hemihepatectomy, excluding the outliers, and reported that the overall hospital cost for the laparoscopic group was 98% and 66%, respectively, of that of the open group. Also, they found that the operating room cost for those resections done laparoscopically was 51% and 47% of the overall hospital cost compared to 39% and 36%, respectively, in the case of an open operation.

Vanounou *et al*[60] used the deviation-based cost modeling to clinically and economically compare the two approaches and showed that the weighted-average median cost of LLR was reduced by about $2.939 in comparison with OLR ($15.104 *vs* $18.043, respectively). They also expanded this comparison to include malignant disease and they proved again that LLR is more cost-effective than OLR, by about $1.527. On the whole, it is clearly understood that the shorter duration of hospital stay accompanied by the lower morbidity rates, offset the higher intraoperative costs reported in the laparoscopic technique, thus ensuring cost-effectiveness.

SPECIAL SITUATIONS

Patient with cirrhosis

Cirrhosis is seen commonly in patients with HCC, and a different approach may be in order in these patients. The most common postoperative complication observed in cirrhotic patients is ascites, seen even in minor surgeries[61,62]. This could be prevented by the utilization of LLR, which also improves the postsurgical status of those patients in general. The reasons for that are: (1) The less traumatic insult to the abdominal wall and the round ligament, which prevents collateral circulation; (2) the protection of visceral organs from exposure to the atmosphere, which decreases the loss of electrolytes and the need for extra fluid administration; and (3) the restricted loss of blood during the operation[50]. In addition, LLR does not require the total emptying of ascites in the cirrhotic patient, therefore reducing the risk of postsurgical ascites and fluid and electrolyte disturbances[48,63]. Another frequent health issue that patients with cirrhosis usually face is bleeding from intra-abdominal varices. Some experts suggest that such a bleeding incident could be prevented thanks to the pneumoperitoneum produced during a LLR, owing to the tamponade effect[64]. Moreover, as we know, liver transplantation is the only therapeutic modality for cirrhosis. In conjunction to this, a study proved that when resecting a hepatic lesion from a potential future liver transplant candidate, LLR should be adopted over OLR, because it can facilitate liver transplantation due to a lesser degree of postoperative adhesions[65].

On the other hand, a LLR in cirrhotic liver has its own challenges. It is necessary that patient selection criteria are established, so that the early learning curve does not cause more harm than good. In other words, some

surgeons suggest that the lesions which are going to be excised should be in the left or anterior right segment of the liver, in order to achieve optimal accessibility, while the lesion's size should not exceed the 5 cm diameter[64]. This concept is included in the international consensus conference on LLR, and the laparoscopic approach is advocated for surgeons with appropriate expertise and in the beginning for peripherally located solitary lesions that do not exceed 5 cm in diameter[66].

Laparoscopic liver resection, immune system and stress response

Surgery initiates a complex systemic response involving multiple cytokines, immune cells, messenger molecules and metabolic pathways. All of these start with the abdominal trauma induced by the scalpel, but what if we could minimize this incision-induced stress reaction? This is where minimally invasive surgery and laparoscopy come into play.

The utilization of LLR leads to a smaller abdominal incision and decreased damage to the tissues. The initiated stress response is assessed by several measures, such as tumor necrosis factor alpha (TNF-α) and interleukins (IL-1β, -2, -6, -8, -10, -12), C-reactive proteins (CRPs), hormones deriving from the adrenals, lymphocytes in the periphery and by the implementation of delayed-type hypersensitivity skin tests[67,68]. The early stress response to the surgical wound is thought to be mediated by IL-6 produced by monocytes, macrophages and endothelial cells, while the severity of tissue damage can also be evaluated by high serum levels of IL-6[69]. In fact, a study suggested that approaches lowering IL-6 levels, such as laparoscopy, may be more beneficial in the future[70].

LLR, compared to OLR, has shown a decrease in postoperative complications, pain, hospital stay, bleeding and need for blood transfusion, time to oral intake, postoperative need for opioid analgesics and more rapid recovery. All these factors clearly highlight the reduced surgical stress response observed in the laparoscopic group and its superiority over the open method.

Diagnostic laparoscopy in HCC patients prior to resection

Apart from clinical and laboratory examinations, imaging plays a key role in the preoperative work-up and evaluation of HCC. Transabdominal ultrasound, three-phase computerized tomography and magnetic resonance imaging are some of the imaging examinations included in the preoperative work-up. However, as HCC is usually associated with cirrhosis and hepatitis, those may underestimate the level of cirrhosis and the regenerative nodules or peritoneal spread of the tumor, which can be more clearly identified only under direct vision[71]. Indeed, Klegar *et al*[71] utilized diagnostic laparoscopy in HCC patients undergoing resection, and it changed the decision made to a significant extent in 9 out of 20 cases (45%). The main reasons for this change were advanced level nodular cirrhosis, incorrect evaluation of intrahepatic metastases, difficulty in recognizing a HCC, peritoneal carcinomatosis and intolerability to general anesthesia. Consequently, diagnostic laparoscopy may be kept in mind for the preoperative imaging assessment of HCC.

Ablation

In the beginning of our review we stated that candidates for surgical resection need to fulfill some specific criteria. In the case of the patients that are excluded, a non-surgical approach, such as transarterial chemoembolization, percutaneous ethanol injection, percutaneous radiofrequency and microwave ablation, can be used. Unfortunately, some HCC patients are not suitable even for percutaneous ablation due to liver dysfunction or tumor characteristics necessitating a more controlled approach, and as a result the implementation of laparoscopic ablation could be helpful.

Laparoscopic radiofrequency ablation is a safe procedure used as an alternative to the percutaneous method in subcapsular tumors or in those in contact with adjacent organs. A European study confirmed the safety and efficacy of this procedure, as the reported initial complete response percentage was 94%, while the sustained one was 70% after the follow-up period[72]. Additionally, overall survival rates at 1, 3 and 5 years were 92.6%, 64.5% and 43%, respectively. Buell *et al*[73] compared laparoscopic radiofrequency ablation to LLR and noticed similar unwanted events and mortality rates (11% *vs* 16%, respectively and 1.5% *vs* 1.6%, respectively). Although the rates of overall recurrent disease were equal between the two techniques (24% *vs* 23%, respectively), local recurrence was more frequently observed in the radiofrequency group (6.3% *vs* 1.5%, respectively).

An Italian study evaluated the use of laparoscopic microwave ablation in 42 patients and had promising results[74]. Specifically, there was 0% mortality, but the morbidity rate was 24%, while survival and recurrence rates after 2 years were 79% and 55%, respectively. After matching 28 of these patients with 28 others receiving laparoscopic radiofrequency ablation, the 2-year recurrence percentages reported were 55% and 77%, respectively.

Microwave thermosphere ablation is a new method utilizing a single antenna so as to ablate spherical areas. Zaidi *et al*[75] evaluated microwave thermosphere ablation laparoscopically in 45 patients and reported a morbidity and mortality rate of 11.3% and 0%, respectively. Significantly, the 99.3% complete tumor ablation percentage and the 0.7% local recurrence rate indicate how promising this new technological advance can be in the future.

Learning curve

The combination of technology and technical challenges make the learning curve a critical part of LLR. He *et al*[76] noticed that the increase in volume of LLRs performed in 2009-2012 *vs* 2000-2008 may be partially attributed

to the Louisville 2009 Consensus[66]. They also observed a decrease in length of hospital stay over time, but no difference regarding morbidity and mortality. Issues that need to be addressed are the qualifications necessary to perform the procedure and the path required to learning it. As expected, the vast majority of LLRs have been performed in liver cancer and liver transplantation centers by experienced surgeons with great knowledge and skills in both laparoscopic and hepatobiliary surgeries. Therefore, Tsinberg *et al*[77] proposed the formation of a dynamic duo, a laparoscopic surgeon and a hepatobiliary surgeon, who could work together and learn from each other. They also suggest that a surgeon with little experience should start from laparoscopically resecting peripherally located lesions (*i.e.*, segments Ⅱ, Ⅲ, Ⅳb, Ⅴ and Ⅵ), as well as benefiting from the usage of the hand-assisted technique.

A study assessing the outcomes of LLR in three different groups in three different eras showed that the last group included more complex and demanding cases, as well as more cirrhotic patients, thus indicating the increased comfort and expertise of surgeons performing LLR during a period of time[29]. Even though cases gradually became more and more complex, operating time was reduced for about 3/4 of an hour from the first till the last group. Blood loss, 30-d mortality and length of hospital stay were similar among the three groups. Vigano *et al*[41] also evaluated LLRs performed in three different periods of time and concluded that the volume of LLRs increased, rate of conversion, operating time and loss of blood decreased, but most significantly, after adjusting for case-mix, cumulative sum analysis showed that LLRs required a learning curve of 60 patients. On the other hand, a study assessing the LLR learning curve of a single surgeon again in three periods, reported that 50 cases were required, so that a significant reduction in blood loss was observed, while no less than 160 cases were needed so as to perform a wide range of different LLR with safety[78].

There are issues regarding the nature of the learning curve. Even though it is thought of as an "idealized" curve, gradually progressing until reaching a plateau, Villani *et al*[79] could not but notice several improvements and regressions regarding complications, operative time and blood loss, associated partially to the constantly increasing complexity of the procedures attempted. As a consequence, they proposed the model of the "true" learning curve for LLR, which is characterized by a pattern of "ups and downs" until surgeons become experienced, when their performance reaches peak and the beneficial outcomes are constantly seen.

Koffron *et al*[38] commented on the need for randomized controlled trials, saying that patients would hesitate to enroll in these studies due to the fear of having OLR. On the contrary, the authors suggested that LLR may become the technique of choice, just as laparoscopic cholecystectomy, and propose a way to deviously avoid the learning curve of LLR. Thus, an inexperienced surgeon should start with using the hybrid method, initially for wedge excision of peripherally located lesions, and as time goes by and he/she becomes more comfortable with it, it is advisable to turn to the hand-assisted approaches. When the surgeon reaches a high level of expertise regarding the laparoscopic skills, it is time to gradually move on to the pure laparoscopic method, again initially for peripheral lesions.

FUTURE PROSPECTS

Nowadays, the swift advances in technology have led to several novel instruments and machines in the everyday surgical routine. Robotic surgery is just one of them. In general, help provided by the robot facilitated a new era for minimally invasive surgery including minor incisions, reduced estimated blood loss, postsurgical pain and length of hospital stay, while concurrently expediting the learning curve for transitioning from the open to minimally invasive approach[80,81]. Inevitably, the da Vinci robot (da Vinci Surgical System; Intuitive Surgical, Inc, Sunnyvale, CA, United States) entered the world of hepatobiliary surgery with increasing popularity. LLR is widely adopted, but mostly for left lateral segmentectomy and less for left and right hepatectomies. Thus, the robotic liver resection through its 3D imaging and advanced-mobility instruments may accommodate such resections[82] and promises to play a key role in the evolution of LLR. However, a study comparing robotic to laparoscopic left lateral sectionectomy reported in the robotic group more admissions to the intensive care unit and more minor complications, as well as increased length of hospital stay and indirect costs[83].

To our knowledge, up to this time, Giulianotti *et al*[84] have published the largest series for robotic major hepatectomy, consisting of 27 patients (20 right hepatectomies, 5 left hepatectomies and 2 right trisegmentectomies), 74% of which had malignant liver disease. Their median operating time was 313 min, the rate of conversion to open was 4%, while morbidity and mortality rates were 30% and 0%, respectively. Spampinato *et al*[85] published another large study of 25 patients, 68% of which had malignant disease, with a median operative time of 430 min, 4% conversion rate, but reduced transfusion rate, blood loss and morbidity in contrast to Giulianotti *et al*[84]. Both studies had a similar length of hospital stay, of 8 d.

Moreover, the largest study, to the best of our knowledge, regarding robotic minor hepatectomy was from Kingham *et al*[86] in 2016 from the Memorial Sloan Kettering Cancer Center, which included 65 patients (78% with malignant disease). Median operative time was 163 min, conversion rate was 6.3%, morbidity rate was 11% and mortality rate was 2%. Giulianotti *et al*[84] included 43 cases of robotic minor hepatectomy and reported a median operative time of 198 min, conversion rate of 7%, while morbidity and mortality rates were 16% and 0%, respectively. Data suggest that most published series of robotic major or minor hepatectomy achieved a near 100% R0 resection[87].

The interesting approach of robotic-assisted laparo-

scopic anatomic hepatectomy has been reported in a study from China[88]. Although this technique was characterized by increased operating time and hospital costs when compared to laparoscopic or open hepatectomy, it was superior in terms of blood loss, transfusion rate and morbidity, hence proving its safety and feasibility over the other two methods. This significant technique is promising because it can overcome the increased surgical trauma, postoperative pain, loss of blood and diminished recovery of the open approach, but simultaneously expand the indications of LLR, therefore representing an efficient combination. The robot's advantages are the elimination of tremor produced by the surgeon, the accurate resemblance of human wrist movements, the scaling of hand motions into micro-motions, as well as the 3D visualization, which further enhances hand-eye coordination[89,90].

Notably, this robotic-assisted laparoscopic technique can be very helpful when performing hilar dissection, transection of hepatic parenchymal tissue and control of liver outflow, and when dealing with posteriorly located hepatic lesions. Also, robotic surgery can more easily manage bleeding during parenchyma transection, the most common cause of laparoscopic to open conversion[88]. However, there are also disadvantages. For instance, lack of tactile feedback is prominent due to absence of haptic sensors, but the 3D imaging may offset this problem. Additionally, the robotic cart and arms take a great deal of space in the operating room, which may impede additional non-robotic surgical movements or even make the work of the anesthesiologist inconvenient[91]. Robotic surgery is completely different from traditional surgery and many adjustments need to be made, including robotic port placement, development of more advanced surgical instruments and training of table-side surgeons, while hospital costs should always be taken into consideration.

There are other applications of minimally invasive surgery in hepatic surgery. Specifically, the shortage of liver donor grafts is widely known as a major issue in liver transplantation and, thus, many patients resort to live donor liver transplantation, which is a unique procedure given the significant health risk to the living donor; we have to remind ourselves that this is a healthy individual undergoing a high-risk surgery for no benefit to the donor. Consequently, a study compared open to laparoscopic live donor left lateral sectionectomy and reported that the laparoscopic group exhibited a diminished length of hospital stay and time to oral intake, while operative time, estimated blood loss and costs were similar between the two groups with zero mortality observed in both[92]. The same surgical team published in 2017 a study of three pure laparoscopic living donor right hepatectomies, which are very rarely performed, and reported zero complications, reduced surgical trauma morbidity and more rapid recuperation[93]. In 2017, a Japanese study published was the first one to compare laparoscopic to laparoscopy-assisted donor hepatectomy[94]. It showed that although the pure laparoscopic approach may take longer than the laparoscopy-assisted one, it is associated with decreased loss of blood, better cosmetic outcomes and similar complication rates and acceptable liver allograft results.

On the whole, LLR is a challenging procedure requiring a lot of experience, which is not easy to accomplish. Nevertheless, even experienced surgeons may face difficulties intraoperatively. As a result, improved liver and surgical site visualization is needed so as to achieve optimal outcomes. Thus, a surgical simulation 3D system has been developed in order to facilitate surgeons in recognizing vascular structures and the location of the tumor[95]. The aim of this system is to facilitate surgical training, as well as to ultimately provide navigation guidance in real time intra-operatively. Moreover, we have witnessed the evolution of an open liver imaging system to a laparoscopic one, mainly through clinician feedback, which accommodates a high quality intra-operative 3D image, especially useful in LLRs[96]. The future seems quite promising for laparoscopic liver surgery, both in terms of surgical technique, as well as in terms of navigation guidance in the operating room.

CONCLUSION

In conclusion, minimally invasive surgery has made tremendous strides in hepatobiliary surgery, starting with cholecystectomy and ultimately dealing with liver resection. Laparoscopic liver resections have proven to be superior to the traditional open approach in respect to decreased loss of blood, transfusion rate, surgical trauma-induced stress response, postoperative pain and morbidity, time to recovery, time to oral intake, need for postsurgical opioid analgesics, operating theatre time, length of hospital stay, R0 resection and similar mortality and oncologic outcomes, let alone cost-effectiveness.

The majority of the resections are wedge and left lateral segmentectomies, because major (right or left) hepatectomies are more challenging and difficult to perform and are attempted only by highly skilled and experienced surgeons in tertiary centers. Current indications for laparoscopic liver resections involve peripheral solitary tumors not exceeding 5 cm in diameter, particularly in segments II through VI, according to the 2008 Consensus Louisville Conference.

Unfortunately, as indicated by a 2017 meta-analysis, only one randomized controlled trial has been published and thus most data come from matched comparative studies and meta-analyses. Those studies, though, are subject to publication bias, as those with positive and more significant results are more easily published in world class English journals in comparison with the negative results published in local journals, if ever. Selection and attrition bias may also influence the results of meta-analyses. Consequently, we cannot but wait for more high quality and methodologically well-designed studies that will facilitate the adoption of laparoscopic liver resection as the treatment of choice not only for HCC, but also for many other lesions.

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REVIEW

Role of oral antibiotics for prophylaxis against surgical site infections after elective colorectal surgery

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Abstract

Over the past few decades, surgeons have made many attempts to reduce the incidence of surgical site infections (SSI) after elective colorectal surgery. Routine faecal diversion is no longer practiced in elective colonic surgery and mechanical bowel preparation is on the verge of being eliminated altogether. Intravenous antibiotics have become the standard of care as prophylaxis against SSI for elective colorectal operations. However, the role of oral antibiotics is still being debated. We review the available data evaluating the role of oral antibiotics as prophylaxis for SSI in colorectal surgery.

Key words: Colorectal; Anastomosis; Leak; Antibiotics; Bowel preparation

Core tip: The role of oral antibiotics to reduce surgical site infections (SSI) after elective colorectal surgery is not yet settled. The research in this area has been overshadowed by studies examining mechanical bowel preparation (MBP) and intravenous antibiotics. Existing data show that intravenous antibiotics are now considered standardized prophylaxis, and MBP is on the verge of being eliminated altogether. We review the available data evaluating the role of oral antibiotics as prophylaxis for SSI in colorectal surgery.

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INTRODUCTION

Even in this modern era, surgical site infections (SSI) still occur in 26% of patients after elective colorectal resections[1]. When a SSI develops, it lengthens hospital stay, prolongs the recovery period and delays the commencement of adjuvant systemic therapy for malignancies[1]. In addition, the associated health care expenditure increases on average by $11000-40000.00 United States dollars[2]. Therefore, SSI prevention is an important area of medical research.

Despite the existence of evidence-based recommendations for prophylaxis[1-9], there is still a wide variation of clinical practices to prevent SSIs after elective colorectal surgery. Less than a decade ago, the combination of mechanical bowel preparation (MBP) and intravenous antibiotic was the commonest form of prophylaxis in the elective setting. However, the role of MBP is now questionable since several good quality studies have challenged its value[9-19]. If the present trend continues, it appears that patients undergoing elective colorectal surgery may not need any specific intervention to reduce infectious morbidity, except for a single dose of intravenous antibiotics at induction.

On the other hand, there are other interventions that might have been overlooked and it may be worthwhile to re-visit them in order to establish their value in the current era. In this review, we discuss the available methods of SSI prophylaxis in elective colorectal surgery comprehensively by analysing their historical evolution as well as their current value. The role of oral antibiotic prophylaxis is examined in this context.

LITERATURE SEARCH

A systematic literature search was conducted using medical archiving platforms, including Pubmed, Medline, Google Scholar and the Cochrane database of Systematic Reviews. We searched for studies evaluating SSI prophylaxis in elective colorectal surgery using the following search terms: "surgical site, infection, prophylaxis, antibiotics, mechanical preparation, bowel, surgery, elective" and "oral antibiotics". The data is discussed below from a chronological perspective so that the reader will understand the evolution of SSI prophylaxis in elective colorectal surgery.

History of antibiotics in colorectal surgery

In the pre-antibiotic era, elective colorectal surgery was plagued by infections and high overall morbidity. This contributed to mortality rates in excess of 40% in the 19th century. Since faeces was known to be heavily laden with bacteria, it appeared logical that reducing faecal load would reduce infectious complications. This was initially achieved using a diverting stoma proximal to the anastomosis and by leaving the surgical wound open for healing by secondary intention.

At the turn of the 20th century, surgeons also began to manipulate dietary intake and administer oral agents such as charcoal. Over the subsequent decades, MBP evolved and by the mid-20th century became standard practice in elective colorectal operations, although there was no clear evidence of its effectiveness.

During this era, antibiotics had not yet been developed. It was not until 1928 that Alexander Fleming discovered penicillin[20] - and its first recorded clinical use was on February 12, 1941 when it was administered to 43-year old Albert Alexander to treat a facial abscess in the United Kingdom[21]. The clinical application of this discovery ushered in the antibiotic era, when significant research into new antibiotics was launched.

In the next two decades, three classes of antibiotics were discovered that shaped the future of colorectal surgery: Aminoglycosides in 1943[22], macrolides in 1952[23,24] and polymixins in 1958[25]. These antibiotics all had poor enteral absorption and exerted their actions primarily in the bowel lumen.

Albert Schatz discovered streptomycin, the first aminoglycoside, which he isolated from Streptomyces griseus on October 19, 1943[25]. By binding to the 30S sub-unit of bacterial ribosomal RNA, streptomycin interferes with the coupling of tRNA, leading to inhibition of protein synthesis[25]. Its efficacy to treat tuberculosis was proven conclusively by the very first randomized, double-blinded, placebo-controlled trial on record, designed by Sir Geoffrey Marshall of the MRC Tuberculosis Research Unit[26]. It was also used to sterilize the colon as a part of MBP, but when Lockwood *et al*[27] evaluated its efficacy by culturing stool samples in 24 patients who were treated with oral streptomycin, they found that the reduction in intestinal flora was unreliable. There were insignificant reductions in 39% of clostridia, 50% of coliforms and 88% of streptococci[27]. More importantly, they demonstrated rapid development of resistant strains of *Escherichia coli* (*E. coli*) in the patients who showed a favourable early response[27]. Based on these results Lockwood *et al*[27] recommended reserving streptomycin for tuberculosis treatment rather than expend the drug to sterilize the bowel for surgery. When Selman Waksman isolated the second aminoglycoside, neomycin, from streptomyces fradiae in 1944[22], it naturally became the choice for bowel sterilization. It also found application in the treatment of hepatic encephalopathy by killing ammonia-producing bacteria in the gastrointestinal tract.

Colistin, the first polymixin to be discovered, was isolated from Bacillus polymyxa var. colistinus in 1949[25]. It acts by disrupting lipopolysaccharides in the bacterial cell membrane. It was popular to sterilize bowel because it was poorly absorbed enterally and quite effective against luminal gram-negative bacilli such as *E. coli, Klebsiella Spp* and *Pseudomonas Spp*.

McGuire *et al*[23] isolated Erythromycin, the first macrolide, from strains of streptomyces erythreus in 1952. Erythromycin, through an incompletely understood mechanism, also binds to bacterial rRNA and interferes with aminoacyl translocation, preventing coupling of tRNA and so inhibiting protein synthesis[24,28]. It was attractive

for colorectal surgery since it was poorly absorbed from the gut[28].

The discovery of these three new classes of antibiotics that were poorly absorbed from the gastrointestinal tract provided a new opportunity to reduce the colonic bacterial counts because they exerted their action primarily in the bowel lumen. But there were mixed results to control SSIs in this era because most of the drugs were only effective against gram-negative bacteria with little anti-anaerobic effect[29,30]. Therefore, the use of oral antibiotic prophylaxis was slow to gain traction. It was not until the 1970s that reproducible results were obtained showing benefit from oral antibiotic prophylaxis.

In 1973, Nichols *et al*[31] published their landmark paper in which the oral neomycin-erythromycin combination was administered in three doses over 19 h preoperatively. They randomized 20 patients undergoing elective colorectal surgery to MPB with and without the oral antibiotic regime. All patients had colonic samples taken intra-operatively for culture. Nichols *et al*[31] reported "luxuriant growth of aerobes and anaerobes" in the patients who had MBP alone with mean concentrations that were "similar to those normally found in stool". However, addition of the oral antibiotic regime significantly reduced colonic anaerobes, total aerobes, coliforms, streptococci, bacteroides and peptostreptococci[31]. It was not surprising, then, that the incidence of wound infections was significantly greater with MBP alone (30% *vs* 0%) - and cultures revealed that they were all due to *E. coli* and *Bacteroides fragilis*[31]. *Peptostreptococci* and *Clostridia* were also common pathogens in Nichols' subsequent study where they retrospectively evaluated erythromycin/neomycin regimes in 98 elective colectomies in a case-control study[31]. There was also a greater incidence of wound infections when MBP was used alone, without antibiotics, in this study (17% *vs* 0%)[31].

In 1978, Bartlett *et al*[3] carried out a prospective randomized trial across 10 Veterans Administration Hospitals to compare the oral neomycin/erythromycin regime *vs* placebo. The oral antibiotics significantly reduced the incidence of SSIs from 35% to 9% and anastomotic leaks from 10% to 0%[3]. Cultures of luminal contents showed that oral antibiotics significantly reduced the concentrations of both aerobes and anaerobes by approximately 10^5 bacteria/mL at the time of operation and there was no notable emergence of resistant forms on post-operative samples[3].

There was now an accumulation of data to show that when oral antibiotics were administered after the colon was cleansed by MBP, there was a measurable decrease in SSIs associated with colorectal operations[3,32-35]. The findings were so impressive that in 1979, Proud and Chamberlain[36] wrote "there is no justification for including a placebo in trials of this nature. Nor is mechanical preparation of the bowel alone sufficient for patients about to undergo elective colonic surgery". By the late 1970s, there was wide acceptance of oral antibiotics for SSI prophylaxis. However, continued developments in intravenous antibiotics would soon dampen the enthusiasm for oral antibiotics.

clavulanate in 1981[37]. By the mid-1990s, intravenous antibiotics were rapidly being popularized. With convenient dosing regimes, reliable bioavailability profiles and a wider spectrum of coverage, these newer agents overshadowed the oral non-absorbable antibiotics.

Although Benjamin Duggar discovered aureomycin, the first tetracycline, in 1945[38], it was not available for clinical use until 1955[39] and only became popular as a broad-spectrum antibiotic in the 1970s[39]. Metronidazole had been used since 1959 for parasitic infestations but the anti-bacterial effect was not appreciated until 1962 when it was prescribed for trichomonal vaginitis and cured the patient of bacterial gingivitis[40]. Similarly, it was not until the 1970s that metronidazole became used as an anti-anaerobic drug[41] after Nastro *et al*[42] demonstrated an *in vitro* effect and Whelan *et al*[43] proved an anti-anaerobic effect in humans. By the late 1970s, intra-venous metronidazole and tetracycline regime were becoming popular for SSI prophylaxis.

Further change came with the development of the cephalosporins, a group of antibiotics that inhibited cell wall synthesis. Cephalothin, the original cephalosporin, became available in 1964[44] and was soon followed by second-generation cephalosporins that had a wider spectrum of gram-negative cover[45]. The cephalosporins became popular due to the powerful effects against gram-positive and gram-negative bacteria, especially with the extended spectrum of second and third generation drugs in the late 1970s. They were also attractive for patients with penicillin and tetracycline allergies because they had low cross-reactivity rates[46]. Campagna *et al*[46] reported that patients with penicillin allergies had 1% cross-reaction with first generation cephalosporins and "negligible" cross-reactivity with second-generation cephalosporins[46].

Aminopenicillin was the first β-lactam to be identified in 1961 but the clinically useful derivative, amoxicillin, only became available in 1972[37]. By inhibiting peptidoglycan cross-linking in bacterial cell walls, β-lactam antibiotics have activity against a moderate spectrum of gram-positive and gram-negative organisms. Amoxicillin fell out of favour when resistance emerged due to its susceptibility to β-lactamase produced by some organisms[37]. But in 1972 a potent β-lactamase inhibitor, clavulanic acid, was isolated from Streptococcus clavuligerus[37]. It was combined with amoxicillin to produce a combination that became available for clinical use in the United Kingdom as oral preparations in 1981 and intravenous preparations in 1985[37].

In the next few years, these new intravenous broad-spectrum agents were quickly adopted for prophylaxis against SSI at the expense of oral non-absorbable antibiotics[8].

MBP

MBP was in routine use by the mid-20th century. A

variety of methods were employed including enemas, whole gut irrigation and/or cathartics. Several theories were proposed as the mechanisms through which MBP could reduce infectious morbidity: the empty colon was easier for the surgeon to handle, so improving technical creation of the anastomosis[47]; there would be no faecal bulk to mechanically shear the fresh anastomosis[48]; the absence of faeces would avoid intra-operative contamination that led to SSI[49]; the reduced colonic bacterial load would leave less organisms with opportunity to cause SSI[49,50]; and the resultant drop in luminal pH would reduce ammonia production that had a cytotoxic effect on colonic anastomoses[51,52].

Evidence supporting these concepts came primarily from small animal studies suggesting that MBP increased anastomotic bursting pressure (intra-luminal pressure needed to mechanically disrupt an anastomosis)[51-53] and reduced anastomotic leaks on imaging or *ex-vivo* inspection[53]. Perhaps the most convincing evidence to support MBP was published by O'Dwyer *et al*[53] in 1989. They randomized 36 dogs to low anterior resection with or without MBP. At post-operative day 9, dogs subjected to MBP had significantly less anastomotic leaks (13% *vs* 47%) and pelvic abscesses (6% *vs* 29%).

But in the latter part of the 20th century, anastomotic failure rates still ranged widely from 5%-30% despite routine MBP[54]. It also became increasingly apparent that there were undesirable effects from MBP, including fluid shifts, electrolyte disturbances, nausea, vomiting, abdominal pain and poor patient tolerability[55-57]. But it was the growing trauma experience with emergency surgery for penetrating colon injuries that prompted surgeons to seriously question MBP. Multiple reports surfaced revealing good outcomes after emergent surgery in unprepared colon with irregular lacerations, faecal contamination and significant delay before repair[58-60]. A Cochrane Systematic Review of all randomized controlled trials evaluating diversion *vs* primary repair for penetrating colon injuries settled this issue by showing that primary repair in unprepared bowel significantly reduced overall morbidity, infectious complications, dehiscence and wound complications[61].

These good outcomes prompted investigators to design prospective randomized blinded trials to evaluate MBP for elective colorectal surgery[55,62-69]. Three trials actually suggested that MBP was harmful[55,67,68]. Santos *et al*[67] randomized 149 patients to elective colorectal surgery with and without to MBP. They reported that MBP led to significantly more wound infections (24% *vs* 12%, $P < 0.05$) and a worrisome trend toward increased anastomotic leaks (10% *vs* 5%). Bucher *et al*[55], in their multicentre prospective randomized trial of 153 patients, also reported that the MBP group had significantly more wound abscesses (13% *vs* 4%; $P = 0.07$; RR = 1.58; 95%CI: 0.97-2.34), infectious morbidity (22% *vs* 8%; $P = 0.028$; RR = 1.58; 95%CI: 1.16-2.14), extra-abdominal complications (24% *vs* 11%; $P = 0.034$; RR = 1.5; 95%CI: 1.11-2.04) and prolonged hospital stay - even in the sub-group without complications (11.7 ± 5.2 d *vs* 9.1 ± 2.7 d; $P = 0.001$). Bucher *et al*[68] histologically examined macroscopically healthy colon at the proximal resection margins in 50 patients who had MBP in a blinded prospective randomized trial. They noted that MBP produced potentially deleterious microscopic changes, including greater loss of superficial mucus (96% *vs* 52%; $P < 0.001$), loss of epithelial cells (88% *vs* 40%; $P < 0.01$), significant mucosal inflammation (48% *vs* 12%; $P < 0.02$) and infiltration of polymorphonuclear cells (52% *vs* 8%; $P < 0.02$)[68].

Several large meta-analyses were then commissioned to evaluate the available data from the prospective trials that randomized patients to elective colorectal surgery with or without MBP[10-19,70]. The first few meta-analyses also suggested that MBP was harmful[10-13,70]. Three meta-analyses independently demonstrated a statistically significant increase in anastomotic leaks with MBP[11-13]. One meta-analysis demonstrated a significant increase in wound infections with MBP[70] and another demonstrated a significant increase in post-operative cardiac events[10]. More recent meta-analyses, however, that have included larger patient numbers and better trial designs have not corroborated the harmful effects, although they do provide robust level I evidence that there is no benefit to MBP prior to elective colorectal surgery[15-19].

Although it initially appeared logical that reducing faecal load in the colon would reduce infectious morbidity and anastomotic failures, current data does not support this logic. The prevailing theory to explain this is that a fundamental difference exists between in intra-luminal bacteria and mucosa-associated bacteria. Mucosa-associated bacteria are found within the epithelium and they may be adherent to or trapped in mucus lining the colonic wall. While MPB physically evacuates faeces and bacteria from the lumen, there is insignificant effect on mucosa-associated bacteria[71]. Smith *et al*[72] used animal models to study intra-operative colonic lavage. In their study, they used tissue cultures to quantitatively assess the counts of intraluminal and mucosa-associated bacteria. They demonstrated 10000-fold reductions in intraluminal bacteria but insignificant changes in mucosa-associated bacteria[72]. This strengthened the theory that the intra-mucosal environment was a separate ecologic niche[72].

The overwhelming data from well-designed good quality studies demanded that MBP be abandoned as a part of modern colorectal surgery. Currently MBP is relegated only to specific circumstances for patients with: Tumours < 2 cm diameter that may not be easily appreciated intra-operatively, intra-operative colonoscopy is required, a laparoscopic approach is used or restorative proctectomy is scheduled[55]. However, this paradigm change depleted the armamentarium in the quest to minimize infectious morbidity. In our search for other interventions to combat infection, it may be worth re-considering the use of non-absorbable antibiotics.

Firstly, surgeons reported encountering undigested capsules in the colon intra-operatively[73]. They argued that the timing, absorption and dose of oral antibiotics

were not sufficiently refined to allow for reliable tissue concentrations intra-operatively[73]. The mixed results from early trials gave credence to this argument and there was no available data to counter this argument.

Secondly, it became increasingly recognized that anaerobes were being cultured in 50%[74] to 90%[75] of SSIs after elective colonic operations[76-78]. However, effective anaerobic agents were not available until Nastro *et al*[43] demonstrated the anti-anaerobic effect of metronidazole *in vitro* in 1972, and in 1973 when Whelan *et al*[44] demonstrated the *in-vivo* effect against *Bacteroides fragilis* and *Clostridium welchii* from the colon. But this coincided with the advent of intravenous agents and the oral preparations were overshadowed as clinicians' focus shifted toward intravenous metronidazole coupled with the newer broad-spectrum agents.

The cephalosporins, β-lactams and clauvulanic acid were rapidly being developed in the 1970's and 1980's. They were more attractive than oral antibiotics because of their powerful action against a wide spectrum of gram-positive and gram-negative organisms, predictable drug kinetics and better bioavailability[73]. Oral antibiotics sustained a serious blow in 1998 when Song and Glenny[4] carried out a meta-analysis of all randomized controlled trials between 1984 and 1995 that evaluated antimicrobial prophylaxis against postoperative SSI after colorectal surgery. After evaluating many regimes, they declared that the following regimes were ineffective: Metronidazole alone, doxycycline alone, piperacillin alone, and oral neomycin-erythromycin combinations[4]. Song and Glenny[4] recommended prophylaxis with a single pre-operative dose of intravenous second generation cephalosporin coupled with metronidazole.

With the increasing complement of antibiotics, concerns over drug resistance deepened. Lockwood *et al*[27] had already demonstrated that *E. coli* rapidly developed resistance after brief exposure to oral streptomycin. In the 1970s Nichols *et al*[79], having popularized the erythromycin-neomycin regime[29-31], warned that it could suppress endogenous organisms leading to overgrowth of resistant organisms. In the 1980's reports of *Clostridium difficile*-related pseudomembranous colitis "due to intestinal antiseptics such as oral neomycin" began to surface[80,81]. Although several studies have since disproved the significance of the potential overgrowth of resistant organisms[31,82-84], the suggestion that oral antibiotics could be harmful certainly slowed the enthusiasm for its use.

The final blow came in the late 1990s with the surmounting challenges to MBP. Up to this point, oral antibiotics were administered after mechanical cleansing of the colon. So oral antibiotics fell further into disuse in the late 1990's when MBP was seriously challenged in emergency[38,39,61,85] and elective colorectal surgery[10-13,15-19,71]. Without prior MBP, the prevailing thought was that oral antibiotics could not clear organisms effectively if faeces remained in the lumen.

Because of these factors in the late 1990's, oral antibiotics were over shadowed and debate raged on about the optimal choice of Ⅳ antibiotics and MBP. Therefore, it was not surprising that the use of oral antibiotics in colorectal operations steadily declined over the past three decades from 86% in the 1990s[86] to 36% in 2010[87].

At the turn of the 21st century, a few prospective randomized trials attempted to evaluate the role of oral antibiotic prophylaxis[3,5,31,88-92]. However, there was great heterogeneity between the studies in antibiotic selection, methods of administration, dosing schedules and study protocols. Therefore, mixed results were obtained. Some prospective randomized trials showed no further reduction in SSI when oral antibiotics were added to MBP plus intravenous antibiotics[90,91]. However, when Lau *et al*[89] randomized 194 patients to MBP with either the standard oral erythromycin/neomycin combination, intravenous metronidazole/gentamicin or both oral plus intravenous antibiotics, they found a significantly greater incidence of SSI with MBP and oral antibiotics (27.4%) compared to intravenous antibiotics alone (11.9%) or combined intravenous-oral preparations (12.3%). This study provided conflicting results by now suggesting that oral antibiotics were harmful[89]. The findings also conflicted with the results of prospective randomized trials[3,5,31,88,92] that suggested significant reductions in SSI rates when oral plus intravenous antibiotics were used for prophylaxis. The presence of multiple randomized controlled trials with conflicting results prompted three groups to perform meta-analyses[1,5,8]. Table 1 evaluates the data from recent published meta-analyses evaluating oral antibiotic prophylaxis.

Lewis[5] published a meta-analysis in 2002 in which they examined randomized, controlled trials that compared 1077 patients receiving systemic antibiotics alone *vs* combined oral and intravenous antibiotics in 988 patients in order to prevent SSI in elective colorectal surgery between 1979 and 1995. They recorded SSIs in 6.88% of patients who received combined prophylaxis compared to 13.56% with intravenous antibiotics alone. The overall trend favoured combination therapy for prophylaxis, with a weighted mean risk difference for SSI of 0.56.

Bellows *et al*[1] published a meta-analysis in 2011 that included newer prospective randomized blinded trials[25] and only those that evaluated non-absorbable oral antibiotics. They evaluated 2669 patients across 16 randomized controlled trials comparing combined oral non-absorbable plus intravenous antibiotics *vs* intravenous antibiotics alone in elective colorectal surgery[1]. They found that the combination of oral non-absorbable plus intravenous antibiotics significantly reduced the risk of superficial and deep SSI compared to intravenous antibiotics only, although there was no effect on organ space infections or anastomotic leaks. Bellows *et al*[1] came to the same conclusion endorsing combined oral and intravenous antibiotics as prophylaxis during elective colorectal surgery.

Nelson *et al*[8] evaluated the effect of prophylactic

Table 1 Published meta-analyses evaluating the use of oral antibiotics for surgical site infection prophylaxis in elective colorectal surgery

Ref.	Summary	Surgical Site Infections in patients who received antibiotic prophylaxis *via*			Strength/weakness of study	Conclusion
		Combined oral + IV routes	IV route alone	Oral route alone		
Lewis *et al*[5] (2002)	Meta-analysis of randomized trials comparing Ⅳ *vs* combined antibiotic prophylaxis in 2065 patients	68/988 (6.88%)	146/1077 (13.56%)	0	The major criticism was that they included studies that used absorbable and non-absorbable oral antibiotics.	Combination therapy significantly reduced overall SSI rates (RR = 0.51, 95%CI: 0.24-0.78; $P < 0.001$) *vs* Ⅳ antibiotics alone
Nelson *et al*[8] (2014 revision)	Metanalysis of 2929 patients across 15 randomized studies compared combined *vs* Ⅳ alone	100/1456 (6.87%)	188/1473 (12.76%)	0	All 13 trials were randomized controlled trials but only 5 were blinded studies Some included MBP Antibiotics not standardized Included absorbable oral antibiotics	Combination therapy significantly reduced SSI rates (RR = 0.55, 95%CI: 0.43 to 0.71; $P = 0.0001$) compared to Ⅳ alone
Nelson *et al*[8] (2014 revision)	Metanalysis of 1880 patients across 9 randomized studies comparing combined oral + IV antibiotics *vs* oral alone	39/943 (4.14%)	0	74/931 (7.95%)	7 studies used adequate randomization and 4 were blinded studies Many study variables Some included MBP Antibiotics not standardized Included absorbable oral antibiotics	Combination therapy significantly reduced SSI rates (RR = 0.52, 95%CI: 0.35 to 0.76; $P = 0.0003$) *vs* oral alone
Bellows *et al*[1] (2011)	Metanalysis of 2669 patients across 16 randomized trials comparing combined oral + Ⅳ antibiotics *vs* Ⅳ antibiotics alone	91/1352 (6.73%)	159/1317 (12.07%)	0	Only evaluated recent studies using non-absorbable oral antibiotics 7 were blinded studies 7 studies followed patients for hospital duration only	Combination therapy significantly reduced rates of superficial and deep SSI [RR = 0.57 (95%CI: 0.43–0.76), $P = 0.0002$; risk difference, -0.05 (95%CI: -0.08 to -0.02), $P = 0.0003$] *vs* IV alone No difference in organ space infections [RR = 0.71 (95%CI: 0.43–1.16), $P = 0.2$] or anastomotic leaks [RR = 0.63 (95%CI: 0.28–1.41), $P = 0.3$]

SSI: Surgical site infections; MBP: Mechanical bowel preparation.

antibiotics on SSIs in patients who underwent colorectal surgery in 24 randomized controlled trials. The latest 2014 revision of the Cochrane Systematic Review[8] proved that combined regimes of oral plus intravenous antibiotics provided better SSI prophylaxis than intravenous antibiotics alone or oral antibiotics alone. However, some of the individual studies that evaluated oral antibiotics were flawed, many including varied antibiotics and absorbable oral antibiotics and/or MBP. Nevertheless, Nelson *et al*[8] recommended the use of antibiotics covering aerobic and anaerobic bacteria to be delivered orally and intravenously prior to colorectal surgery for SSI prophylaxis.

Therefore, all 3 recently published meta-analyses[1,5,8] suggested that combined oral and intravenous antibiotics should be used for prophylaxis in elective colorectal surgery. Since these meta-analyses were published, further studies supporting the use of oral antibiotic prophylaxis[93-95] have been reported.

Toneva *et al*[93] retrospectively evaluated the post-operative course of 1161 patients who were readmitted to hospital after elective colorectal resections from 2005-2009. When they evaluated readmissions according to the type of prophylaxis used, it was noted that the patients who had oral antibiotic preparation had significantly less 30-day readmissions for infections (3.9% *vs* 5.4%; $P < 0.001$; OR = 0.81; 95%CI: 0.68-0.97) and a lower than average post-operative hospital stay than those who had MBP alone[93].

Canno *et al*[94] retrospectively studied 9,940 patients who underwent colorectal operations from 2005-2009 across 112 Veterans Affairs Hospitals where SCIP protocols were followed. They reported a significantly lower incidence of SSIs in the patients who had oral antibiotics alone (8.3%) compared to those who had MBP alone (18%) and those receiving no MBP (20%). This represented a 67% decrease in SSI (OR = 0.33; 95%CI: 0.21-0.50) when oral antibiotics were used. The use of oral antibiotics plus MBP resulted in 9.2% SSI rates, representing a 57% reduction in SSI occurrence (OR = 0.43; 95%CI: 0.34-0.55).

Sadahiro *et al*[95] evaluated 310 patients who underwent colonic resections for malignant disease who had MBP and intravenous flomoxef that were randomized to non-absorbable antibiotics antibiotics, probiotics or neither. They showed that oral non-absorbable antibiotic group had a significantly lower incidence of SSI (6.1% *vs* 18% *vs* 17.9% respectively). These patients also had a lower incidence of anastomotic leaks (1% *vs* 12% *vs* 7.4% respectively).

There is level Ⅰ evidence proving that intravenous

antibiotics are efficacious in reducing the incidence of SSI during elective colorectal surgery**.** Ideally, they should be administered intravenously, within 60 min of the surgical incision. A single pre-operative dose of a second or third generation cephalosporin (for extended gram negative coverage) combined with metronidazole (for anaerobic cover) is recommended for prophylaxis in elective colorectal surgery.

Good-quality data has now emerged supporting the role of oral antibiotics, in combination with intravenous antibiotics, for SSI prophylaxis. The existing data suggest that combination therapy is more effective than oral antibiotics alone and intravenous antibiotics alone. Therefore, in addition to the above intravenous regime, we also recommend administration of non-absorbable oral agents, such as neomycin sulphate with erythromycin, in the 18-h period prior to elective colorectal surgery.

We do recognize that the choice of antibiotics is still not yet settled, but it should include appropriate gram negative, gram positive and anaerobic coverage, with non-absorbable agents administered orally. The chosen regime should be guided by institutional antimicrobial protocols, taking into account the spectrum of microbes in the local environment, their resistance patterns and the availability of the individual agents.

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ORIGINAL ARTICLE

Retrospective Study

Hepatocellular carcinoma with child Pugh-A Cirrhosis treated with stereotactic body radiotherapy

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Abstract

AIM

To evaluate the control, survival, and hepatic function for Child Pugh (CP)-A patients after Stereotactic body radiotherapy (SBRT) in hepatocellular carcinoma (HCC).

METHODS

From 2009 to 2016, 40 patients with Barcelona Liver Clinic (BCLC) stages 0-B HCC and CP-A cirrhosis completed liver SBRT. The mean prescription dose was 45 Gy (40 to 50 Gy in 4-5 fractions). Local relapse, defined as recurrence within the planning target volume was assessed with intravenous multiphase contrast computed tomography or magnetic resonance imaging every 4-6 mo after completion of SBRT. Progression of cirrhosis was evaluated by CP and Model for End Stage Liver Disease scores every 3-4 mo. Toxicities were graded per the Common Terminology Criteria for Adverse Events (v4.03). Median follow-up was 24 mo.

RESULTS

Forty-nine HCC lesions among 40 patients were analyzed in this IRB approved retrospective study. Median tumor diameter was 3.5 cm (1.5-8.9 cm). Six patients with tumors ⩾ 5 cm completed planned selected transarterial chemoembolization (TACE) in combination with SBRT. Eight patients underwent orthotropic live transplant (OLT) with SBRT as a bridging treatment (median time to transplant was 12 mo, range 5 to 23 mo). The Pathologic complete response (PCR) rate in this group was 62.5%. The 2-year in-field local control was 98% (1 failure). Intrahepatic control was 82% and 62% at 1 and 2 years, respectively. Overall survival (OS) was 92% and 60% at 1 and 2 years, with a median survival of 41 mo per Kaplan Meier analysis. At 1 and 2 years, 71% and 61% of patients retained CPA status. Of the patients with intrahepatic failures, 58% developed progressive cirrhosis, compared to 27% with controlled disease (P = 0.06). Survival specific to hepatic failure was 92%, 81%, and 69% at 12, 18, and 24 mo. There was no grade 3 or higher toxicity. On univariate analysis, gross tumor volume (GTV) < 23 cc was associated with freedom from CP progression (P = 0.05), hepatic failure-specific survival (P = 0.02), and trended with OS (P = 0.10).

CONCLUSION

SBRT is safe and effective in HCC with early cirrhosis and may extend waiting time for transplant in patients who may not otherwise be immediate candidates.

Key words: Stereotactic body radiotherapy; Hepatocellular carcinoma; Child-Pugh A; Cirrhosis; Hepatoma; Local control; Radiotherapy; Radiation

Core tip: This retrospective review demonstrates excellent long term local control of hepatocellular carcinoma (HCC) in early stage cirrhosis treated by Stereotactic body radiotherapy (SBRT), while retaining hepatic function. However, the overall prognosis of HCC remains poor despite successful local therapy and transplant remains the standard of care. Given the rising incidence of HCC, liver procurement and selection of candidates for transplant will become increasingly stringent. The long term control and maintenance of hepatic reserve demonstrated in this series suggests that SBRT as a bridging therapy may extend waiting time for transplant in patients who may not otherwise be immediate candidates for it.

Hasan S, Thai N, Uemura T, Kudithipudi V, Renz P, Abel S, Kirichenko AV. Hepatocellular carcinoma with child Pugh-A Cirrhosis treated with stereotactic body radiotherapy. *World J Gastrointest Surg* 2017; 9(12): 256-263 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i12/256.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i12.256

INTRODUCTION

Accounting for the second most cancer-related deaths worldwide, hepatocellular carcinoma (HCC) is an aggressive malignancy that is diagnosed in at least 6 of every 100000 Americans, a rate nearly triple that of thirty years ago[1,2]. In the United States, Chronic Hepatitis C (HCV), alcohol abuse, and non-alcoholic steatohepatitis (NASH) are the leading causes of HCC, which is diagnosed at a growing rate in light of more sophisticated imaging and vigilant surveillance with serum markers[3-5]. Liver transplant remains the gold standard for definitive treatment, however the vast majority of patients fail to meet the surgical or medical criteria for transplant, with high mortality rates if not properly selected[6]. Further complicating management is the cirrhosis that accompanies HCC, which often renders patients medically inoperable or at high risk for surgery.

Therapeutic alternatives include partial hepatectomy, radiofrequency ablation, trans-arterial chemoembolization (TACE), and radioembolization among others. Each treatment modality is associated with procedural complications especially in patients with portal hypertension. In non-cirrhotic patients, partial hepatectomy or surgical resection of hepatocellular carcinoma is potentially curative, with average long-term intrahepatic control rates over 40% and 5-year survival over 60%[7,8]. However, cirrhotic patients must be carefully selected for partial resection to avoid access perioperative mortality[9,10]. Further limiting patient selection for resection are tumors with vascular invasion or those in a centralized location, even in otherwise healthy livers[11]. Ultimately, 15%-30% of HCC patients are eligible for curative partial hepatectomy[12,13]. Other widely used modalities such as TACE and RFA in non-surgical candidates have shown a control and survival benefit, however selection is limited by vascular invasion and biliary obstruction with TACE[14], and by size (< 3 cm) and location (infradiaphragmatic or adjacent to large vessels) with RFA[15,16].

Stereotactic body radiotherapy (SBRT) has emerged as non-invasive treatment that serves as another alternative for local tumor control or used as a bridge to liver transplant. SBRT by definition is an ultraconformal radiotherapy technique administering high radiotherapy doses in 1-5 fractions. It uses multiple external radiation beams/arcs deliver an ablative tumoricidal dose with sharp dose fall-off which limits unacceptable dose to the liver as well as adjacent vasculature, gallbladder, chest wall, kidney or diaphragm.

Several prospective studies have shown that SBRT can be delivered safely in Child Pugh A patients with local control rates between 75%-90% for median tumor size between 20 - 30 cc[17,18].

Although the data for SBRT in HCC is promising, current guidelines recommend it only when patients are

not amenable to, or have failed, other local therapies. Furthermore, while a favorable short-term SBRT-related toxicity profile in early cirrhotic patients is well documented, its long-term impact on progression of hepatic failure is not widely reported. The objective of this retrospective study is to analyze the tumor control, survival, toxicity and preservation of hepatic function, in HCC patients with Child-Pugh A cirrhosis treated with SBRT.

MATERIALS AND METHODS

Patient selection

Between 2009 and 2016, 49 intrahepatic lesions among 40 patients with BCLC stages 0-B hepatocellular carcinoma and Child-Pugh class A cirrhosis were treated with SBRT at a single institution in this IRB approved study. Patients who were treated with palliative intent at a dose range below 30 Gy, had large multinodular tumors (aggregate > 9 cm), metastatic disease, or an ECOG performance status > 2 were excluded from this study. No patients had previous external beam radiation or Yttrium-90 radioembolization. Six patients with large tumors (median diameter 5.4 cm) received planned TACE prior to SBRT for radiosensitization. All patients were evaluated for hepatectomy and transplant in a multidisciplinary setting prior to undergoing SBRT.

Treatment

Treatment planning consisted of a IV contrast-enhanced free breathing helical computed tomography (CT) scan with 3 mm slice thickness, followed by immediate 4-D CT simulation utilizing a Siemens Somatom Sensation Open scanner (Siemens Medical) with an Anzai belt (AZ733V, Anzai Medical) and immobilization with a Vac-Loc® vacuum bag (Bionix, Toledo, OH, Spain). An internal target volume (ITV) was generated based on hepatic motion during the respiratory cycle, with a planning target volume (PTV) generated in the standard fashion around this volume. PTV included the ITV with a 0.3-0.5 cm margin. SBRT dose was prescribed to the isodose line encompassing the PTV (generally 80%-90% isodose line) allowing up to 20% higher dose to the target volume. Dose per fraction varied based on tumor size, location, and normal tissue tolerance. Twenty-two of the 38 patients utilized 4DCT co-registered with 99mTc-sulfur colloid Single Photon Emission Computed Tomography (SPECT) for visualization and conformal avoidance of best perfused hepatic parenchyma. Details of SPECT/CT co-registration and treatment planning have been previously reported for liver SBRT in cirrhotic HCC patients[19,20]. Dose limits were set such that at least 35% of predicted liver volume by SPECT imaging received $\leqslant$ 18 Gy in 5 fractions or $\leqslant$ 16 Gy in 4 fractions. The median dose to the PTV was 45 Gy (range 40 to 50 Gy) at a median dose per fraction of 9 Gy. Median biologic equivalent dose (BED_{10}) was 85.5 Gy (range 72-105.6 Gy).

Outcome assessment

Local response with contrast-enhanced triple phase CT or MRI was documented every 4-6 mo following radiotherapy as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria[21]. Failures were considered local if within or on the edge of the PTV. Intrahepatic failures were defined as radiographic evidence of progressive hepatocellular carcinoma within the liver and outside of the PTV. Fluctuations in alpha-feto protein (AFP) levels were not considered when assessing response or tumor control. The progression of cirrhosis was evaluated by Child-Pugh and End Stage Liver Disease (MELD) scores at least every 4 mo. Potential prognostic correlates including initial stage, tumor size, radiation dose, performance status, and initial MELD stage were analyzed against intrahepatic control, overall survival, and hepatic-failure specific survival, which we define as the portion of patients who did not die from liver failure. We also evaluated potential correlates of freedom from C-P progression, which we define as advancing from the Child Pugh A to the Child Pugh B classification[22]. Toxicities were graded per the Common Terminology Criteria for Adverse Events (CTCAE) (v4.03). Survival and tumor control analyses are based on Kaplan Meier (KM) methodology, and univariate analysis was conducted *via* Cox proportional hazard regression models using MedCalc.

RESULTS

Patient characteristics

Thirty-two males and eight females with HCC and CP-A cirrhosis who completed liver SBRT were analyzed with a median follow up of 24 mo (4 to 64 mo). Seven of the 40 patients had two tumors treated simultaneously, and one patient had 3 treated at the same time. The maximum tumor diameter ranged from 1.5 to 8.9 cm, with a median of 3.5 cm. Gross tumor volume varied between 2.6 to 220.1 cc with median 23 cc, and the corresponding planning target volume was between 11.5 and 351 cc (median 67.6). BCLC stages 0 (very early), A (early), and B (intermediate) comprised of 6, 10, and 24 patients, respectively. This corresponds to American Joint Committee on Cancer (AJCC) stages Ⅰ (n = 6), Ⅱ (n = 12), ⅢA (n = 8) and ⅢB (n = 8). SBRT was used as a bridging therapy for orthotropic liver transplant in eight patients. The causes of HCC include Hepatitis C (n = 17), alcohol abuse (n = 8), a combination of both (n = 8), NASH (n = 4), biliary cirrhosis (n = 1), immunosuppression following kidney transplant (n = 1), and one was cryptogenic. Eastern Cooperative Oncology Group (ECOG) performance status was equal to 0, 1, and 2 in 21, 14, and 3 patients respectively (2 unknown). Although all patients were classified as Child Pugh A, 9 of the 40 patients had a MELD score of 10 or higher. A summary of patient characteristics is demonstrated on Table 1.

Control

At last follow up, 48 of 49 lesions (98%) were controlled locally (within the PTV). The one failure was a 4.3

Table 1 Patient characteristics

	Number	Percentage
Gender		
Male	32	82%
Female	8	18%
ECOG performance status[1]		
0	21	55%
1	14	37%
2	3	8%
Etiology of hepatocellular carcinoma[2]		
Hepatitis C	17	46%
Alcohol	8	22%
Combination of Hepatitis C/alcohol	8	22%
NASH	4	8%
BCLC Stage		
0 (very early)	6	15%
A (early)	10	25%
B (intermediate)	24	60%
Previous treatment		
None	34	85%
TACE	6	15%
Number of treated lesions		
Single	32	80%
Multiple[3]	8	20%
Initial MELD score		
< 10	31	78%
> 10	9	22%
Median tumor size (range)	3.5 cm	(1.5 to 8.9 cm)
Median gross tumor volume (range)	23 cc	(2.6 to 220.1 cc)
Median planning target volume (range)	67.6 cc	(11.5 to 351 cc)

[1]2 patients unknown; [2]1 patient with biliary cirrhosis and 1 immunosuppressed; [3]7 patients with 2 lesions and 1 with 3 lesions. ECOG: Eastern cooperative oncology group; NASH: Non-alcoholic steatohepatitis; BCLC: Barcelona liver clinic; TACE: Transarterial chemo-embolization; MELD: Model for end stage liver disease.

cm tumor with a GTV of 80 cc treated to 4500 cGy in 5 fractions. The recurrence occurred 10 mo after completing SBRT. Intrahepatic control, defined as no evidence of disease within the entire liver was 82%, 77%, and 62% at 12, 18, and 24 mo, respectively, with a median time to progression of 47 mo per KM analysis. Five of the intrahepatic failures were treated with additional SBRT and five were salvaged with either TACE (1), Y-90 (2), or resection (1). Distant metastases occurred in the peritoneum, bone, and lungs among 6 patients. SBRT served as bridge for orthotropic liver transplant in 8 patients, 5 of whom demonstrated a pathologic complete response (62.5%). The median time to transplant was 12 mo (5-23 mo). One patient developed an intrahepatic failure which was successfully treated with a second SBRT prior to transplant. No patient developed recurrence after transplant.

Survival

Twenty-three of 40 (58%) patients were alive at last follow up. Three patients died from perioperative complications after liver transplant, all of whom retained Child Pugh A status and had a pathologic complete response. The remaining 5 transplant patients were all long term survivors. One (89% *vs* 88%) and two-year survival (60% *vs* 63%) was similar for patients who received SBRT with or without transplant. Progressive HCC was the cause of death in 9 patients treated with SBRT, and five patients died without evidence of recurrence, 3 of whom had progressive cirrhosis, one with heart disease, and one with metastatic lung cancer.

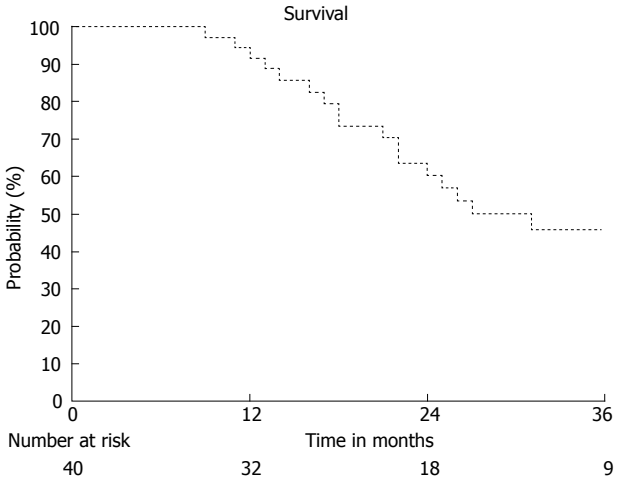

Figure 1 Overall Survival of all patients.

The median survival was 41 mo with a 1-year, 18-month, and 2-year overall survival rate of 92%, 74%, and 60%, respectively. Disease-free survival was 79%, 58%, and 44% at 1 year, 18 mo, and 2 years. Hepatic failure-specific survival was 92%, 81%, and 69% at 1 year, 18 mo, and 2 years, respectively. Univariate analysis suggested that a GTV > 23 cc correlated with a decreased hepatic failure-free survival (HR = 5.72, P = 0.01) and trended towards a decreased overall survival (HR = 2.14, P = 0.10). Advancing Child Pugh cirrhosis also strongly correlated with survival (HR 5.05, P = 0.01) (Figures 1-3).

Hepatic function and toxicity

Of the 40 patients treated, 24 retained Child Pugh A class cirrhosis (63%) and 27 maintained their initial MELD score (68%) at the time of last follow up. The median time to progression within Child Pugh category was 37 mo, with a freedom from Child Pugh progression rate of 89%, 71%, and 62% at 6, 12, and 18 mo respectively (Figure 2). The median time to progression of MELD score was 33 mo with a freedom from MELD progression rate of 95%, 88%, and 79% at 6, 12, and 18 mo respectively. Of the patients with intrahepatic failures, 58% also developed progressive cirrhosis, compared to 27% whom were regionally controlled (HR = 3.8, P = 0.06). As with survival, a GTV > 23 cc (median 60 cc, up to 220 cc) correlated with an increased rate of Child Pugh progression (HR = 2.89, P = 0.05) (Figure 3). There was no incidence of grade 3 or higher toxicity, and 3 patients had grade 2 fatigue. Grade 1 elevation in transaminases was seen in 9 patients, and 1 patient developed grade 2 rise in Alkaline Phosphatase, without any incidence of radiation induced liver disease (RILD).

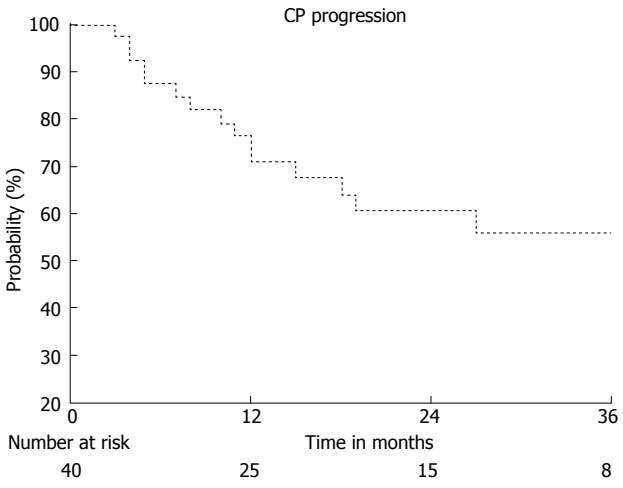

Figure 2 Freedom from child Pugh Progression of all patients. CP progression: Percentage of patients retaining child Pugh A status.

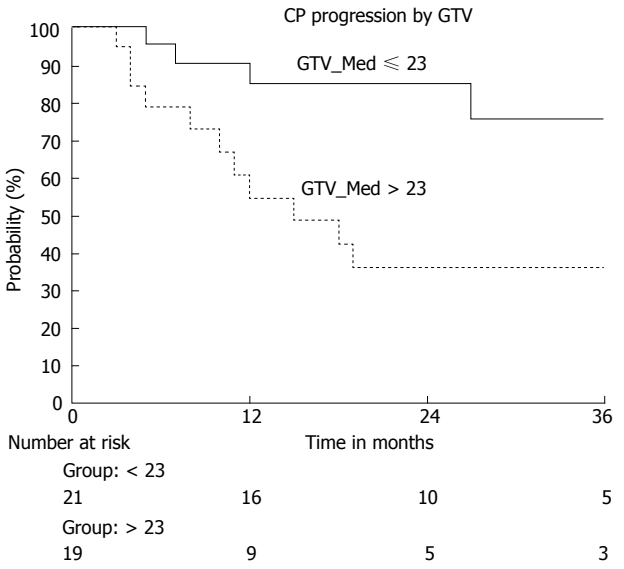

Figure 3 Freedom from child Pugh progression by gross tumor volume. CP progression: Percentage of patients retaining child Pugh A status; GTV: Gross tumor volume in cubic centimeters; Group ⩽ 23: Number of patients with a GTV less than or equal to 23 cc; Group > 23: Number of patients with a GTV greater than 23 cc.

DISCUSSION

Until recently, radiotherapy has been only infrequently used in targeting hepatocellular carcinoma because of the low tolerance of the whole liver to radiation and challenges associated with underlying liver dysfunction. Conversely, dose escalation studies at the University of Michigan with CT-based 3D-conformal radiotherapy planning established a correlation between the irradiated liver volume, the dose delivered, and the risk of radiation-induced liver disease[23]. The liver is a parallel organ and small volumes of liver can tolerate high doses of radiation when the whole liver mean dose can be minimized with techniques such as SBRT. As a result, several prospective SBRT studies have established a dose-response relationship in HCC with early stage cirrhosis, without compromising safety.

Mendez-Romero *et al*[17] and Tse *et al*[24] demonstrated long term local control rates of 75% and 65% with a median dose of 5 Gy x 5 fractions and 6 Gy x 6 fractions, respectively. Dose escalation to 48 Gy in 3 fractions yielded an 87% local control rate for CPA patients in a phase Ⅰ/Ⅱ study by Lasley *et al*[25] Similarly, Bujold *et al*[33] found that doses over 30 Gy (in 6 fractions) improved local control rates. Building on these and other data, the patients in our study were treated to a median BED_{10} of 85.5 Gy (45 Gy in 5 fractions). The 98% local control rate in this study compares favorably to already excellent historical controls, and the overall survival falls within the wide range of reported outcomes in the current literature (Table 2).

In this report of CP-A patients with limited HCC treated with SBRT, 1 and 2 year survival was similar for patients with and without transplant. Given the inherent perioperative mortality risk of liver transplantation, these well selected early CP-A cirrhotic patients with limited extent of HCC may benefit from watchful waiting, reserving orthotopic liver transplantation at the time of further intrahepatic progression or following their natural cirrhosis progression to higher MELD scores. Such a preposition has been suggested by Merion and Wedd *et al*[26,27] whose large retrospective studies independently reported no detriment in survival when delaying transplant in very early stage cirrhosis. Accordingly, close follow-up and careful selection is essential with a watchful waiting approach. Additionally, with 2 year follow up survival is similar with or without transplant, yet long term cure of both HCC and cirrhosis with transplant, may yield a separation of survival curves with longer follow up.

Among the most important aspects of patient selection in HCC is the risk stratification based on hepatic function, such as the Child-Pugh or Model for End Stage Liver Disease (MELD), as patients with worse baseline cirrhosis are at higher risk for therapeutic toxicity. Teh and Cucchetti *et al*[28,29] have shown that a MELD score over 9 preceding partial liver resection is associated with increased perioperative mortality and decreased survival Other studies corroborate a link between initial MELD or Child Pugh score and survival in hepatocellular carcinoma[21,27]. Even in early stage cirrhosis, HCC has been known to accelerate the natural progression of liver failure, which can be impacted regardless of its initial severity[30]. It has also been suggested that a linear progression of liver failure, or serial trend in increasing MELD score, is a better predictor of outcome compared to initial MELD score[31]. These data underline the importance of preserving hepatic function while treating the malignancy that exacerbates it, even at an early stage.

Unsurprisingly, in this study, intrahepatic failure correlated strongly with progressive liver disease, which consequently correlated with overall mortality. Among

Table 2 Summary of prospective stereotactic body radiotherapy studies in hepatocellular carcinoma patients with Child Pugh-A cirrhosis

Study	No of lesions	Median dose-fractionation	Median GTV (cc)	Local control	Overall survival	Grade 3+ toxicity	Median follow-up (m)
Mendez-Romero *et al*[17], 2006	11[1]	5 Gy × 5	22.3	75% (22 mo)	75%, 40% (1, 2 yr)	36%	12.9
Tse *et al*[24], 2008	21	6 Gy × 6	173	65% (1 yr)	48% (1 yr)	12%	17.6
Lasley *et al*[25], 2012	39	16 Gy × 3	-	91% (2 yr)	72% (2 yr)	4.60%	33.3
Bujold *et al*[33], 2013	102	6 Gy × 6	117	87% (1 yr)	55%, 34% (1 yr, 2 yr)	2%	31
Current study	47	9 Gy × 5	23	98% (2 yr)	92%, 60% (1 yr, 2 yr)	None	24

[1]Study includes Child Pugh B patients. GTV: Gross tumor volume; cc: Cubic centimeters; Gy: Gray.

patients treated with SBRT with controlled disease in the liver, 73% retained long term hepatic function which compares favorably to the natural progression of cirrhosis[32]. Three patients advanced to Child Pugh B cirrhosis within 6 mo of SBRT, none of whom had radiographic evidence of HCC. There was no evidence of classic RILD or radiation-induced grade 2 or higher toxicity.

This retrospective review demonstrates excellent long term local control of HCC in early stage cirrhosis treated by SBRT, while retaining hepatic function at a rate similar to historical norms. Unfortunately, the overall prognosis of HCC remains poor despite successful local therapy. Liver transplant remains the standard of care for definitive management. However, with the rising incidence of HCC, demand for healthy livers may outpace supply, and consequently, the selection of appropriate candidates for transplant will become more stringent. The long term local control and maintenance of hepatic reserve demonstrated in this series suggests that SBRT as a bridging therapy may extend waiting time for transplant in patients who may not otherwise be immediate candidates for it, such as those with Child-Pugh A cirrhosis and early stage HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatocellular carcinoma (HCC) is an aggressive malignancy that is diagnosed in at least 6 of every 100000 Americans, a rate nearly triple that of thirty years ago. Liver transplant remains the gold standard for definitive treatment, however many patients fail to meet the surgical or medical criteria for transplant, with high mortality rates if not properly selected. Stereotactic body radiotherapy (SBRT) has emerged as non-invasive treatment option for HCC to achieve local tumor control and may be used as a bridge to liver transplant. Multiple external radiation beams/arcs delivered ablative doses with sharp dose fall-off at surrounding normal tissues allowing SBRT to be administered without limitations of unacceptable toxicity to the liver and adjacent vasculature, gallbladder, chest wall, kidney or diaphragm. Several prospective studies have shown that SBRT can be delivered safely in Child Pugh A patients with local control rates between 75%-90%.

Research motivations

Although the data for SBRT in HCC is promising, current guidelines recommend it only when patients are not amenable to, or have failed, other local therapies. Furthermore, while short-term SBRT-related toxicity in early cirrhotic patients is well documented, its long-term impact on hepatic failure progression is not widely reported.

Research objectives

The objective of this retrospective study is to analyze the tumor control, survival, toxicity and preservation of hepatic function, in HCC patients with Child-Pugh A cirrhosis treated with SBRT.

Research methods

We retrospectively reviewed 40 patients with Barcelona Liver Clinic (BCLC) stages 0-B HCC and CP-A cirrhosis completed liver SBRT from 2009-2016. Local relapse, defined as recurrence within the planning target volume was assessed with intravenous multiphase contrast CT or MRI every 4-6 mo after completion of SBRT. Progression of cirrhosis was evaluated by CP and Model for End Stage Liver Disease (MELD) scores every 3-4 mo. Toxicities were graded per the Common Terminology Criteria for Adverse Events (v4.03). Median follow-up was 24 mo.

Research results

The 2-year in-field local control was 98% (1 failure). Intrahepatic control was 82% and 62% at 1 and 2 years, respectively. Overall survival (OS) was 92% and 60% at 1 and 2 years, with a median survival of 41 mo. At 1 and 2 years, 71% and 61% of patients retained CPA status. Of the patients with intrahepatic failures, 58% developed progressive cirrhosis, compared to 27% with controlled disease (P = 0.06). Survival specific to hepatic failure was 92%, 81%, and 69% at 12, 18, and 24 mo. There was no grade 3 or higher toxicity. On univariate analysis, gross tumor volume (GTV) < 23 cc was associated with freedom from CP progression (P = 0.05), hepatic failure-specific survival (P = 0.02), and trended with OS (P = 0.10). Eight patients underwent orthotropic live transplant (OLT) with SBRT as a bridging treatment (median time to transplant was 12 mo, range 5 to 23 mo). The Pathologic complete response (PCR) rate in this group was 62.5%.

Research conclusions

This retrospective review demonstrates excellent long term local control of HCC in early stage cirrhosis treated by SBRT, while retaining hepatic function. However, the overall prognosis of HCC remains poor despite successful local therapy and transplant remains the standard of care. Given the rising incidence of HCC, liver procurement and selection of candidates for transplant will become increasingly stringent. The long term control and maintenance of hepatic reserve demonstrated in this series suggests that SBRT as a bridging therapy may extend waiting time for transplant in patients who may not otherwise be immediate candidates for it.

Research perspectives

Further prospective studies utilizing SBRT for HCC as a bridge to transplant are warranted.

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ORIGINAL ARTICLE

Retrospective Study

Utility of single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection

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Abstract

AIM

To study the utility of single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection.

METHODS

A 2 cm transverse skin incision was made in the umbilicus, extending to the intraperitoneal cavity. Carbon dioxide was insufflated followed by insertion of laparoscope to observe the intraperitoneal cavity. The type of hernia was diagnosed and whether there was the presence of intestinal incarceration was confirmed. When an intestinal incarceration in the hernia sac was found, the forceps were inserted through the incision site and the intestine was returned to the intraperitoneal cavity without increasing the number of trocars. Once the peritoneum was closed, totally extraperitoneal inguinal hernia repair was performed, and finally, intraperitoneal observation was performed to reconfirm the repair.

RESULTS

Of the 75 hernias treated, 58 were on one side, 17 were on both sides, and 10 were recurrences. The respective median operation times for these 3 groups of patients were 100 min (range, 66 to 168), 136 min (range, 114 to 165), and 125 min (range, 108 to 156), with median bleeding amounts of 5 g (range, 1 to 26), 3 g

(range, 1 to 52), and 5 g (range, 1 to 26), respectively. Intraperitoneal observation showed hernia on the opposite side in 2 cases, intestinal incarceration in 3 cases, omental adhesion into the hernia sac in 2 cases, severe postoperative intraperitoneal adhesions in 2 cases, and bladder protrusion in 1 case. There was only 1 case of recurrence.

CONCLUSION

Single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection makes hernia repairs safer and reducing postoperative complications. The technique also has excellent cosmetic outcomes.

Key words: Inguinal hernia; Intestinal incarceration; Totally extraperitoneal inguinal hernia repair; Intraperitoneal inspection; Single incision

Core tip: Single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection (iSTEP) makes hernia repairs safer and more effectively. Totally extraperitoneal inguinal hernia repair had the disadvantages for difficulty with confirming the type of hernia as well as difficulty with large indirect inguinal hernia, intestinal incompetence and postoperative prostatectomy. However, iSTEP can be used to diagnose the type of hernia easily. It enables observation of the opposite side and reconfirmation of treatment after mesh repair making the technique safer and reducing postoperative complications. The technique also has excellent cosmetic outcomes.

Yamamoto M, Urushihara T, Itamoto T. Utility of single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection. *World J Gastrointest Surg* 2017; 9(12): 264-269 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i12/264.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i12.264

INTRODUCTION

Prudent observation of inguinal hernia is recommended for asymptomatic patients according to the guideline for inguinal hernia treatment released by the European Hernia Society[1]. However, surgery is the standard treatment. The surgical techniques used for inguinal hernia consist of the traditional anterior technique and laparoscopic surgery. Two approaches are utilized in laparoscopic surgery: Transabdominal preperitoneal approach (TAPP) and totally extraperitoneal hernia repair (TEP). In cases of intestinal incarceration, intraperitoneal observation may be necessary to confirm the presence of intestinal damage after reduction, but many inguinal hernias can be repaired without entering the abdominal cavity. TEP shortens the operation time, enhances patient satisfaction, and reduces postoperative pain[2]. However, using conventional TEP, only the hernia on one side can be identified, and there is a possibility of missing occulting inguinal hernia on the opposite side. By combining TEP with intraperitoneal observation, it is possible to diagnose the type of hernia, confirm repair after covering the hernia with mesh, and perform both procedures safely and reliably. We report herein our experiences with single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection (iSTEP), which was performed on 75 patients.

MATERIALS AND METHODS

From April 2009 when iSTEP was first introduced until May 2016, the 75 patients who underwent the procedure at the Prefectural Hiroshima Hospital were enrolled. All surgeries were performed by the same experienced surgeon. Data on patient demographics, clinical data, intraoperative findings, and postoperative course were prospectively collected. All patients underwent surgery after providing informed consent. The procedure was approved by the Ethics Committee at the Prefectural Hiroshima Hospital and the study was performed in accordance with the Declaration of Helsinki. We excluded patients who met the following criteria: History of prostate surgery, giant inguinal hernia, young patients with small indirect inguinal hernia, strangulated hernia, and patients who could not tolerate general anesthesia, which was employed for laparoscopic hernia repair at our hospital.

During the surgery, the patient was placed in a supine position under general anesthesia. A 2 cm transverse skin incision was made in the umbilicus, followed by an incision in the peritoneum from the fascia defect to the abdominal cavity. A trocar attached to an access port was inserted and carbon dioxide was insufflated to 8 mmHg (Figure 1). The type of hernia was diagnosed and the presence of intestinal incarceration was confirmed in the intraperitoneal cavity (Figure 2). The trocar was removed and the peritoneum was closed after inserting a catheter to degas the cavity. The peritoneum was ligated by 3-0 Vicryl, once the peritoneum was closed (the ligation was unfolded at the time performing intraperitoneal observation). TEP was then started. The subcutaneous tissue was dissected to the rectus abdominis anterior sheath and a transecting incision was made at the anterior sheath. The rectus abdominis was split and the posterior sheath was exposed. Blunt dissection using an electrical scalpel or a finger was performed between the muscle and the posterior sheath to create a preperitoneal space. A multi-channel access port (GelPOINT MINI; Applied Medical, Rancho Santa Margarita, CA, United States) was installed and carbon dioxide was insufflated to 8mmHg again (Figure 3). The preperitoneal space was dissected using a bipolar forceps by grasping the forceps and pulling toward the Retzius cavity and the peritoneal edge was checked. The cord structures were freed from the hernia sac and parietalisation was performed gently without perforation of the peritoneum. The hernia sac was extracorporeally ligated with a Fisherman'

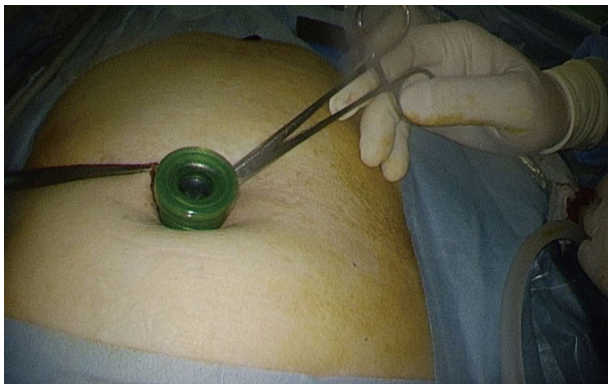

Figure 1 A 2 cm skin incision was made in the umbilicus. A trocar attached to an access port was inserted into the abdominal cavity and carbon dioxide was insufflated.

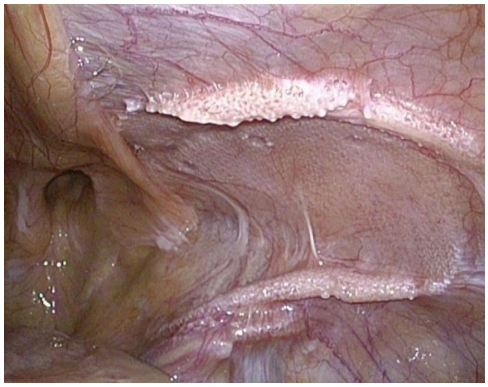

Figure 2 The hernia was viewed and diagnosed within the intraperitoneal cavity. This patient had recurrent hernia at the median part of the Kugel Patch.

s knot using 2-0 Prolene and dissected. The edge of the peritoneum was grasped and dissected toward the dorsal side and the lateral side to secure a space for mesh. The Gel Seal CAP was detached and an artificial patch (3D Max light Mesh L size; Bard, Murray Hill, NJ, United States) (10.8 cm × 16 cm) or TiLENE Mesh; pfm medical, Koln, Germany) (10 cm × 15 cm) was inserted through the incision. After the mesh was positioned to cover the Hesselbach triangle, femoral rings, and inguinal ring, it was fixed to the Cooper's ligaments. The interior and lateral sides of the mesh were secured using a tracking device (Pro Tack; Medtronic, Fridley, MN, United States), applied carefully to avoid injury to the inferior epigastric vessels. Finally, the abdominal cavity was observed to confirm that the repair was complete (Figure 4). The peritoneum, anterior rectus sheath and skin were each closed.

RESULTS

iSTEP hernia repair was successfully completed in 75 patients. Patient demographics and characteristics are summarized in Table 1. There were 66 men and 9 women. The median age of the patients was 68 years (range, 17 to 82 years), median weight was 63 kg (range, 38 to 106 kg), and median body mass index was 23.0

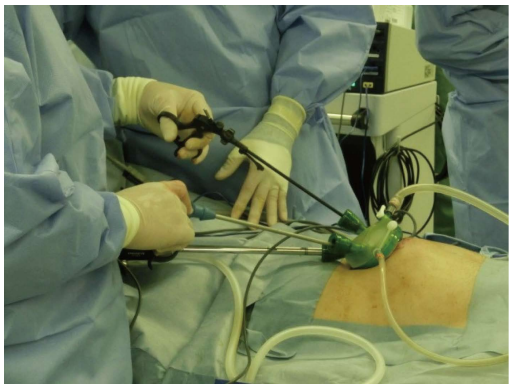

Figure 3 GelPOINT MINI was installed and carbon dioxide was insufflated to 8 mmHg before starting totally extraperitoneal hernia repair.

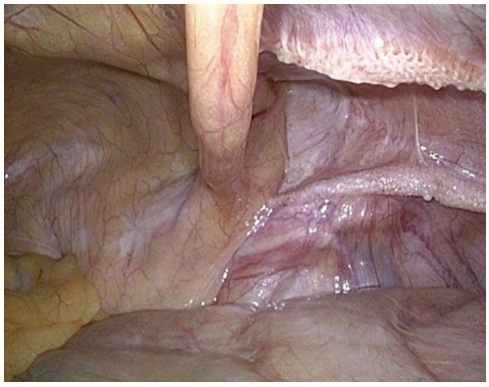

Figure 4 The intraperitoneal cavity was viewed again to confirm the repair.

kg/m^2 (17.3 to 32.7 kg/m^2). The number of patients with a physical status of ASA Ⅰ, Ⅱ, and Ⅲ according to the American Society of Anesthesiologists classification was 25, 49, and 1, respectively. The subjects included smokers, individuals with hypertension, diabetes, respiratory disease, coronary artery disease, or taking anticoagulant/antiplatelet medicine. Fifty-eight hernias were on one side, 17 were on both sides, and 10 were recurrences. The median operation time for these 3 groups of patients was 100 minutes (range, 66 to 168), 136 min (range, 114 to 165), and 125 min (range, 108 to 156) and the median bleeding amount was 5 g (range, 1 to 26), 3 g (range, 1 to 52), 5 g (range, 1 to 26), respectively (Table 2). Intraperitoneal observation showed hernia on the opposite side in 2 cases, intestinal incarceration in 3 cases, omental adhesion to the hernia sac in 2 cases, severe postoperative intraperitoneal adhesions in 2 cases, and bladder protrusion in 1 case. Postoperative hemorrhage and wound infection were not observed, and there was only 1 case of recurrence.

DISCUSSION

Compared to the conventional anterior approach, TEP results in less postoperative pain, fewer postoperative complications, lower recurrence rates, early discharge, and faster return to daily life[3]. TEP is classified as Level 1A treatment in the European hernia guidelines[1].

Table 1 Patient demographics

Variable	*n* (%)
Number of patients	75
Male	66 (88)
Female	9 (12)
Median age, yr (range)	68 (17-82)
Median body weight, kg (range)	63 (17.3-32.7)
Median BMI, kg/m^2 (range)	23.0 (17.3-32.7)
ASA score	
Ⅰ	25 (33.3)
Ⅱ	49 (65.3)
Ⅲ	1 (1.4)
Site of hernia	
Right	33 (44)
Left	25 (33.3)
Both	17 (22.7)
Smoking	37 (49.3)
Hypertension	26 (34.7)
Diabetes mellitus	7 (9.3)
Respiratory disease	10 (13.3)
Coronary artery disease	6 (8)
Anticoagulant/antiplatelet medicine	7 (9.3)

BMI: Body mass index; ASA: American Society of Anesthesiologists.

Table 2 Perioperative data

Variable	Value	%
Operative time		
Unilateral (min)	100 (66-168)	
Bilateral (min)	136 (114-165)	
Recurrence (min)	125 (108-156)	
Bleeding volume (mL)	4 (1-52)	
Conversion to multi-port or open	0	0
Intraoperative complication	0	0
Postoperative complication		
Seroma	0	0
Wound infection	0	0
Chronic pain	0	0
Recurrence	1	1.4

Moreover, it has a superior cosmetic outcome as it is performed through single-incision laparoscopic surgery[4]. Coupled with intraperitoneal observation, it is possible to diagnose the type of hernia, restore the intestinal tract incompetence and confirm the repair afterward. Hernia repairs can therefore be performed more safely and effectively.

A minimally invasive surgical technique for the repair of inguinal hernia, TEP was introduced for laparoscopic hernia repair in the early 1990s[5] and many studies involving the procedure have been reported since. Advantages of TEP include a wide range of exfoliation, ease of mesh placement, short operation time, and no need to perform peritoneal closure. Furthermore, by conducting TEP with single-incision laparoscopic surgery, it is possible to obtain excellent cosmetic outcomes as reported by Filipovic-Cugura *et al*[6] in 2009. However, the disadvantages of the procedure include difficulty with confirming the type of hernia as well as difficulty with large indirect inguinal hernia, intestinal incompetence and postoperative prostatectomy.

We complemented STEP with intraperitoneal observation to compensate for these drawbacks and obtained good results. Although the operation time is longer than that of the conventional procedure and the multiport laparoscopic surgery, the bleeding volume is equivalent, and the outcome is excellent with respect to postoperative complications[7-9]. Cost is also equal because special equipment is not required. Furthermore, compared to single-incision TAPP, STEP is easier in terms of exfoliation and thus the operation time can be shortened[2]. For patients with recurrent hernia, however, the surgical time was longer because of difficulties with the exfoliation procedure, but there was no conversion to TAPP at our hospital.

By using intraperitoneal observation in combination with STEP, it is possible to view the inguinal region without overlooking coexisting lesions, for example, the presence of hernia on the opposite side (Figure 5). Through intraperitoneal observation, it is possible to confirm the mesh coverage in cases where the hernia extends not only to direct and indirect inguinal lesions but also to femoral and obturator lesions. We could confirm the herniated gates extended to the femoral and obturator in 2 of our patients and could perform the necessary repairs reliably. A small hernia was also detected on the opposite side in some of the patients and this was treated simultaneously by performing hernia repair on both sides. In recurrent cases, iSTEP facilitates reliable repair due to reliable identification of the hernia gates.

In addition, if an intestinal incarceration in the hernia sac was found in the intraperitoneal cavity, forceps were inserted through the incision site and the intestine was returned to the abdominal cavity without increasing the number of trocars. Moreover, the presence of intestinal damage could be confirmed. The intestine protruded into the sac in 3 patients. In all 3 cases, we returned the intestine to the abdominal cavity, confirmed that there was no damage, and then performed TEP safely. If it was difficult to perform hernia repair using TEP, we could easily switch to TAPP. We used TAPP for patients that underwent prostate surgery and had severe adhesion in the preperitoneal space. However, we used TEP for 2 patients for whom TAPP would have been difficult due to severe adhesion in the abdominal cavity after abdominal surgery. Since the mesh is located in the preperitoneal space, even if there is adhesion in the abdominal cavity, the adhesion causes no issues during surgery and the risk of organ damage is low.

In cases of large direct inguinal hernia, it is difficult to identify the hernia gate using the anterior approach and it is difficult to dissect the medial and ventral sides using TAPP. Both sides can be dissected easily with TEP. When using the mesh recommended by the European Hernia Society, which is 15 cm × 10 cm in size[1], it is necessary to secure a sufficient dissection range, which is easy to do with TEP. In addition, peritoneal closure is difficult when performing TAPP through a single-incision procedure. Compared to TAPP, the advantages of TEP

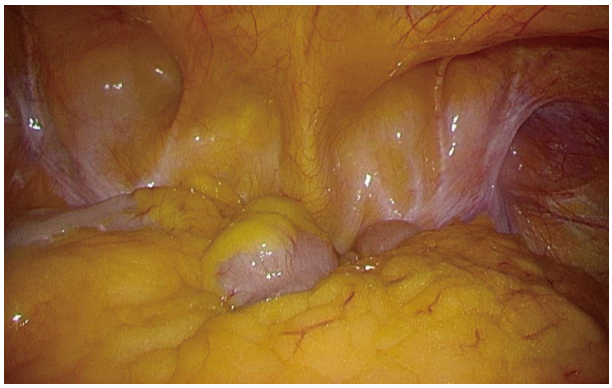

Figure 5 By using intraperitoneal observation simultaneously, it was possible to observe the inguinal region without overlooking the opposite side.

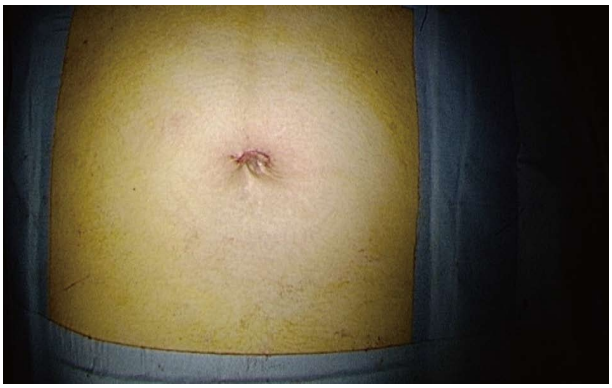

Figure 6 We could obtain better cosmetic outcomes.

are that it does not require intraperitoneal manipulation and adhesion exfoliation can be omitted.

Postoperatively, there is a risk of bowel obstruction caused by intraperitoneal operation using TAPP and adhesion at the peritoneal closure region. The risk of intestinal obstruction after inguinal hernia repair using TAPP or TEP is 2.8 and 0.6 times the risk using the Lichtenstein method, respectively[10]. Additionally, by observing the interior of the abdominal cavity again after hernia repair, it can be confirmed that the fragile portion is covered by mesh and the risk of recurrence can be reduced. By conducting hernia repair with single-incision laparoscopic surgery, we could obtain excellent cosmetic outcomes (Figure 6). As demonstrated above, STEP with intraperitoneal inspection is a very useful technique because diagnosis and reinforcement can be performed reliably and the cosmetic outcome is excellent.

The present study has several limitations. First, this study was carried out at a single high-volume center and was retrospective in nature; hence, patient selection bias may have been inevitable. Patients who met the exclusion criteria were excluded. Second, the population number was small. Further studies on a larger scale are necessary.

ARTICLE HIGHLIGHTS

Research background

Surgery is the standard treatment for inguinal hernia. The surgical techniques used for inguinal hernia consist of the traditional anterior technique and laparoscopic surgery. One type of laparoscopic surgery has totally extraperitoneal hernia repair (TEP). The outcome of TEP is superior to the conventional anterior approach; less postoperative pain, fewer postoperative complications, lower recurrence rates, early discharge, and faster return to daily life and superior cosmetic outcome. The authors cannot observe intraperitoneal cavity on TEP, so the opposite side hernia might be overlooked if the hernia is present. And it is difficult to perform the procedure for patients with intestinal incarceration in the hernia sac.

Research motivation

It is difficult to repair hernia by TEP for patients with large indirect inguinal hernia, intestinal incarceration and postoperative prostatectomy. The authors must compensate for these drawbacks of TEP.

Research objectives

By using intraperitoneal inspection (iSTEP), it is possible to view the inguinal region without overlooking coexisting lesions if the hernia present on the opposite side. And when an intestinal incarceration in the hernia sac was found, we can return the intestine and confirm the presence of intestinal damage. iSTEP is a very useful technique because diagnosis and reinforcement can be performed reliably.

Research methods

Seventy-five patients who underwent iSTEP at the Prefectural Hiroshima Hospital were enrolled. Small skin incision was made in the umbilicus, extending to the intraperitoneal cavity. First of all, insert the laparoscope into the abdominal cavity to observe the intraperitoneal cavity. The type of hernia was diagnosed and whether there was the presence of intestinal incarceration was confirmed. Once the peritoneum was closed, STEP was performed, and finally, intraperitoneal observation was performed to reconfirm the repair. And data on patient demographics, clinical data, intraoperative findings, and postoperative course is prospectively collected.

Research results

The authors performed iSTEP for 75 hernias, 58 were on one side, 17 were on both sides, and 10 were recurrences. The respective median operation times were 100 min (range, 66 to 168), 136 min (range, 114 to 165), and 125 min (range, 108 to 156), with median bleeding amounts of 5 g (range, 1 to 26), 3 g (range, 1 to 52), and 5 g (range, 1 to 26), respectively. Intraperitoneal observation showed hernia on the opposite side in 2 cases, intestinal incarceration in 3 cases, omental adhesion into the hernia sac in 2 cases, severe postoperative intraperitoneal adhesions in 2 cases, and bladder protrusion in 1 case. There was only 1 case of recurrence. Compared with previous reports which repaired by conventional method and TEP, the operation time is longer, but the bleeding volume is equivalent, and the outcome is excellent with respect to postoperative complications. Cost is equal because special equipment is not required.

Research conclusions

Single-incision totally extraperitoneal inguinal hernia repair with intraperitoneal inspection is very useful technique and makes hernia repairs safer and reducing postoperative complications.

Research perspectives

This study suggests that iSTEP is a very useful technique for inguinal hernia repair without history of prostate surgery, giant inguinal hernia, young patients with small indirect inguinal hernia, strangulated hernia, and patients who could not tolerate general anesthesia. The study described a modification of conventional TEP approach with the addition of intraperitoneal observation. We suggested advantage of inspecting the contralateral side for hernia and the possibility to examine incarcerated bowel. It also allowed easy conversion between TEP and TAPP when necessary. The authors will compare with iSTEP

and conventional SILS-TEP and so we report that results.

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ORIGINAL ARTICLE

Clinical Practice Study

Risk factors for pancreatic fistula following pancreaticoduodenectomy: A retrospective study in a Thai tertiary center

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Abstract

AIM

To analyze the risk factors of postoperative pancreatic fistula following pancreaticoduodenectomy in a Thai tertiary care center.

METHODS

We retrospectively analyzed 179 patients who underwent pancreaticoduodenectomy at our hospital from January 2001 to December 2016. Pancreatic fistula were classified into three categories according to a definition made by an International Study Group on Pancreatic Fistula. The risk factors for pancreatic fistula were analyzed by univariate analysis and multivariate logistic regression analysis.

RESULTS
Pancreatic fistula were detected in 88/179 patients (49%) who underwent pancreaticoduodenectomy. Fifty-eight pancreatic fistula (65.9%) were grade A, 22 cases (25.0%) were grade B and eight cases (9.1%) were grade C. Clinically relevant pancreatic fistula were detected in 30/179 patients (16.7%). The 30-d mortality rate was 1.67% (3/179 patients). Multivariate logistic regression analysis revealed that soft pancreatic texture (odds ratio = 3.598, 95%CI: 1.77-7.32) was the most significant risk factor for pancreatic fistula. A preoperative serum bilirubin level of > 3 mg/dL was the most significant risk factor for clinically relevant pancreatic fistula according to univariate and multivariate analysis.

CONCLUSION
Soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

Key words: Risk factors; Pancreatic fistula; Pancreas; Pancreatectomy; Pancreaticoduodenectomy

Core tip: Pancreaticoduodenectomy is a high morbidity operation. The most common perioperative complication is postoperative pancreatic fistula. We retrospectively analyzed 179 patients who underwent pancreaticoduodenectomy at our hospital. We found that soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

Rungsakulkij N, Mingphruedhi S, Tangtawee P, Krutsri C, Muangkaew P, Suragul W, Tannaphai P, Aeesoa S. Risk factors for pancreatic fistula following pancreaticoduodenectomy: A retrospective study in a Thai tertiary center. *World J Gastrointest Surg* 2017; 9(12): 270-280 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i12/270.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i12.270

INTRODUCTION

Pancreaticoduodenectomy (PD) is the standard treatment for resectable periampullary and pancreatic tumors. PD is an example of major surgery and is a complicated operation to perform for the general surgeon. Current mortality rates are low; previous reports have suggested a perioperative mortality rate of less than 5%[1-3]. However, high morbidity rates have also been reported, some reaching up to 50%[3-7]. The most common complication following PD is postoperative pancreatic fistula (POPF). POPF is the major cause of complications such as delayed gastric emptying (DGE), postoperative hemorrhage, intra-abdominal infection and increased length of hospital stay (LOH)[8].

Many risk factors have been reported for POPF, including obesity, soft pancreatic texture, small pancreatic duct and low volume center[9-15]. Some studies have investigated ways to improve the surgical outcome and reduce POPF, including the placement of an external and internal trans-anastomotic pancreatic duct[16,17], pancreatogastrostomy[18-20], omental roll-up around pancreaticoenteric (PE) anastomosis[21], application of fibrin sealants around PE anastomosis[22,23] and prophylaxis with somatostatin analogs[24-25]. However, the outcomes of these different methods remain controversial.

Recently, a soft pancreas and high body mass index (BMI) were reported as the most common risk factors for POPF[9-13]. However, POPF risk factors have not been studied in a Thai population before. The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

MATERIALS AND METHODS

Patients

From January 2001 to December 2016, 210 consecutive patients underwent PD at the Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand and were considered for inclusion in the study. Patients who underwent a concomitant hepatic resection were excluded; in the end, a total of 179 patients were included. Patient data were retrospectively reviewed. These included age, gender, weight, BMI, underlying disease, serum albumin, preoperative total bilirubin levels and preoperative biliary drainage (PBD). In addition, we recorded the use of percutaneous transhepatic biliary drainage or placement of an endoscopic internal biliary stent. We also reviewed the type of operation, pancreatic texture, pancreatic duct size, type of PE anastomosis, use of trans-anastomotic pancreatic duct stent, pathological diagnosis, operative time and operative blood loss. Ethical permission for this study was obtained from the hospital's ethics committee.

Preoperative evaluation

The general condition of patients and any co-morbid conditions were preoperatively assessed by a physician, surgeon and internist. The diagnosis and clinical staging of the disease were reviewed preoperatively by a multidisciplinary team including surgeons, radiologists and gastroenterologists.

Operative approach

Routine antibiotic prophylaxis was administered 30 min before the incision. PD is classified into classical PD and pylorus-preserved PD (PPPD) and the type of surgery depended on the surgeon's own preference. Reconstruction after resection was performed using

Child's technique, starting with a pancreaticojejunostomy (PJ). A PJ can be performed using either a invagination or duct to mucosa technique and this was decided based on the surgeon's preference. A trans-anastomotic pancreatic duct stent was placed in selected patients, depending on surgeon's preference. The trans-anastomotic pancreatic duct stent was either internal (in the jejunum) or external (partly outside the body). After PJ, biliary-enteric anastomosis was performed followed by a gastro-jejunostomy or duodeno-jejunostomy. A Braun loop jejunojejunostomy was performed in some patients, according to the surgeon's preference. Pancreatic texture was classified into hard, firm or soft consistency based on palpitation by the surgeon. A closed peri-anastomotic drainage system was placed routinely.

Postoperative complications

After surgery, patients were transferred to a critical care unit or intermediate ward. Routine biochemical analyses of patients' blood were performed. An oral diet was started as soon as the output gastric content was < 400 mL and a positive bowel movement occurred. Parenteral nutrition was initiated if the patients did not have a bowel movement or the gastric content was > 400 mL after postoperative day (POD) 3.

POPF was defined according to International Study Group of Pancreatic Fistula (ISGPF) guidelines by amylase levels that were three times higher in the drainage fluid than the serum. POPFs were classified into three categories: (1) Grade A: Transient pancreatic fistula with no clinical impact; (2) grade B: Required a change in management or adjustment of the clinical course; and (3) grade C: Required a major change in clinical management or deviated from the normal clinical course[26]. Combined grade B + C fistulas were defined as "clinically relevant pancreatic fistula" (CR-POPF). DGE was defined as either nasogastric tube insertion after POD 3 or as the inability to tolerate solid food intake by POD 7. Chyle leakage was defined as a milky drain output or triglyceride levels of > 110 mg/dL in the drain fluid on any POD. Postoperative mortality was recorded as the 30-d mortality and in-hospital mortality.

Statistical analysis

Patient characteristics were compared by *t*-test, Wilcoxon Mann-Whitney test, χ^2 test and Fisher's exact test. A *P*-value of < 0.05 was considered statistically significant. Risk factors were analyzed by univariate and multivariate methods using binary logistic regression analysis. Independent risk factors were expressed as odds ratios (ORs) with 95%CI.

RESULTS

Patient characteristics and perioperative status

A total of 179 consecutive patients (95 males, 84 females) that underwent PD were included. One hundred and twenty-eight (71.5%) patients had classical PD and 51 (28.5%) patients had PPPD. Malignancy was diagnosed in 145 patients (79.9%) as follows: 62 ampullary carcinoma patients (44.8%), 40 pancreatic cancer patients (27.6%), 18 cholangiocarcinoma patients (12.4%) and 11 duodenal cancer patients (7.6%) (Table 1).

Patient characteristics and operative outcomes in patients with and without POPF

POPF were detected in 88 patients (49%). Fifty-eight patients (65.9%) had grade A POPF, 22 patients (25%) had grade B POPFs and eight patients (9.1%) had grade C POPFs. CR-POPF were detected in 30/179 patients (16.7%). The 30-d mortality rate was 1.67% (3/179). Table 1 compares the post-PD complications between POPF and no POPF groups. Age, serum albumin levels, operative blood loss, gender, diabetes mellitus and PBD were not statistically different between the two groups. However, statistically significant differences were observed in BMI, preoperative total serum bilirubin, pancreatic duct diameter, operative time, cardiovascular disease, pancreatic texture and trans-anastomotic stent between the two groups. The POPF group had a higher rate of other complications (5.5% *vs* 25%, $P < 0.001$) and a longer LOH (15 d *vs* 25 d, $P < 0.001$).

Risk factors for POPF

Univariate and multivariate analyses were used to identify risk factors for POPF (Table 2). Univariate analyses of the 88 patients with pancreatic fistula revealed the following risk factors for POPF: BMI > 25 (OR 2.38, 95%CI: 1.13-5.03, $P = 0.005$), pancreatic duct diameter (OR 2.765, 95%CI: 1.47-5.18, $P = 0.002$), operative time (OR 2.39, 95%CI: 1.26-4.55, $P = 0.008$), history of cardiovascular disease (OR 3.41, 95%CI: 1.48-7.86, $P = 0.004$), soft pancreatic texture (OR 4.682, 95%CI: 2.47-8.87, $P < 0.001$) and placement of a trans-anastomotic pancreatic duct stent (OR 2.55, 95%CI: 1.31-4.99, $P = 0.006$). Multivariate logistic regression analysis revealed soft pancreatic texture (OR 3.59, 95%CI: 3.01-17.35, $P < 0.001$) as the most significant risk factor for POPF.

Effect of POPF grade on patient characteristics and operative outcomes and predictive factors for CR-POPF

Preoperative total bilirubin and pancreatic reconstruction techniques (duct to mucosa *vs* invagination) were significantly different between grade A POPF and CR-POPF (Table 3). Univariate analysis revealed preoperative total serum bilirubin levels of more than 3 mg/dL as a potential risk factor for grade A POPF (OR 3.749, 95%CI: 1.48-9.51, $P = 0.005$). Multivariate analysis revealed total serum bilirubin levels of more than 3 mg/dL as the most significant predictive factor for CR-POPF (OR 4.50, 95%CI: 1.54-13.15, $P = 0.006$) (Table 4).

DISCUSSION

The most common perioperative complication of PD is

Table 1 Patient characteristics in postoperative pancreatic fistula and no postoperative pancreatic fistula groups

Characteristic data	No POPF (*n* = 91)	POPF (*n* = 88)	*P*-value	95%CI
Age, mean (SD)	60.7 (10.6)	59.1 (11.2)	0.33	58.22-61.44
BMI, median (IQR)	21.4 (20, 23.9)	23.1 (20.8, 25.5)	0.005	22.05-23.22
Albumin, median (IQR)	34.1 (31, 38.3)	34.9 (32, 37.95)	0.667	33.38-35.10
Total bilirubin, median (IQR)	4.1 (1.3, 13.2)	1.3 (0.7, 5.6)	0.002	5.01-7.16
Pancreatic duct diameter (mm), median (IQR)	3 (3, 5)	3 (2, 5)	0.048	3.44-3.99
Operative time, median (IQR)	420 (360, 540)	480 (420, 570)	0.014	448.46-486.23
Blood loss (mL), median (IQR)	1000 (600, 1500)	800 (500, 1500)	0.236	1082-1459.66
LOH day, median (IQR)	15 (12, 20)	25 (17, 39.5)	< 0.001	23.14-32.87
Gender, *n* (%)				
Male	49 (53.8)	46 (52.3)	0.833	
Female	42 (46.2)	42 (47.7)		
DM, *n* (%)				
No	64 (70.3)	69 (78.4)	0.216	
Yes	27 (29.7)	19 (21.6)		
Hx of cardiovascular disease, *n* (%)				
No	82 (90.1)	64 (72.7)	0.003	
Yes	9 (9.9)	24 (27.3)		
PBD, *n* (%)				
No	36 (39.6)	25 (28.4)	0.116	
Yes	55 (60.4)	63 (71.6)		
Pancreatic texture, *n* (%)[1]				
Hard/firm	60 (68.2)	27 (31.4)	< 0.001	
Soft	28 (31.8)	59 (68.6)		
Type of resection, *n* (%)				
PPPD	20 (22.0)	31 (35.2)	0.05	
Classical PD	71 (78.0)	57 (64.8)		
Duct to mucosa *vs* Invagination				
Duct to mucosa	56 (61.5)	63 (71.6)	0.154	
Invagination	35 (38.5)	25 (28.4)		
Stent, *n* (%)				
No	73 (80.2)	54 (61.4)	0.005	
Yes	18 (19.8)	34 (38.6)		
External *vs* Internal, *n* (%)				
External	4 (22.2)	12 (36.4)	0.298	
Internal	14 (77.8)	21 (63.6)		
Malignant, *n* (%)				
No	18 (19.8)	16 (18.2)	0.785	
Yes	73 (80.2)	72 (81.8)		
Final diagnosis, *n* (%)				
CA ampulla	25 (27.5)	37 (42.1)	0.04	
CA pancreas	28 (27.5)	12 (13.6)		
CA duodenal	8 (8.8)	3 (3.4)		
CA distal CBD	7 (7.7)	11 (12.5)		
Other	26 (28.5)	25 (28.4)		
Grading, *n* (%)				
No	91 (100)	0	0	
A	0	58 (65.9)		
B	0	22 (25.0)		
C	0	8 (9.1)		
Other complications				
No	86 (94.5)	66 (75.0)	< 0.001	
Yes	5 (5.5)	22 (25.0)		
30-d mortality, *n* (%)				
No	91 (100)	85 (96.6)	0.117	
Yes	0	3 (3.4)		
Age, *n* (%)				
< 70	73 (80.2)	73 (82.9)	0.637	
⩾ 70	18 (19.8)	15 (17.1)		
BMI, *n* (%)				
< 25	78 (85.7)	63 (71.6)	0.021	
⩾ 25	13 (14.3)	25 (28.4)		
Albumin, *n* (%)				
⩾ 30	75 (82.4)	77 (87.5)	0.342	
< 30	16 (17.6)	11 (12.5)		
Total bilirubin, *n* (%)				
< 3	41 (45.1)	56 (63.6)	0.013	
⩾ 3	50 (54.9)	32 (36.4)		

Pancreatic duct diameter, *n* (%)			
⩾ 5	45 (49.4)	23 (26.1)	0.001
< 5	46 (50.6)	65 (73.9)	
Operative time, *n* (%)			
< 420	39 (42.9)	21 (23.9)	0.007
⩾ 420	52 (57.1)	67 (76.1)	
Blood loss, *n* (%)			
< 1000	45 (49.5)	54 (61.4)	0.109
⩾ 1000	46 (50.5)	34 (38.6)	

[1]*n* = 174 patients. Other complications: DGE, postoperative hemorrhage, chyle leakage. POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

Table 2 Univariate and multivariate logistic regression analysis of postoperative pancreatic fistula risk factors

Variable	Univariate OR (95%CI)	Univariate *P*-value	Multivariate OR (95%CI)	Multivariate *P*-value
Age (yr)				
< 70				
⩾ 70	0.833 (0.39-1.78)	0.637		
Body mass index (kg/cm^2)				
< 25				
⩾ 25	2.381 (1.13-5.03)	0.023	2.081 (0.86-5.03)	0.104
Albumin				
⩾ 30				
< 30	0.669 (0.29-1.54)	0.344		
Total bilirubin				
< 3				
⩾ 3	0.468 (0.26-0.85)	0.013	1.455 (0.38-5.55)	0.583
Pancreatic duct diameter				
⩾ 5 mm				
< 5 mm	2.765 (1.47-5.18)	0.002	3.148 (0.81-12.27)	0.098
Operative time				
< 420 min				
⩾ 420 min	2.393 (1.26-4.55)	0.008	1.355 (0.59-3.07)	0.465
Blood loss				
< 1000				
⩾ 1000	0.616 (0.34-1.12)	0.11		
Gender				
Male				
Female	1.065 (0.59-1.92)	0.833		
DM				
No				
Yes	0.653 (0.33-1.29)	0.218		
Hx of cardiovascular disease				
No				
Yes	3.417 (1.48-7.86)	0.004	2.612 (0.96-7.08)	0.059
Preop biliary stent (no)				
No				
Yes	1.649 (0.88-3.08)	0.117		
Pancreatic texture				
Hard/firm				
Soft	4.682 (2.47-8.87)	< 0.001	3.598 (1.77-7.32)	< 0.001
Type of resection				
Pylorus-preserved pancreaticoduodenectomy				
Pancreaticoduodenectomy	0.518 (0.27-1.00)	0.051	0.807 (0.37-1.78)	0.597
Duct to mucosa				
Invagination	0.635 (0.34-1.19)	0.156		
Stent (no)				
No				
Yes	2.553 (1.31-4.99)	0.006	1.272 (0.52-3.09)	0.595
External				
Internal	0.500 (0.13-1.87)	0.303		
Malignant (no)				
No				
Yes	1.109 (0.52-2.34)	0.785		
Final diagnosis (CA ampulla)				
CA pancreas	0.324 (0.14-0.76)	0.01	0.439 (0.16-1.19)	0.105
CA duodenal	0.253 (0.06-1.05)	0.058	0.533 (0.11-2.59)	0.435
CA distal CBD	1.062 (0.36-3.11)	0.913	1.188 (0.33-4.29)	0.793
Other	0.650 (0.31-1.37)	0.258	0.543 (0.22-1.35)	0.189

Table 3 Relationships between patient characteristics, operative outcome and postoperative pancreatic fistula grade

Characteristic data	POPF (grading)		*P*-value	95%CI
	A (*n* = 58)	B + C (*n* = 30)		
Age, mean (SD)	59.2 (11.3)	58.8 (11.4)	0.874	56.67-61.46
Body mass index, median (IQR)	23.1 (20.4, 25.1)	23.1 (21.1, 26.5)	0.805	22.62-24.45
Albumin, median (IQR)	34.7 (32, 38)	35.4 (32, 37.9)	0.603	33.38-35.58
Total bilirubin, median (IQR)	0.9 (2, 5)	3.3 (1.2, 12)	0.01	3.44-6.66
Pancreatic duct diameter (mm), median (IQR)	3 (2, 5)	3 (2, 4)	0.175	3.07-3.79
Operative time, median (IQR)	480 (420, 600)	480 (360, 540)	0.49	462.22-511.75
Blood loss (mL), median (IQR)	800 (500, 1500)	900 (600, 1500)	0.071	985.10-1616.95
LOH day, median (IQR)	21 (14, 30)	42.5 (30, 60)	< 0.001	28.14-46.32
Gender, *n* (%)				
Male	34 (58.6)	12 (40.0)	0.097	
Female	24 (41.4)	18 (60.0)		
DM, *n* (%)				
No	45 (77.6)	24 (80.0)	0.794	
Yes	13 (22.4)	6 (20.0)		
Hx of cardiovascular disease, *n* (%)				
No	42 (72.4)	22 (73.3)	0.927	
Yes	16 (27.6)	8 (26.7)		
PBD, *n* (%)				
No	20 (34.5)	5 (16.7)	0.079	
Yes	38 (65.5)	25 (83.3)		
Pancreatic texture, *n* (%)				
Hard/Firm	20 (35.1)	7 (24.1)	0.301	
Soft	37 (64.9)	22 (75.9)		
Type of resection, *n* (%)				
PPPD	24 (41.4)	7 (23.3)	0.093	
PD	34 (58.6)	23 (76.7)		
Duct, *n* (%)				
Duct to mucosa	46 (79.3)	17 (56.7)	0.026	
Invagination	12 (20.7)	13 (43.3)		
Stent, *n* (%)				
No	32 (55.2)	22 (73.3)	0.097	
Yes	26 (44.8)	8 (26.7)		
External *vs* Internal, *n* (%)				
External	8 (32.0)	4 (50.0)	0.42	
Internal	14 (68.0)	4 (50.0)		
Malignant, *n* (%)				
No	12 (20.7)	4 (13.3)	0.396	
Yes	46 (79.3)	26 (86.7)		
Final diagnosis, *n* (%)				
CA ampulla	23 (39.6)	14 (46.7)	0.33	
CA pancreas	8 (13.8)	4 (13.3)		
CA duodenal	3 (5.2)	0		
CA distal CBD	5 (8.6)	6 (20.0)		
Other	19 (32.8)	6 (20.0)		
Age, *n* (%)				
< 70	47 (81.0)	26 (86.7)	0.505	
⩾ 70	11 (19.0)	4 (13.3)		
BMI, *n* (%)				
< 25	42 (71.4)	21 (70.0)	0.812	
⩾ 25	16 (27.6)	9 (30.0)		
Albumin, *n* (%)				
⩾ 30	50 (86.2)	27 (90.0)	0.743	
< 30	8 (13.8)	3 (10.0)		
Total bilirubin, *n* (%)				
< 3	43 (74.1)	13 (43.3)	0.004	
⩾ 3	15 (28.9)	17 (56.7)		
Pancreatic duct diameter, *n* (%)				
⩾ 5	12 (20.7)	11 (36.7)	0.106	
< 5	46 (79.3)	19 (63.3)		
Operative time, *n* (%)				
< 420	12 (20.7)	9 (30.0)	0.331	
⩾ 420	46 (79.3)	21 (70.0)		
Blood loss, *n* (%)				
< 1000	37 (63.8)	17 (56.7)	0.515	
⩾ 1000	21 (36.2)	13 (43.3)		

POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

Table 4 Univariate and multivariate logistic regression analysis of risk factors for clinically relevant-postoperative pancreatic fistula

Variable	Univariate OR (95%CI)	Univariate *P*-value	Multivariate OR (95%CI)	Multivariate *P*-value
Age (yr)				
< 70				
⩾ 70	0.657 (0.19-2.27)	0.507		
BMI (kg/cm^2)				
< 25				
⩾ 25	1.125 (0.43-2.96)	0.812		
Albumin				
⩾ 30				
< 30	0.694 (0.17-2.84)	0.611		
Total bilirubin				
< 3				
⩾ 3	3.749 (1.48-9.51)	0.005	4.506 (1.54-13.15)	0.006
Pancreatic duct diameter (mm)				
⩾ 5				
< 5	0.451 (0.17-1.20)	0.11		
Operative time (min)				
< 420				
⩾ 420	0.609 (0.22-1.66)	0.334		
Blood loss				
< 1000				
⩾ 1000	1.347 (0.55-3.31)	0.516		
Gender				
Male				
Female	2.125 (0.86-5.22)	0.1		
DM				
No				
Yes	0.865 (0.29-2.56)	0.794		
Hx of cardiovascular disease				
No				
Yes	0.954 (0.35-2.58)	0.927		
Preop biliary stent (no)				
No				
Yes	2.631 (0.87-7.92)	0.085	2.24 (0.67-7.49)	0.191
Pancreatic texture				
Hard/firm				
Soft				
Type of resection				
PPPD				
PD	2.319 (0.86-6.27)		1.787 (0.54-5.92)	0.342
Duct to mucosa				
Invagination	2.931 (1.12-7.67)	0.028	2.837 (0.89-9.08)	0.079
Stent (no)				
No				
Yes	0.447 (0.17-1.17)	0.101		
External				
Internal	0.471 (0.09-2.38)	0.362		
Malignant (no)				
No				
Yes	1.695 (0.50-5.80)	0.4		
Final diagnosis (CA ampulla)				
CA pancreas	0.821 (0.21-3.24)	0.779		
CA duodenal	-	-	-	-
CA distal CBD	1.971 (0.51-7.68)	0.328		
Other	0.519 (0.17-1.61)	0.256		

POPF: Postoperative pancreatic fistul; PBD: Preoperative biliary drainage; PPPD: Pylorus-preserved pancreaticoduodenectomy; PD: Pancreaticoduodenectomy; BMI: Body mass index.

POPF. POPF remains the leading cause of complications such as DGE and postoperative hemorrhage, which increase mortality[1-3] and the LOH. Many risk factors for POPF have been reported previously[4-9]. In the present study, the incidence of POPF and the 30-d mortality rate were similar to previous studies. In addition, we identified soft pancreatic texture as a main risk factor for POPF[8-12].

Our multivariate analysis showed that a soft pancreas is the most independent predictive factor for POPF. This is in agreement with previous studies[5,9-12,27]. There are many reasons why soft pancreatic tissue increases the risk of POPF. First, a soft pancreas makes it more difficult to secure PEA because friable pancreatic tissue cannot

hold suture tension. As a result, suture materials cut through the pancreatic parenchyma and anastomosis fails. A soft pancreas is also prone to ischemia when manipulated, which disrupts anastomosis. Finally, a soft pancreas has enriched exocrine function and pancreatic enzymes are released when leakage occurs[9,11,27,28].

The assessment of pancreatic texture is controversial and subjective. Pancreatic texture is commonly assessed intraoperatively by palpation. Callery *et al*[11] reported the clinical risk score for POPF based on pancreatic texture, pancreatic duct diameter and intraoperative blood loss. They classified the pancreatic texture as firm or soft[11]. Some studies have classified pancreatic texture as hard, firm or soft, but the distinction between a hard and firm pancreas remains unclear[1,5].

Recently, Ansorge *et al*[29] reported similar risk factors for POPF. They classified the pancreatic texture into four grades, including very hard (severe chronic pancreatitis), hard (fibrotic or atrophic obstructed pancreatic gland), soft (unaffected compact gland), and very soft (unaffected fatty pancreas). They found that 44/100 patients had a hard pancreas. The rate of POPF in the very hard/hard groups was significantly different to that in the soft/very soft groups[29]. There is a newly developed tissue strain imaging technology reflecting tissue fibrosis or stiffness and is integrated into a conventional ultrasound system called acoustic radiation force impulse (ARFI). Lee *et al*[30] and Harada *et al*[30] reported the high accuracy of ARFI for prediction of the stiffness of pancreas preoperatively.

The relationship between soft and fatty pancreatic tissue has been well studied[28-29,32]. A fatty pancreas refers to the increasing infiltration of adipose tissue into the pancreas[28]. Ansorge *et al*[29] found that the softness of pancreatic tissue was strongly associated with fat levels in the tissue. This was supported by previous reports that a fatty pancreas is a risk factor for POPF[13,28,32]. Taken together, these findings suggest that the infiltration of adipose tissue into the pancreas is associated with soft pancreatic texture.

The assessment of pancreatic texture is difficult and subjective. Currently, there are no standard procedures for the intraoperative assessment of pancreatic texture. Pancreatic texture has commonly been assessed intraoperatively by palpation[5,11,29]. In the present study, we also assessed pancreatic texture by palpation. This subjective assessment of pancreatic texture could have differed from surgeon to surgeon.

Unfortunately, it was not possible to assess pancreatic texture during the preoperative evaluation. Tranchart *et al*[33] used computed tomography to predict the occurrence of severe pancreatic fistula following PD. They found that a visceral fat area of more than 84 cm^3 was associated with a fatty pancreas (58.4% *vs* 48.1%, $P = 0.005$) and was a risk factor for CR-POPF (OR 8.16 95%CI: 2.2-3, $P = 0.002$). They suggested preoperative assessment of body fat distribution as a means of evaluating fat levels in the pancreas and predicting the occurrence of CR-POPF[33]. In our study, the incidence of CR-POPF is high when compared to previous studies[5,6,11,12]. This could be explained by the lower population of pancreatic cancer in this study that the pancreatic cancer is more likely to obstruct the pancreatic duct and therefore increase fibrosis of the pancreas[11].

Obstructive jaundice was previously regarded as the main factor increasing perioperative morbidity and mortality. The pathophysiology of obstructive jaundice includes increasing endotoxin concentrations in the portal circulation, altered Kupffer cell function affecting the reticuloendothelial system in the liver, over-activation of inflammatory cascades, decreased cellular immunity and renal dysfunction. These manifestations influence the nutritional status of patients. PBD decreased postoperative septic complications in mice by improving liver function, nutritional status, cell-mediated immune function, systemic endotoxemia, cytokine release and the overall immune response[34]. Regarding periampullary obstruction, endoscopic drainage approach today represents the procedure of choice with high succession rate[35,36].

In this study, a preoperative serum bilirubin level of more than 3 mg/dL was a risk factor for CR-POPF. Kimura *et al*[3] reported that serum bilirubin of more than 2.0 mg/dL was a significant preoperative risk factor for higher 30-d and in-hospital mortality rates following PD[3]. Gebauer *et al*[37] found that patients with POPF who underwent repeated surgery had higher in-hospital mortality (0.6 *vs* 0.7, $P = 0.002$) and total serum bilirubin levels (0.7 *vs* 1.1, $P = 0.003$) than POPF patients that did not undergo reoperation). In a previous study, multivariate binary logistic regression model analysis revealed that a serum bilirubin level of > 2.0 mg/dL is an independent risk factor for reoperation (OR 25.053, 95%CI: 3.486-180.069)[37]. Some previous studies have identified higher serum bilirubin levels in CR-POPF patients, but these differences were not statistically significant. For example, El Nakeeb *et al*[12] reported a preoperative bilirubin level of 4.6 mg/dL in patients with grade A POPF and 9.7 mg/dL in patients with CR-POPF, but this difference was not significant. This was supported by Braga *et al*[38], who detected higher total serum bilirubin in patients with grade Ⅲ-Ⅳ complications than patients with grade 0-Ⅱ complications (3.5 mg/dL *vs* 1.6 mg/dL). Again, this difference was not statistically significant. Fujii *et al*[39] found that endoscopic internal drainage posed a higher risk for POPF than endoscopic nasobiliary drainage.

In a recent systematic review, Scheufele *et al*[40] reported that POPF rates do not differ between PBD and no drainage groups. However, a higher infectious complications rate was detected in the PBD group. Most of the studies included in this review were retrospective studies, and the most frequent complications were wound-related[40]. A few randomized control trial studies have now been performed by a Dutch group. In these studies, the POPF rate did not differ between PBD and surgery first groups following PD. However, the population in the POPF group was only 16%, which may

not have been high enough to obtain sufficient statistical power[31]. Current evidence does not recommend routine PBD because the rate of infectious (usually wound-related) complications is higher. However, a randomized control trial of a large population is needed to clarify this in the case of CR-POPF.

In this study, 66.8% of patients underwent PBD, which is higher than previous reports[39-41]. This could be explained by the fact that Thailand is a low to mid-income country, therefore patients with periampullary tumor and pancreatic cancer usually present with severe obstructive jaundice and have poor nutritional status. Serum bilirubin levels were higher than 15 mg/dL and serum albumin levels were less than 30 mg/dL in most patients. In addition, high-volume centers have patient congestion, limited resources and long waiting lists for operations.

This study was limited by the small study population. A larger population study might have revealed more significant risk factors of POPF.

In conclusion, we have identified a soft pancreas as an independent risk factor of POPF. A fatty pancreas is strongly associated with a soft pancreas and can be measured to predict CR-POPF. Preoperative detection of a fatty pancreas by CT and newly developed ultrasound technology is a potential method for predicting a soft pancreas preoperatively. However, this needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

ARTICLE HIGHLIGHTS

Research background

Many risk factors have been reported for postoperative pancreatic fistula (POPF), including obesity, soft pancreatic texture, small pancreatic duct and low volume center. Some studies have investigated ways to improve the surgical outcome and reduce POPF, including the placement of an external and internal trans-anastomotic pancreatic duct, pancreatogastrostomy, omental roll-up around pancreaticoenteric (PE) anastomosis, application of fibrin sealants around PE anastomosis and prophylaxis with somatostatin analogs. However, the outcomes of these different methods remain controversial. Recently, a soft pancreas and high body mass index (BMI) were reported as the most common risk factors for POPF. However, POPF risk factors have not been studied in a Thai population before. The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

Research motivation

The most common perioperative complication of pancreaticoduodenectomy is POPF. POPF remains the leading cause of complications such as DGE and postoperative hemorrhage, which increase mortality and the LOH. Many risk factors for POPF have been reported previously.

Research objectives

The aim of this study was to analyze the risk factors of POPF following PD in a Thai tertiary care center.

Research methods

The retrospective study design were required by reviewed data from January 2001 to December 2016, 210 consecutive patients underwent PD at the Department of Surgery in Ramathibodi Hospital, Bangkok, Thailand.

Research results

This is the study from tertiary care center from Thailand. To the best of the authors knowledge, this is the largest study from Thailand. The authors found that soft pancreatic tissue is the most significant risk factor for postoperative pancreatic fistula. A high preoperative serum bilirubin level (> 3 mg/dL) is the most significant risk factor for clinically relevant pancreatic fistula.

Research conclusions

The authors have identified a soft pancreas as an independent risk factor of POPF. A fatty pancreas is strongly associated with a soft pancreas and can be measured to predict CR-POPF. Preoperative detection of a fatty pancreas by CT is a potential method for predicting a soft pancreas preoperatively. Recently, the newly developed technology of ultrasonography have high accuracy to prediction of the stiffness of pancreas preoperatively. However, this needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

Research perspectives

Preoperative detection of a fatty pancreas by CT and newly developed ultrasound technology is a potential method for predicting a soft pancreas preoperatively. which needs to be confirmed by large population studies. At the moment, PBD is not routinely recommended because the rate of infectious complications is higher. Further studies are required to clarify the link between preoperative obstructive jaundice and CR-POPF.

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CASE REPORT

Surgically treated diaphragmatic perforation after radiofrequency ablation for hepatocellular carcinoma

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Abstract

We review 6 cases of diaphragmatic perforation, with and without herniation, treated in our institution. All patients with diaphragmatic perforation underwent radiofrequency ablation (RFA) treatments for hepatocellular carcinoma (HCC) performed at Kurume University Hospital and Tobata Kyoritsu Hospital. We investigated the clinical profiles of the 6 patients between January 2003 and December 2013. We further describe the clinical presentation, diagnosis, and treatment of diaphragmatic perforation. The change in the volume of liver and the change in the Child-Pugh score from just after the RFA to the onset of perforation was evaluated using a paired *t*-test. At the time of perforation, 4 patients had herniation of the viscera, while the other 2 patients had no herniation. The majority of ablated tumors were located adjacent to the diaphragm, in segments 4, 6, and 8. The average interval from RFA to the onset of perforation was 12.8 mo (range, 6-21 mo). The median Child-Pugh score at the onset of perforation (8.2) was significantly higher compared to the median Child-Pugh score just after RFA (6.5) (P = 0.031). All patients underwent laparotomy and direct suture of the diaphragm defect, with uneventful post-surgical recovery. Diaphragmatic perforation after RFA is not a matter that can be ignored. Clinicians should

carefully address this complication by performing RFA for HCC adjacent to diaphragm.

Key words: Diaphragmatic perforation; Diaphragmatic hernia; Radiofrequency ablation; Hepatocellular carcinoma

Core tip: Diaphragmatic perforation after radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) has been rarely described in the literature; however, it is one of the most serious complications. We conducted a retrospective analysis of 6 cases of diaphragmatic perforation after RFA, and considered the following 3 causative factors for this complication: Location, thermal damage, and liver cirrhosis. Moreover, we found that this complication tends to develop late after RFA. We propose that diaphragmatic perforation after RFA is a rare complication. Clinicians should take steps to prevent thermal injury to the diaphragm by performing RFA for HCC adjacent to the diaphragm and carefully follow up after RFA.

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INTRODUCTION

Radiofrequency ablation (RFA) for hepatocellular carcinoma (HCC) is a minimally invasive treatment commonly used for unresectable primary and metastatic hepatic tumors. Although studies have provided evidence of the safety of RFA, including a low rate of mortality and of major complication[1-4]. Numerous studies have reported complications associated with RFA. Mulier *et al*[1] calculated a complication rate of 8.9% and a mortality rate of 0.5%, with only 5 cases (0.1%) of injury to the diaphragm described. Curley *et al*[2] classified complications after hepatic RFA into early complications (within 30 d), including death, abscess at the RFA lesion, and hemorrhage, as well as late complications (more than 30 d after operation), including biliary fistula, hepatic insufficiency, and pleural effusion. They reported a rate of early complications of 7.1% and of late complications of 2.4%. However, they did not describe any occurrence of injury to the diaphragm. In the previous literature only 12 cases of diaphragm perforation with herniation and 3 cases of without herniation after hepatic RFA have been reported[5-19]. Yet, over the last decade, we have encountered 6 cases of late-onset perforation of the diaphragm, with and without herniation, after hepatic RFA, requiring surgical treatment. The etiology of the perforation of the diaphragm might be collateral thermal damage to the diaphragm during RFA. However, the clinical course of diaphragm perforation and herniation has not been sufficiently clarified. Therefore, the aims of our case report were to describe the clinical presentation, diagnosis, and treatment of our 6 cases of diaphragm perforation, with and without herniation, after RFA.

CASE REPORT

Patients

The study protocol was approved by the Institutional Review Board of Kurume University, Japan (No. 14113). All participants provided informed, written consent. Six patients were diagnosed with a perforation of the diaphragm after RFA for HCC, with a concomitant diaphragm herniation identified in 4 of the 6 patients. All patients underwent surgical treatment of the perforation, and herniation when present, at the division of Hepatobiliary Pancreatic Surgery of the Department of Surgery, Kurume University Hospital. All patients treated with RFA for HCC from January 2003 and December 2013 were evaluated for this study to define complications that happened within 6 mo after RFA (late-onset). Initial RFA treatments were performed at two different institutions: the Department of Gastrointestinal Medicine, Kurume University Hospital, and the Department of Surgery, Tobata Kyoritsu Hospital.

Procedure of RFA

The total number of the patients who underwent RFA during this period was 1427 patients, who carried 2134 tumors. In 1 of our 6 cases, RFA was performed using a cluster cool tip electrode for ablation (Cool-Tip Radiofrequency System, Radionics2, Cosman Medical; RF 3000, Boston Scientific), with return electrodes applied to the patient's legs. For the other 5 cases, RFA was performed using monopolar internally cooled electrodes, (Radionics, Cosman Medical). Expandable needles (LeVeen needle, Boston Scientific) were used to position the electrode on the target tissue in 5 of the 6 cases.

Under local anesthesia, the needle electrode was inserted percutaneously in 5 cases, and placed at the target tissue under ultrasonography guidance. In the remaining case, the needle electrode was inserted with the patient under general anesthesia and placed at the target tissue using a transthoracic approach *via* an artificial pneumothorax, under computed tomography (CT) guidance. No evidence of excessive bleeding at the needle insertion site was observed in any of the cases.

Follow up schedules of after RFA

Follow-up CT was performed one week after RFA ("just after RFA"), with subsequent CT follow-up conducted every 6-12 mo. Blood tests, including assessment of tumor markers, were performed every 3 mo.

Volumetry of the liver

A dynamic CT was performed in all cases at the onset of

Table 1 Clinical characteristics of patients

Case	Age/sex	Tumor location/size (mm)	Time from RFA to DP/DH (mo)	Underlying liver disease/CP sore	Previous intractable pleural effusion	Herniation viscera	Symptom	Treatment for DP/DH	Prognosis after DP/DH treatment
1	49/M	S4/17	17	Alcoholic-LC Child A	Absent	Absent	Absent	Surgical repair (laparotomy)	2 yr alive
2	79/F	S8/19	9	HCV-LC Child B	Present	Present (small intestine)	Abdominal pain	Surgical repair (laparotomy)	3 yr alive
3	68/M	S8/26	21	HCV-LC Child C	Present	Present (mesenteric fat)	Abdominal pain	Surgical repair (laparotomy)	6 mo died by LF
4	70/F	S6/23	8	HCV-LC Child C	Present	Present (large intestine)	Dyspnea	Surgical repair and colectomy (laparotomy)	4 yr died by LF
5	65/M	S8/21	16	HCV-LC Child B	Absent	Present (Large intestine)	Abdominal pain	Surgical repair (laparotomy)	2 yr died by LF
6	76/F	S8/20	6	HCV-LC Child A	Absent	Absent	Absent	Surgical repair (laparotomy)	4 yr alive

LC: Liver cirrhosis; LF: Liver failure; CP score: Child-Pugh score; DP: Diaphragmatic perforation; DH: Diaphragmatic hernia.

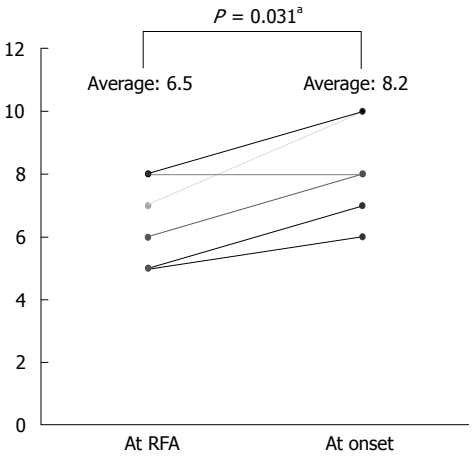

Figure 1 Child-Pugh score significantly increased between "just after radiofrequency ablation" to at the onset of perforation (P = 0.031). [a]Indicates values that are statistically significant (P < 0.05). RFA: Radiofrequency ablation.

perforation, using a 256 slice multi-detector computed tomography scanners (Brilliance iCT, PHILIPS/Aquilion, TOSHIBA) according to a standard protocol. Oyparomin or Iopaque (Fujiyakuhin Co., Saitama) was used as the contrast medium for CT imaging. The contrast medium was injected *via* peripheral intravenous administration using a power injector at a rate of 3 to 4 mL/s, with a total dosage of 1.5 mL/kg calculated from the patient's body weight. The change in the volume of the liver was measured from the dynamic CT images using a commercially available workstation (Synaps Vincent, Fujifilm Co. Kanagawa).

Statistical analyses

The change in the volume of liver and in the Child-Pugh score from just after the RFA to the onset of perforation was evaluated using a paired *t*-test analysis. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using JMP 11.0.0 (SAS: Roppongi, Minatoku, Tokyo, Japan).

Clinical data

The clinical profiles of all patients are summarized in Table 1 (Table 1). A perforation of the diaphragm developed in 6 patients, 3 men and 3 women, 49 to 79 years old. All patients had underlying liver cirrhosis, with two cases belonging to each of the cirrhosis Child-Pugh classes A, B, or C. The median Child-Pugh score just after RFA was 6.5, with a significant increase to 8.2 at the onset of perforation (P = 0.031; Figure 1). The tumors treated by RFA were single lesions; 21 to 31 mm in diameter; located in liver segments 4, 6, or 8; and adjacent to the diaphragm (Figure 2 A-B: Case 4). At the time of perforation, 4 patients had a perforation with herniated viscera, with the other 2 patients having a perforation without herniation. The interval between RFA and onset of perforation ranged from 6 mo to 21 mo. Three patients had a history of long standing refractory pleural effusion prior to the perforation.

Symptoms

Four cases with the herniation had symptoms, such as upper abdominal pain and dyspnea, but the case without herniation did not have symptoms. Symptom onset in cases with symptoms was sudden, which did not prevent progress. Meanwhile, 2 cases (Cases 1 and 6) were asymptomatic and were diagnosed at that time of operation of recurrent HCC incidentally.

Findings of CT

In 4 cases presenting with clinical symptoms, a right diaphragm defect, with and without herniated viscera in the right pleural cavity, was identified on coronal dynamic CT image (Figure 3: Case 4). The herniated viscera included the small intestine in 3 cases and the large intestine in 1 case. All cases were diagnosed with liver cirrhosis based on serum chemistry and CT findings of the morphological features of the liver and spleen. Table 2 shows findings of CT at just after RFA and at the onset (Table 2). At the onset of perforation,

Table 2 Findings of dynamic modified discrete cosine transform

Case	Just after RFA				At onset			
	Disintegration of diaphragm	Thickening of diaphragm	Ascites	Pleural effusion	Disintegration of diaphragm	Thickening of diaphragm	Ascites	Pleural effusion
1	No	No	No	No	No	No	No	No
2	No	No	No	Yes	Yes	Yes	Yes	Yes
3	No	No	No	Yes	Yes	No	Yes	Yes
4	No	No	No	Yes	Yes	No	Yes	Yes
5	No	No	No	No	Yes	No	No	Yes
6	No	No	No	No	No	No	Yes	Yes

RFA: Radiofrequency ablation.

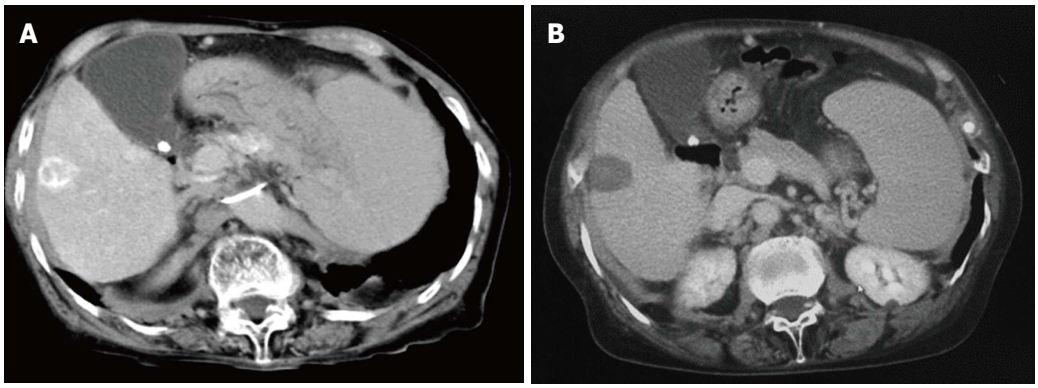

Figure 2 Tumors treated by radiofrequency ablation. A: Contrast-enhanced computed tomography (CT) shows hepatocellular carcinoma in segment 6 of the liver (Case 4); B: Abdominal CT image at just radiofrequency ablation shows a lesion of ablation (Case 4).

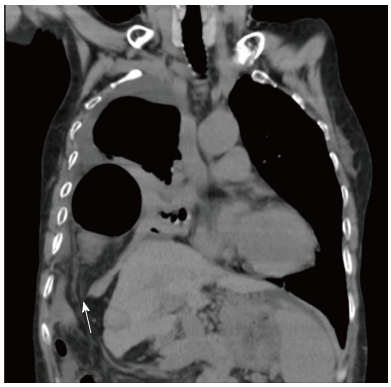

Figure 3 Coronal computed tomography image at onset of diaphragm perforation, showing a right diaphragm hernia. The right colon is deviated into the thoracic cavity through the diaphragm defect (white arrow) (Case 4).

disintegration of the diaphragm (4 of 6 cases) and pleural effusion (5 of 6 cases) were visible on CT imaging. However, characteristic findings of diaphragm injury were not visible on CT images obtained just after RFA. Liver volume at the onset of perforation was decreased from at just after RFA volume in 5 of the 6 cases, although this difference was not statistically significant (P = 0.138; Table 3).

RFA procedure

Relevant parameters of RFA procedures are summarized in Table 4. All cases underwent RFA with the electrode inserted *via* an intercostal approach. The peak power attained was 80 W, and the temperature of the ablated tissue was increased to 68℃-95℃. Total irradiation time ranged between 10 and 28 min. Dynamic CT performed just after RFA identified viability of a part of the HCC in 3 cases. Among these 3 patients, 2 underwent additional RFA using the same technique on the viable part of the tumor, with the other patient undergoing real-time CT guided RFA under pneumothorax.

Treatment of diaphragmatic perforation

All cases of diaphragm rupture were treated by surgical laparotomy and simple suture of the diaphragm defect (Figure 4 A-B: Case 2). In case 4, resection of the incarcerated large intestine was also performed. All cases had an uneventful postoperative course. Three patients died of hepatic deterioration due to advanced cirrhosis at 6, 24, and 48 mo postoperatively, respectively.

DISCUSSION

The mechanism of diaphragm perforation after RFA has not been clarified. In our cases, the RFA needle electrode did not penetrate the diaphragm directly except in one case in which RFA was performed under CT guidance using a transthoracic approach *via* an artificial pneumothorax. Therefore, mechanical damage caused by the needle itself may not completely explain

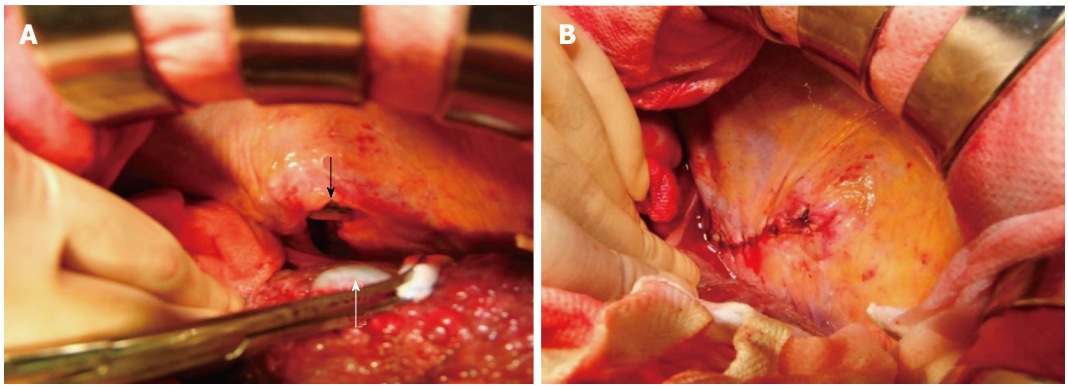

Figure 4 All cases of diaphragm rupture were treated by surgical laparotomy and simple suture of the diaphragm defect. A: A 5 cm defect of diaphragm is visible (black arrow), with evidence of post-ablation scarring (white arrow) (Case 2); B: The defect was repaired with interrupted sutures (Case 2).

Table 3 Changes of liver volume between radiofrequency ablation and onset

Case	Just after RFA (mL)	At onset (mL)
1	1005	1055
2		
3	653-	539
4	1130	893
5	971	946
6	987	866
Median	987	893

RFA: Radiofrequency ablation.

diaphragmatic injury. Considering the clinical profiles of our cases, there are 3 causative factors of diaphragm perforation after RFA: The location of the targeted lesions, collateral thermal injury during RFA, and the advanced cirrhosis status.

Collateral thermal damage to the diaphragm during RFA to these target areas adjacent to the diaphragm is common. In previous clinical case series, the targeted tumor was usually located adjacent to the diaphragm, in liver segments 7, 8, or 5[13]. Head *et al*[20] reported injury to the diaphragm in 5 of 29 patients (17%) who underwent ablation of hepatic tumors adjacent to the diaphragm. In our cases, all tumors that were treated by RFA were located adjacent to the diaphragm.

The thermal damage to the diaphragm may result in an inflammatory response, leading to fibrosis that could ultimately weaken the muscle fibers of the diaphragm and cause a late-onset defect[10,17]. Poor liver function might prevent the injured tissue from healing adequately, with complications, such as ascites and pleural effusion, thereby further contributing to tissue damage[5].

In this study, we found that the median Child-Pugh score at the onset was significantly higher than at just after RFA. As liver function gradually turns worse, the restoration for the diaphragmatic inflammatory change delays, and it is thought that it leads to diaphragmatic perforation.

Furthermore, one of the complications of aggravated liver function is Chilaiditi's syndrome. Moaven *et al*[21] reported that the incidence of Chilaiditi's syndrome inevitably increases in patients with cirrhosis due to atrophy of the right lobe of the liver, which creates space between the diaphragm and the liver. In our study, progressive atrophy of the liver was identified, on sequential dynamic CT after RFA, in 4 of 5 cases. Therefore, it is plausible that this atrophy of the liver was one of the factors contributing to the development of perforation and herniation of the diaphragm.

In the absence of characteristic symptoms of injury to the diaphragm and the relatively long interval between RFA and the onset of the perforation, it is difficult to predict and diagnose a late-onset diaphragm perforation caused by RFA. In this study, we experienced sudden symptom onset after more than 6 mo. Head *et al*[20] indicated that thickening of the diaphragm and localized fluid collection on post-ablation (just before perforation) CT scan were the most common imaging findings related to diaphragm damage. However, as in our cases, there may not be symptoms and CT findings specialized in diaphragm perforation at just RFA.

Development of intractable pleural effusion during the follow up period after RFA is another possible sign of diaphragm perforation[16,22]. In our cases, intractable plural effusion before the onset of diaphragmatic herniation was present in 3 of our 6 cases. Ascites following liver cirrhosis might have collected in the plural cavity through a defect in the diaphragm. In cases of intractable pleural effusion in which no defect of the diaphragm is detected by CT and ultrasonography, it would be helpful to perform a dual scope thoracoscopy or peritoneoscopy[22].

Diaphragm perforation and herniation, particularly with symptoms, must be surgically repaired as much as possible. In our experience, when there is not ileus, intestinal necrosis and breathing disorder, it is not necessary to hurry. Although the majority of our patients had advanced liver cirrhosis, prompt and appropriate surgical treatment was safe and effective, with patients recovering rapidly and uneventfully after surgery.

In summary, diaphragmatic herniation consequent

Table 4 Radiofrequency ablation procedure

Case	Anesthesia	Guidance	Approach	Electrode	Number of session	Max power (W)	Max Temperature (°C)	Additional RFA	Irradiation duration (min)
1	Local	US	Intercostal	Single cool-tip	1	50	76	Yes	10
2	Local	US	Intercostal	Single cool-tip	1	60	84	Yes	11
3	General	CT	Intercostal	Expansion-type	8	80		No	28
4	Local	US	Intercostal	Single cool-tip	2	80	86	No	16
5	Local	US	Intercostal	Single cool-tip	1	50	87	No	11
6	Local	US	Intercostal	Single cool-tip	2	80	95	Yes	21

RFA: Radiofrequency ablation.

to thermal injury of RFA is a rare complication, but it is not a matter that can be ignored in the management of HCC. In performing RFA for liver tumors located adjacent to the diaphragm, clinicians must devise methods for avoiding thermal injury of the diaphragm and regularly monitor the integrity of the diaphragm to achieve early diagnosis of defects over a long-term postoperative follow up.

ARTICLE HIGHLIGHTS

Case characteristics

In the case of diaphragmatic perforation with herniation after radiofrequency ablation (RFA), symptoms, such as upper abdominal pain or dyspnea, develop suddenly, while in the case of perforation without herniation, there may be no symptoms.

Clinical diagnosis

Diaphragmatic perforation with or without herniation after radiofrequency ablation for hepatocellular carcinoma.

Differential diagnosis

In case of acute onset, it is necessary to distinguish from acute abdomen and respiratory failure and the history of RFA for hepatocellular carcinoma located adjacent to the diaphragm and computed tomography (CT) findings would be helpful to diagnose.

Laboratory diagnosis

In the case of diaphragmatic perforation with and without herniation after RFA, liver function, such as Child-Pugh score, may decline in many cases.

Imaging diagnosis

In the case of diaphragmatic perforation with herniation after RFA, a right diaphragm defect and herniated viscera in the right pleural cavity is identified on coronal dynamic CT image.

Pathological diagnosis

There were no pathological findings as all cases may undergo direct discontinued sutures without trimming in this study.

Treatment

Diaphragm perforation and herniation, particularly with symptoms, must be surgically repaired as much as possible, but when there is not ileus, intestinal necrosis and breathing disorder, it is not necessary to hurry.

Experiences and lessons

In performing RFA for liver tumors located adjacent to the diaphragm, clinicians must devise methods for avoiding thermal injury of the diaphragm and regularly monitor the integrity of the diaphragm to achieve early diagnosis of defects over a long-term postoperative follow up.

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CASE REPORT

Ectopic gastrointestinal variceal bleeding with portal hypertension

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Author contributions: Minowa K, Komatsu S, Takashina K, Tanaka S, Kumano T, Imura K, Shimomura K, Ikeda J, Taniguchi F, Ueshima Y, Lee T, Ikeda E, Otsuji E and Shioaki Y performed research and analyzed the data; Minowa K and Komatsu S wrote the paper and contributed equally to this work.

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Abstract

Massive gastrointestinal bleeding from gastrointestinal varices is one of the most serious complications in patients with portal hypertension. However, if no bleeding point can be detected by endoscopy in the predilection sites of gastrointestinal varices, such as the esophagus and stomach, ectopic gastrointestinal variceal bleeding should be considered as a differential diagnosis. Herein, we report a case of ectopic ileal variceal bleeding in a 57-year-old woman, which was successfully diagnosed by multi-detector row CT (MDCT) and angiography and treated by segmental ileum resection. To date, there have been no consensus for the treatment of ectopic ileal variceal bleeding. This review was designed to clarify the clinical characteristics of patients with ectopic

ileal variceal and discuss possible treatment strategies. From the PubMed database and our own database, we reviewed 21 consecutive cases of ileal variceal bleeding diagnosed from 1982 to 2017. MDCT and angiography is useful for the rapid examination and surgical resection of an affected lesion and is a safe and effective treatment strategy to avoid further bleeding.

Key words: Ectopic gastrointestinal bleeding; Ileal varix; Portal hypertension

Core tip: Massive gastrointestinal bleeding from gastrointestinal varices is one of the most serious complications in patients with portal hypertension. If no bleeding point can be detected by endoscopy in the predilection sites of gastrointestinal varices, ectopic gastrointestinal variceal bleeding should be considered as a differential diagnosis. We report here a 57-year-old female case of ectopic ileal variceal bleeding, which were diagnosed by multidetector row CT (MDCT) and its angiography and treated by segmental ileum resection. From the review results of previous reports, MDCT and its angiography is a rapid and useful examination. Moreover, surgical resection of responsible lesion is safe and effective treatment strategy to avoid further bleeding.

Minowa K, Komatsu S, Takashina K, Tanaka S, Kumano T, Imura K, Shimomura K, Ikeda J, Taniguchi F, Ueshima Y, Lee T, Ikeda E, Otsuji E, Shioaki Y. Ectopic gastrointestinal variceal bleeding with portal hypertension. *World J Gastrointest Surg* 2017; 9(12): 288-292 Available from: URL: http://www.wjgnet.com/1948-9366/full/v9/i12/288.htm DOI: http://dx.doi.org/10.4240/wjgs.v9.i12.288

INTRODUCTION

Massive gastrointestinal bleeding from a gastrointestinal varix is one of the most serious complications in patients with portal hypertension. However, if the point of continuous bleeding in the predilection sites of a gastrointestinal varix, such as the esophagus and stomach, is not found and no further strategy for the accurate diagnosis and effective treatment of the bleeding point exists, the condition may become life threatening.

Lebrec *et al*[1] classified the gastrointestinal varices other than those of the esophagus and stomach as ectopic varices. Ectopic gastrointestinal varices were reported in the sites of the duodenum, small intestine, colon, rectum, peristomal, biliary, peritoneal, umbilical, and other locations. Ectopic gastrointestinal varices cause an unusual hemorrhage and account for 5% of all variceal bleeding. In particular, ectopic ileal variceal bleeding is the major type of ectopic gastrointestinal variceal bleeding[2]. Herein, we report a case of ectopic ileal variceal bleeding, which was diagnosed by MDCT and angiography and was surgically treated. Moreover, we reviewed previous case reports regarding the clinical behaviors, diagnosis, and treatment strategies of ectopic ileal variceal bleeding, including our cases diagnosed between 1982 and 2017 from the PubMed database.

CASE REPORT

A 57-year-old Asian woman with autoimmune portal hypertension due to polymyositis was admitted to our hospital with a 2-d history of hematochezia. She had a history of esophageal variceal rupture, which had been treated by endoscopy 3 years before. At admission, she had a blood pressure of 92/58 mmHg, heart rate of 85/min, respiratory rate of 16/min, and body temperature of 35.2 ℃. Although she was pale and showed conjunctival pallor, and there was no jaundice, abdominal pain, or shifting dullness. Laboratory data were as follows: hemoglobin 7.3 g/dL, hematocrit 23.4%, platelets 112000/mm^3, prothrombin time 98%, serum albumin 3.5 g/dL, total bilirubin 1.1 mg/dL, aspartate aminotransferase/alanine aminotransferase 35/51 IU/L. Hepatitis B surface antigen was positive and hepatitis C virus antibody was negative. There was no encephalopathy. Her Child-Pugh score was 6 (class A).

We performed an emergent upper gastrointestinal endoscopy, which showed a mild esophageal varix without bleeding. However, lower gastrointestinal endoscopy revealed a large blood clot at the ileocecum, but there was no active bleeding lesion during the endoscopy. MDCT showed no definitive liver cirrhosis, but dilation of the hepatic portal vein and umbilical vein and splenomegaly and portosystemic collaterals indicated portal hypertension. In addition, enhanced MDCT and MDCT and angiography revealed the presence of an ileal varix, which showed no active bleeding into the abdominal cavity. In particular, the ileal varix had a portosystemic shunt *via* the superior mesenteric vein into the right ovarian vein.

She was treated conservatively for 2 d with a blood transfusion. On the 3rd day after admission, she had massive hematochezia. We performed a second MDCT and angiography and diagnosed the patient as hematochezia due to massive ileal varix bleeding because there was a massive coagula at the distal ileal lumen of the ileal varix. We performed emergent segmental ileal resection, which included the ileal varix, *via* a small laparotomy (Figure 1). The varix was located at the 20-cm proximal portion of the ileocecal valve. Her postoperative condition was uneventful. She had no further bleeding and was discharged on the 8th day after surgery.

DISCUSSION

Portal hypertensive enteropathy is present in 5%-11% of patients with portal hypertension and often gives rise to gastrointestinal varices in the esophagus and stomach, which cause active bleeding[3]. Gastrointestinal varices other than those of the esophagogastric area

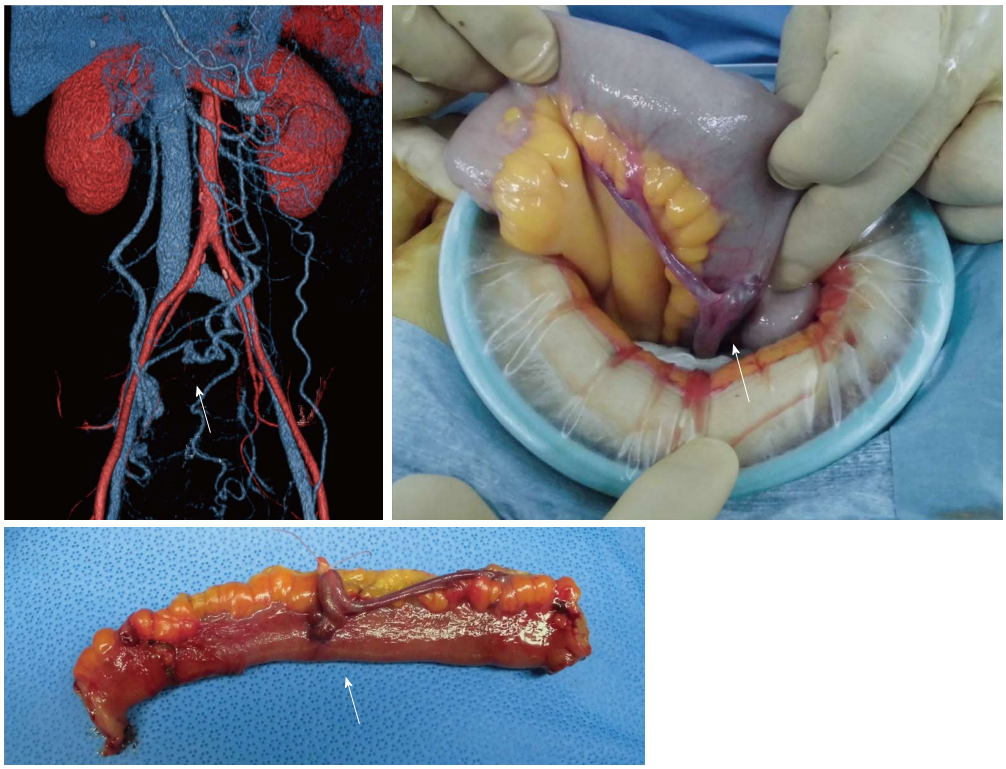

Figure 1 Ileal varices (arrow) were detected using multi-detector row CT and angiography and were resected by laparotomy.

are rare and are classified as ectopic gastrointestinal varices. Ectopic gastrointestinal varices occur at sites such as the duodenum, small intestine, colon, rectum, peristomal, biliary, peritoneal, umbilical, and other locations. Various related factors of an ectopic gastrointestinal varix such as portal hypertension due to cirrhosis, portal vein thrombosis, a history of abdominal surgery, chronic intraperitoneal inflammation, and hematochezia have been reported[4,5].

An ileal varix is the major type of ectopic gastrointestinal varix. In a review 169 cases of ectopic gastrointestinal variceal bleeding, 17% was the highest rate of bleeding among all sites and was derived from jejunal and ileal varices[2]. Ileal varices are associated with a history of abdominal surgery and adhesions[6]. Presumably, abdominal surgery and intraperitoneal inflammation may cause adhesion of the intestinal tract. Then, collateral vessels within the adhesion may give rise to ectopic intestinal varices, particularly, in the jejunum and ileum[7]. Ectopic ileal varices most commonly flow into systemic circulation through the gonadal veins and less commonly through branches of the internal iliac veins[7]. In our case, there were various compatible features such as autoimmune portal hypertension and previous surgeries for appendicitis and hematochezia. Moreover, a portosystemic shunt, which flowed from the superior mesenteric vein into the right ovarian vein, was detected.

From the PubMed database including our own, we reviewed 21 consecutive cases of ileal variceal bleeding diagnosed from 1982 to 2017. The clinical features of 21 patients are shown in Table 1. Patients with ileal variceal bleeding consisted of 5 male and 16 female patients with a median age of 57 years (range 33-80 years). From the medical history, 71.4% (15/21) of patients were associated with portal hypertension due to liver cirrhosis. Previous abdominal surgery was noted in 57.1% (12/21) of patients. Regarding the diagnosis, 61.9% (13/21) of patients were diagnosed by SMA angiography. Capsule endoscopy was used in two cases. However, recent cases were mainly diagnosed by MDCT or MDCT and angiography and treated by surgical resection with no further bleeding. Surgical resection was performed in 76.1% (16/21) of all patients. Some recent patients underwent interventional radiology (IVR) treatment methods such as transjugular intrahepatic portosystemic shunt (TIPS)[8-10] and balloon-occluded retrograde transvenous obliteration (BRTO)[11,12].

There were no patients with re-bleeding in previous reports of ileal variceal bleeding. However, re-bleeding rates of 23%-39% have been reported in TIPS and 5%-16.6% in BRTO in all reports of ectopic gastrointestinal variceal bleeding[13-16]. Although non-invasive treatment such as IVR may be desirable for ectopic gastrointestinal variceal bleeding in high-risk patients with co-morbidities, surgical resection of an affected intestine is currently a safe and effective treatment strategy to avoid further re-bleeding. Moreover, laparoscopic surgical resection of an affected intestine could be possible effective strategy as a minimally invasive procedure (Figure 2).

Ectopic gastrointestinal varices bleeding, especially ileal variceal bleeding, in patients with portal hypertension

Table 1 Summary of the reported ileal variceal bleeding

Case	Year		Age	Sex	Past history	Previous abdominal surgery	Diagnosis	Treatment	Outcome
1	1982	Falchuk	52	F	liver cirrhosis	Cholecystectomy	SMA angiography	Partial enterectomy	Dead
2	1984	Shimada	49	M	liver cirrhosis	Ruputured esophageal varix	SMA angiography	Partial enterectomy	Alive
3	1986	Hojhus	80	F	Periappendicular abscess	(-)	SMA angiography	Partial enterectomy	Dead
4	1986	Arst	56	F	Liver cirrhosis	(-)	Laparotomy	Ileocolectomy	Dead
5	1990	Lewis	72	F	Liver cirrhosis	Hysterectomy	SMA angiography	Ileocolectomy	Alive
6	1994	Kurihara	43	M	(-)	(-)	SMA angiography	Partial enterectomy	Alive
7	1997	Ahn	54	M	Liver cirrhosis	(-)	SMA angiography	ileocolEctomy	Dead
8	1999	Ohtani	66	F	Liver cirrhosis	Ectopic pregnancy	SMA angiography	Partial enterectomy	Alive
9	2001	Kobayashi	62	F	Hepatocellular carcinoma	Hysterectomy	SMA angiography	Ligation of ileocecal and ovarian vein	Alive
10	2006	Ueda	72	F	Liver cirrhosis	Abdominal aortic aneurysm	MDCT	Partial enterectomy	Alive
11	2007	Lopez	56	F	Liver cirrhosis	Pelvic surgery	SMA angiography	TIPS	Alive
12	2007	Mashimo	33	F	Liver cirrhosis	Endometriosis	SMA angiography	Partial enterectomy	Alive
13	2009	Suzuki	74	F	Liver cirrhosis	Acute appendicitis	MDCT	Partial enterectomy	Alive
14	2009	Traina	58	F	Liver cirrhosis	(-)	ES	Sclerotherapy + TIPS	Alive
15	2009	Sato	55	M	Liver cirrhosis	Laparotomy for colonic tumor	Retrograde transvenous venography	BRTO	Alive
16	2010	Konishi	54	F	(-)	(-)	CE	Partial enterectomy	Alive
17	2011	Ambiru	62	F	Liver cirrhosis	Ectopic pregnancy	MDCT	Partial enterectomy	Alive
18	2011	Castagna	70	M	Liver cirrhosis	(-)	CE	TIPS	Alive
19	2013	Vamadevan	48	F	Liver cirrhosis	(-)	MDCT	TIPS	Alive
20	2015	Garcia	74	F	Venous thromboembolism	(-)	MDCT	Partial enterectomy	Alive
21	2017	Our case	57	F	Portal hypertension	Acute appendicitis	MDCT	Partial enterectomy	Alive

CE: Capsule endoscopy; MDCT: Multi-detector raw computed tomography; ES: Enteroscopy; TIPS: Transjugular intrahepatic portosystemic shunt; BRTO: Balloon occluded retrograde transvenous obliteration.

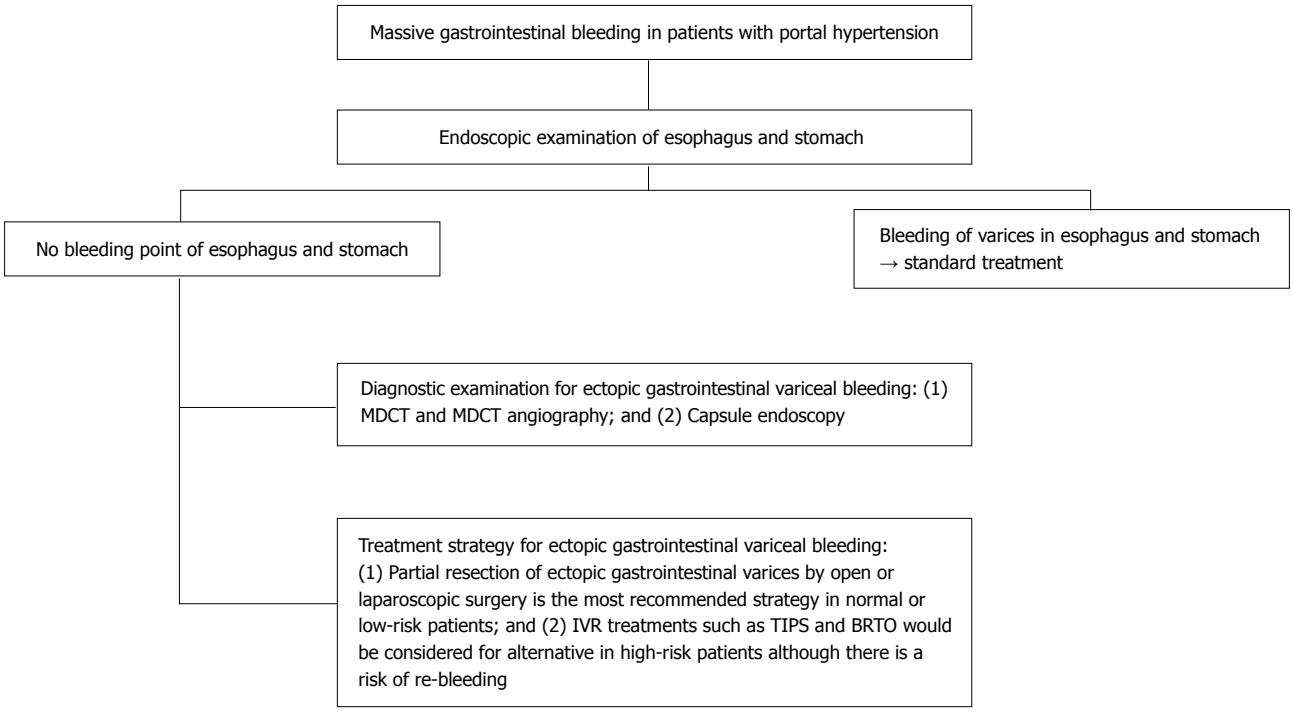

Figure 2 The management algorythm for massive gastrointestinal bleeding in patients with portal hypertension. MDCT: Multi-detector raw computed tomography; TIPS: Transjugular intrahepatic portosystemic shunt; BRTO: Baloon occluded retrograde transvenous obliteration.

might be considered as a differential diagnosis if upper or lower endoscopy cannot detect a bleeding point such as in the esophagus or stomach. MDCT or MDCT angiography is useful for the rapid examination and surgical resection of an affected ileum and is a safe and effective treatment strategy to avoid further bleeding.

ARTICLE HIGHLIGHTS

Case characteristics

A 57-year-old Asian woman with autoimmune portal hypertension due to polymyositis was admitted to our hospital with a 2-d history of hematochezia. She had a history of esophageal variceal rupture, which had been treated by endoscopy 3 years before.

Clinical diagnosis

On the 3rd day after admission, she had massive hematochezia. The authors performed a second multi-detector row CT (MDCT) and angiography and diagnosed as massive ileal varix bleeding because there was a massive coagula at the distal ileal lumen of the ileal varix.

Differential diagnosis

There was no differential diagnosis because upper and lower endoscopic examinations could not detect the responsible lesion.

Laboratory diagnosis

Laboratory diagnosis was a severe anemia with hemoglobin 7.3 g/dL and hematocrit 23.4% because other data showed no apparent disorder.

Imaging diagnosis

Imaging diagnosis by MDCT and its angiography was massive ileal varix bleeding because there was a massive coagula at the distal ileal lumen of the ileal varix.

Pathological diagnosis

Pathological diagnosis was the leal varix.

Treatment

The authors performed emergent segmental ileal resection, which included the ileal varix, *via* a small laparotomy. The varix was located at the 20-cm proximal portion of the ileocecal valve.

Related reports

Jejunal varices as a cause of massive gastrointestinal bleeding. *Am J Gastroenterol* 1992; **87**: 514-517.

Term explanation

The authors used common terms, which were used in previous reports.

Experiences and lessons

Ectopic gastrointestinal variceal bleeding might be considered as a differential diagnosis if upper or lower endoscopy could not detect bleeding point. From the review results of previous reports including our case, MDCT and its angiography is a rapid and useful examination. Moreover, surgical resection of responsible lesion is safe and effective treatment strategy to avoid further bleeding.

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