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REVIEW

Management of complicated acute appendicitis in children: Still an existing controversy

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Abstract

Complicated acute appendicitis (CAA) is a serious condition and carries significant morbidity in children. A strict diagnosis is challenging, as there are many lesions that mimic CAA. The management of CAA is still controversial. There are two options for treatment: Immediate operative management and non-operative management with antibiotics and/or drainage of any abscess or phlegmon. Each method of treatment has advantages and disadvantages. Operative management may be difficult due to the presence of inflamed tissues and may lead to detrimental events. In many cases, non-operative management with or without drainage and interval appendectomy is advised. The reasons for this approach include new medications and policies for the use of antibiotic therapy. Furthermore, advances in radiological interventions may overcome difficulties such as diagnosing and managing the complications of CAA without any surgeries. However, questions have been raised about the risk of recurrence, prolonged use of antibiotics, lengthened hospital stay and delay in returning to daily activities. Moreover, the need for interval appendectomy is currently under debate because of the low risk of recurrence. Due to the paucity of high-quality studies, more randomized controlled trials to determine the precise management strategy are needed. This review aims to study the current data on operative *vs* non-operative management for CAA in children and to extract any useful information from the literature.

Key words: Complicated acute appendicitis; Operative treatment; Non-operative treatment; Antibiotics; Children

Core tip: The management of paediatric patients with complicated acute appendicitis (CAA) is controversial. There are two options for treatment: non-operative management

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with antibiotics and/or drainage of any abscess or phlegmon and immediate operative management. Each method has advantages and disadvantages. However, operative management is suggested for CAA with perforation, while non-operative management is advised for CAA with abscess or phlegmon. There is a paucity of high-quality studies in the current literature. Further investigations with randomized control studies are warranted.

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INTRODUCTION

Appendectomy for acute appendicitis (AA) in children persists as the most common abdominal surgery for paediatric surgeons[1]. It has been estimated that 70000 children are operated on for AA every year in the United States[2]. The lifetime risk of appendectomy is 23.1% for females and 12% for males[3], and the lifetime risk of developing AA is 6.7% for females and 8.6% for males[4]. Interestingly, the peak incidence of AA occurs from ages 10-14 years for males and 15-19 years for females[4].

The clinical history of AA can vary from mild symptoms (uncomplicated AA) to those with sepsis and bowel obstruction [complicated AA (CAA)] with perforation of the appendix and probably development of an intraperitoneal abscess[5]. Approximately 30%-74% of children present with CAA[6], with rates ranging between 69%-93% for children aged 2 to 5 years and up to 100% for 1-year-old children[7]. Although operative management has been considered for many years as the mainstay of treatment in children with AA[8], the presence of distorted anatomy due to inflamed tissues may lead to harmful events such as injury to the surrounding tissues and bowel wall, dissemination of the infection, blood loss, postoperative bowel obstruction, abscess or fistula formation, and postoperative wound complications[2,9,10].

The evidence that AA can be managed with non-operative management is not new. The first case of a spontaneous resolution of CAA was published in 1910[11]. In 1956 and in 1959, Coldrey[12] published a series of 137 patients with AA successfully treated with non-operative management. Almost two decades later, Janik *et al*[13] reported the successful management of 31/37 children with a palpable mass and no established peritonitis with the administration of fluids and close monitoring. In the mid-1990s, the interest in non-operative management in the adult population was renewed, and since then, a number of studies have investigated the efficiency and safety of non-operative management, first in uncomplicated AA and later in CAA[14,15]. Although the literature on paediatric patients is still limited, ongoing evidence indicates that non-operative management may be effective and safe for the management of uncomplicated AA[16,17].

Despite modern diagnostic adjuncts such as imaging techniques and improvements in anaesthetic and surgical care, controversies in the optimal management of CAA in the paediatric population still exist[18].

Taking into account recent improvements in the management of CAA, this review aims to provide an update on the existing controversies in operative management *vs* non-operative management for children with CAA.

LITERATURE SEARCH

A literature review was performed through PubMed and Google Scholar for original articles, reviews and meta-analyses from 1980 to December 2019 using the following Medical Subjects Headings (MeSH) terms: "appendicitis" [MeSH] and "complicated appendicitis" [MeSH] or "appendicular mass" [MeSH] or "abscess" [MeSH] or "phlegmon" [MeSH] or ''perforated" [MeSH] or "conservative treatment" [MeSH] or "operative treatment" [MeSH] or "interval appendectomy" [MeSH] and "children". A secondary search of the most relevant articles was also conducted manually or through PubMed based on the related articles. All randomized controlled trials (RCTs), prospective and retrospective articles and systematic reviews were included. Articles including both adult and paediatric populations and papers based on case

reports, case series, abstracts and letters were excluded. All articles were selected systematically for inclusion and critically evaluated.

Definitions

CAA was defined as perforated appendicitis with or without the presence of an abscess or phlegmon[2] based on the surgeon's findings during operation or the pathology report[19]. A phlegmon was defined as an inflammatory mass without an apparently defined abscess[19].

Operative management was defined as an early appendectomy performed either with laparotomy or laparoscopy within the first 24 h of hospitalization[20].

Non-operative management was defined as initial treatment with or without percutaneous abscess drainage for an abscess followed by interval appendectomy[21].

Treatment failure of non-operative management and percutaneous abscess drainage was defined as the need for an appendectomy operation during the same hospitalization period or within 7 d after discharge[22].

The complications included any surgical, medical or interventional adverse events (postoperative wound infection, small bowel obstruction, abscess or fistula formation)[2,9,10].

Hospital length of stay (LOS) for both operative management and non-operative management was defined as the total number of hospitalization days from admission to discharge and was calculated after reading the relevant articles in the literature.

RESULTS

We included 47 articles published from August 1980 to December 2019 relevant to the management of CAA in children. Of them, three[23-25] were systematic reviews and meta-analyses, two[26,27] were prospective RCTs, seven were prospective non-randomized trials[28-34], one was a prospective observational study[35], and thirty-four[9,13,19-21,36-64] were retrospective studies (Figure 1). The therapeutic options regarding CAA are analysed in detail below.

MANAGEMENT

Once a paediatric surgeon has to treat a patient with CAA, there are three strategies available for treatment: Antibiotics only, antibiotics followed by interval appendectomy, and appendectomy on admission (Table 1). We will separately discuss the three options with the pros and cons of each strategy.

Non-operative management

Advances in antibiotic policy: Currently, the standard of care endorses the prompt administration of antibiotics in the management of CAA[65,66]. A survey of the European Pediatric Surgeons' Association covering 42 countries (24 were from Europe) showed that 96% of surgeons start antibiotic therapy preoperatively in the case of CAA[66]. The same study showed that most surgeons choose a triple "standard therapy" comprising an aminoglycoside, a β-lactam and a regimen covering anaerobes. However, there is growing evidence that broad-spectrum single (piperacillin/tazobactam) or double-agent (ceftriaxone + metronidazole) therapy is equally effective and less expensive than triple-agent therapy and may lead to a shorter LOS[67-70]. This is in line with the recommendations of the American Pediatric Surgical Association (APSA) that state that broad-spectrum single or double-agent therapy is equally efficient and more cost-effective than three drugs[65]. It is noteworthy that a slight shift toward mono- or dual-agent therapy could be observed in the literature after the publication of the APSA recommendations[21,54].

A major issue arises from the use of broad-spectrum anti-Pseudomonas antibiotics such as piperacillin/tazobactam, imipenem or meropenem, *vs* narrow-spectrum antibiotics such as cefoxitin or cefazolin with metronidazole[70]. The clinical guidelines recommend the use of narrow-spectrum antibiotics in adults with complicated intra-abdominal infections and in most previously healthy children with uncomplicated AA who are not assumed to be susceptible to *P. aeruginosa*[71]. Kronman *et al*[71], in a large, retrospective cohort study of children suffering from either uncomplicated AA or CAA, showed that broad-spectrum antibiotics are not superior to narrow-spectrum antibiotics with respect to short-term postoperative complications, *e.g.*, readmission rates, wound infections, bowel obstruction, and percutaneous drainage of abscesses, within 30 d of discharge. Researchers have shown that antibiotic agents with an expanded spectrum against *P. aeruginosa* and *Enterococcus* were efficient in 78% of

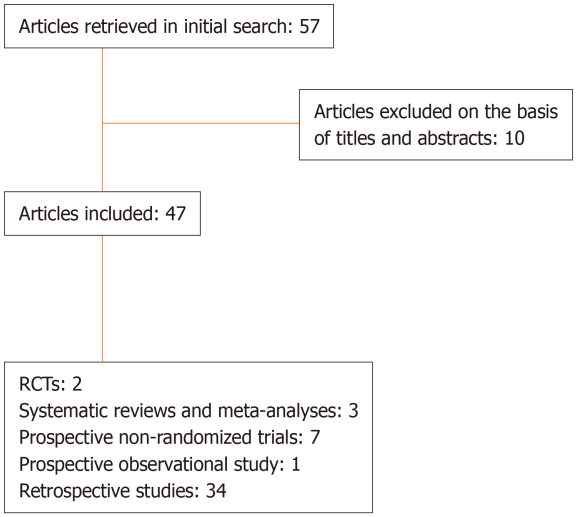

Figure 1 Study selection flowchart. RCTs: Randomized controlled trials.

patients who failed first-line antibiotics and helped them achieve successful non-operative management[72]. In such cases, second-line antibiotics are recommended before surgical intervention[71]. An important question concerns the duration of antibiotics use in children with CAA and non-operative management. The APSA recommendations suggest that the length of antimicrobial agent use should be based on clinical criteria such as pain, fever, bowel function and white blood cell count[43]. Usually, a 5-d policy for intravenous antibiotics followed by a 2-d regimen of oral antibiotics (total 7-d length of antibiotics use) is recommended[65]. This suggestion was supported further by a very late systematic review and meta-analysis that showed that the transition from intravenous to oral administration did not raise the risks for complications such as wound infection, postoperative abscess and re-admission[73].

Antibiotic treatment: The common indications that CAA demands urgent operative intervention has changed in the last decade. Several centres have reported the results of children with appendiceal abscesses or masses treated with antibiotics, both with or without drainage[29,32,35,36,40,43,50,54-56,58,59]. Most of these studies revealed a success rate between 60-100%. However, Svensson *et al*[74] questioned the results of some of these studies because the majority of them were retrospective and included meaningful selection bias. Furthermore, without an operation, it is difficult to declare that all patients had definite CAA despite appropriate blood tests and radiological imaging. Although the presence of an appendicolith is thought to be a predictor of non-operative management failure[50,54] and recurrence, other researchers found no correlation between this factor and the outcomes[75].

We conclude that the optimal antimicrobial therapy and duration of antibiotics use in children with CAA need further investigation with RCTs.

Percutaneous abscess drainage: During the 1980s, a period of growth and acceptance of radiological interventional techniques in children started[76]. Percutaneous abscess drainage is a well-established procedure of choice for treating intra-abdominal abscesses of various aetiologies[77]. In the case of CAA, an intra-abdominal abscess may occur either before or after appendectomy and may be found anywhere in the abdominal cavity and/or pelvis[64]. Drainage is usually performed with the Seldinger technique under ultrasound or computed tomography (CT) guidance or a combination of both imaging modalities[64]. In the case of peri-appendicular abscesses, the anterior abdominal transperitoneal approach is usually performed[78,79], while for abscesses located anterior to the rectum, the transrectal or transgluteal approach may be used[79].

The incidence of intra-abdominal or pelvis abscesses is estimated to be approximately 3.8% in patients with CAA[80]. A delay in the diagnosis of AA is a possible risk factor, although there is evidence that some patients might be prone to abscess formation despite prompt management[81]. Several authors[26,53,54,57,61,62] have documented beneficial results with percutaneous abscess drainage in terms of reduced complication rates, acceptable LOS, and rapid recovery to oral feeding and return to normal activities. In a European Pediatric Surgeons' Association survey, 59% of paediatric surgeons suggested a combination of antibiotics and percutaneous abscess drainage[66]. Luo *et al*[57], in a large series of children with appendiceal

Table 1 Management options of complicated acute appendicitis

Non-operative management	Operative management
Antibiotic treatment	Immediate operative management
Percutaneous abscess drainage	Non-operative management followed by interval appendectomy

abscesses, found that patients treated with non-operative management and percutaneous abscess drainage had a significantly lower percentage of recurrent appendicitis, a lower possibility of requiring an interval appendectomy, and fewer postoperative complications after interval appendectomy than those without percutaneous abscess drainage. In contrast, Bonadio *et al*[58] reported a greater LOS, longer mean duration of fever, longer period of antibiotics use, more radiological procedures, higher complication rates and more unscheduled hospitalizations after discharge for patients who received percutaneous abscess drainage. Keckler *et al*[52] mentioned that multiple CT scans and major complications may follow percutaneous abscess drainage, such as ileal, colonic and bladder perforation and buttock/thigh abscesses, while in the interval appendectomy group, only one patient developed a pelvic phlegmon that responded to intravenous antibiotics. Gasior *et al*[64] suggested that only abscesses greater than 20 cm^2 should be drained. Some authors advocate for the installation of a tissue plasminogen activator into the abdominal cavity[82] to facilitate drainage of thick and septated abscesses. In a recent RCT, St Peter *et al*[83] found that compared to the control group. patients who underwent tissue plasminogen activator installation had a longer duration of hospitalization, while no differences concerning the use of antibiotics, drainage duration or total hospitalization were found.

We could conclude that although arguments may be raised for percutaneous abscess drainage, there is evidence that drainage of the abdominal cavity may have favourable results in selected patients.

Operative management

Immediate operative management *vs* non-operative management with delayed appendectomy: Although many studies[23,26,27,55] propose early operative management for children with CAA, there are only two RCTs supporting this option for treatment. In the first study[26], 40 patients with similar characteristics on admission and a diagnosis of CAA were randomized to immediate operative management and non-operative management group, with the latter undergoing delayed appendectomy. Patients operated on early had fewer health care visits and CT scans than those with delayed surgery. No better outcomes were found in the non-operative management group than in the operative management group. Blakely *et al*[27] studied a cohort of 131 patients who were diagnosed with perforated appendicitis without abscess on admission, and they were randomized in a non-blinded manner for early operative management or non-operative management followed by interval appendectomy. The authors found that patients in the non-operative management group had higher complication rates and higher hospital charges than those in the operative management group. On the other hand, a meta-analysis by Duggan *et al*[23] showed that early appendectomy for patients with perforated appendicitis without abscess significantly reduced unplanned readmissions [Odds ratio (OR) = 0.08, 95% confidence interval (CI): 0.01-0.67], adverse events (OR = 0.28, 95%CI: 0.1-0.77) and total charges. A recent meta-analysis by Vaos *et al*[24] reported that operative management was associated with shorter LOS (SD = 0.25, 95%CI: 0.07-0.43, P = 0.007), but the overall complication rates (OR = 0.22, 95%CI: 0.14-0.38, P = 0.001) and incidence of wound infection(OR = 0.40, 95%CI: 0.17-0.96, P = 0.041) were significantly lower with non-operative management. The presence of intra-abdominal abscess and postoperative ileus was not affected by the treatment option. In a recent meta-analysis, Fugazzola *et al*[25] separately studied patients with free perforated appendicitis and those with abscess or phlegmon. The researchers reported better outcomes regarding complication rates and readmissions in patients with appendicular abscess or phlegmon treated with non-operative management. In contrast, the authors found a lower complication rate and fewer re-admissions for the group of patients with free perforated appendicitis treated with operative management.

Summarizing the results of the abovementioned studies, it seems that there are two main types of CAA: CAA with perforation without abscess and CAA with abscess or phlegmon. The main conclusion is that operative management is the preferred treatment option for patients with perforated appendicitis without abscess, while non-

operative management is advised in cases of perforated appendicitis with abscess or phlegmon.

CONCLUSION

Although AA is a common surgical disease, it may be expressed with a wide range of severity, ranging from simple to severe. In the case of CAA, operative management seems to be the preferable choice of treatment, while non-operative management is recommended for CAA with abscess or phlegmon. However, because of the paucity of high-quality studies, there is a need for more RCTs to determine the precise management strategy.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Newly developed self-expandable Niti-S MD colonic metal stent for malignant colonic obstruction

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Abstract

BACKGROUND

Colonic stents are increasingly used to treat acute malignant colonic obstructions. The WallFlex and Niti-S D type stents are the commonly used self-expandable metallic stents available in Japan since 2012. WallFlex stent has a risk of stent-related perforation because of its axial force, while the Niti-S D type stent has a risk of obstructive colitis because of its weaker radial force. Niti-S MD type stents not only overcome these limitations but also permit delivery through highly flexible-tipped smaller-caliber colonoscopes.

AIM

To compare the efficacy and safety of the newly developed Niti-S MD type colonic stents.

METHODS

This single-center retrospective observational study included 110 patients with endoscopic self-expandable metallic stents placed between November 2011 and December 2018: WallFlex (Group W, n = 37), Niti-S D type (Group N, n = 53), and Niti-S MD type (Group MD, n = 20). The primary outcome was clinical success, defined as a resolution of obstructive colonic symptoms, confirmed by clinical and radiological assessment within 48 h. The secondary outcome was technical success, defined as accurate stent placement with adequate stricture coverage on the first attempt without complications.

Informed consent statement: All participants provided informed consent to the procedure and data collection.

Conflict-of-interest statement: There are no conflicts of interest to declare.

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RESULTS

The technical success rate was 100% in Groups W, N, and MD, and the overall clinical success rate was 89.2% (33/37), 96.2% (51/53), and 100% (20/20) in Groups W, N, and MD, respectively. Early adverse events included pain (3/37, 8.1%), poor expansion (1/37, 2.7%), and fever (1/37, 2.6%) in Group W and perforation due to obstructive colitis (2/53, 3.8%) in Group N (likely due to poor expansion). Late adverse events (after 7 d) included stent-related perforations (4/36, 11.1%) and stent occlusion (1/36, 2.8%) in Group W and stent occlusion (2/51, 3.9%) in Group N. The stent-related perforation rate in Group W was significantly higher than that in Group N ($P < 0.05$). No adverse event was observed in Group MD.

CONCLUSION

In our early and limited experience, the newly developed Niti-S MD type colonic stent was effective and safe for treating acute malignant colonic obstruction.

Key words: Colonic stenting; New endoscopic colonic stent; Malignant colonic obstruction; Niti-S; WallFlex

Core tip: We developed a new self-expandable metallic stent, the Niti-S MD colonic stent (with a diameter of 22 mm), that can be deployed using the 9-Fr delivery system. The stent not only increased the radial force while maintaining the stent structure and low axial force but also permitted delivery through highly flexible-tipped smaller-caliber colonoscope with a working channel of 3.2 mm. In this study, the technical and clinical success rate of the Niti-S MD type was 100%, and its perforation rate was 0%. It was safe and effective for treating acute malignant colonic obstruction.

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INTRODUCTION

Colorectal cancer is ranked third in the United States. Acute colonic obstruction is one of the symptoms seen among patients with colorectal cancer, requiring urgent decompression. Endoscopic stenting with self-expandable metallic stents (SEMS) has become one of the standard treatments for symptomatic malignant colonic obstruction (MCO). SEMS insertion for palliative decompression of MCO was first reported by Dohmoto[1] in 1991; nowadays, SEMS offers an effective alternative option for palliative (PAL) surgery and act as a bridge-to-surgery (BTS)[2]. The incidence of adverse events of SEMS for MCO is considered low; however, the serious complication (such as perforation) -related mortality rate could increase to 50%[3].

Lee *et al*[3] reported the risk factors for perforation and proposed that the axial force, radial force, and shape of the stent, including those of the tip, can be factors for perforation. The WallFlex colonic stent (Enteral Colonic Uncovered Stent; Boston Scientific, Corp., Natick, MA, United States) and Niti-S D type colonic stent (Enteral Colonic Uncovered Stent; Taewoong Medical Co., Gimpo, South Korea) are widely used in Japan. The WallFlex stent is knitted in a spiral shape with a proximal flared end, whereas the Niti-S D type stent is hand-knitted in a net shape and does not have a flared proximal end. With its design and spiral knitting construction, the WallFlex stent has stronger axial force than the Niti-S D type stent, resulting in recoil of the WallFlex stent to a straight position after deployment. This may increase the risk of the stent-related perforation when compared with the Niti-S D type stent[4-6]. On the other hand, the Niti-S D type stent has lower radial force, resulting in weaker horizontal expansion of the radius of the stent to overcome tumor obstruction that can cause obstructive colitis and perforation.

Stents are deployed using a standard colonoscope, which can pose a challenge while overcoming sharp angles. Smaller caliber colonoscopes are designed for passive bending and easy maneuverability, facilitating scope advancement and cecal intubation where the standard colonoscope has failed[7]. A smaller-caliber colonoscope can be ideal for stent deployment, but the main drawback is its channel of 9.2 mm, that would only allow 9Fr delivery catheter (available only with stents of diameter 18 mm that have less radial force than 22 mm stents that require larger scope channels).

To overcome the above, we developed a new SEMS, the Niti-S MD colonic stent (with diameter of 22 mm), that can be deployed using a 9-Fr delivery system. Although this 22-mm Niti-S MD stent has stronger radial force than the conventional 18-mm Niti-S D type, it maintains a low axial force that facilitates maintenance of the shape of the stent when deployed.

This observational study aimed to evaluate the efficacy and safety of the newly developed Niti-S MD type colonic stent and to retrospectively compare it with conventional colonic stents.

MATERIALS AND METHODS

Study design and patients

This single-center retrospective observational study was conducted to evaluate the efficacy, safety, and feasibility of the newly developed Niti-S MD type colonic stent. Additionally, retrospective comparison was carried out with the conventional WallFlex and Niti-S D type colonic stents. Data were collected and analyzed from 105 consecutive patients (110 lesions; male/female, 58/47; average age, 73.5 years), who underwent endoscopic SEMS placement for MCO between November 2011 and December 2018 at the Kure Medical Center and Chugoku Cancer Center.

This study was carried out in accordance with the principles of the Declaration of Helsinki in compliance with good clinical practice and with local regulations. The nature of the procedure was explained, and informed consent for the procedure and data collection was obtained from all patients. The study was approved by the Institutional Review Board Ethics Committees of the National Hospital Organization Kure Medical Center and Chugoku Cancer Center.

The WallFlex colonic stent was used in 35 consecutive patients (37 lesions: Group W) between November 2011 and September 2013. In 2013, the Niti-S D type colonic stent became available in Japan and was used in 51 consecutive patients (53 lesions: Group N) between October 2013 and December 2017. We developed a new stent (Niti-S MD type) in 2018 and used it to treat 20 consecutive patients (20 lesions: Group MD) between January 2018 and December 2018. Data in all cases were analyzed.

Stent devices

The WallFlex stent is a SEMS made from knitted nitinol wire in a spiral shape with flared oral end (proximal side) and a loop anal end (distal end). Because of the spiral structure, the stent extends when pulled on the long axis. In addition, as the axial force is strong, the stent is easy to linearize. The WallFlex stent is available in three sizes (6 cm, 9 cm, and 12 cm) and two diameters (22 mm and 25 mm).

The Niti-S D type stent is a SEMS made from hand-knitted nitinol wire mesh that has neither the flare nor the loop end. Weak axial force enables it to adapt well even in the bent position. This stent is available in two diameters (18 mm and 22 mm) and four sizes (6 cm, 8 cm, 10 cm, and 12 cm).

The newly developed stent, Niti-S MD type, is a 22-mm diameter stent mounted onto a 9-Fr delivery system that maintains the shape and axial force of the Niti-S D type stent but provides additional expansion radial force. Since this stent can be inserted through a working channel, 3.2 mm in diameter, it allows the use of a smaller caliber colonoscope. It is available in four sizes (6 cm, 8 cm, 10 cm, and 12 cm) (Figure 1).

Criteria for colonic SEMS placement

The inclusion criteria for colonic SEMS placement were as follows: Patients presenting with acute colonic obstruction and radiological features (as observed by computed tomography) consistent with a carcinoma.

The exclusion criteria were as follows: Suspected bowel perforation, multiple sites of small bowel or colonic obstruction due to peritoneal dissemination, severe inflammatory changes around the tumor, and contraindication to endoscopic treatment.

Endoscopic procedure for SEMS insertion

Procedures were performed using CF-HQ290ZI (Olympus Optical Co., Tokyo, Japan),

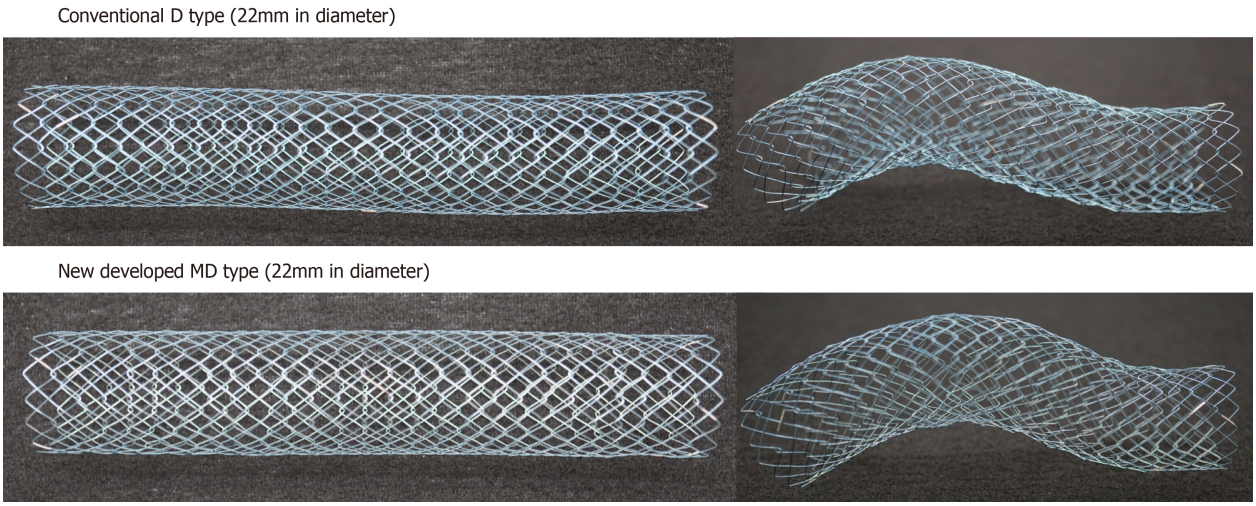

Figure 1 The newly developed Niti-S MD type stent (22 mm in diameter). The newly developed stent, "Niti-S MD type," has a diameter of 22 mm, that can be introduced into a 9-Fr delivery system while maintaining the Niti-S D type structure.

PCF-H290I (smaller-caliber; Olympus Optical Co., Tokyo, Japan), or PCF-Q260AZI (smaller-caliber; Olympus Optical Co., Tokyo, Japan) colonoscopes. A certified endoscopist experienced in stenting performed all the procedures. Combined endoscopic and fluoroscopic approaches were used to deploy the stent.

Glycerin enema was used to prepare and clean the colon distal to the stenosis to improve endoscopic views. After identifying the obstruction site, the length of the stricture was measured under fluoroscopy by a contrast agent using an endoscopic retrograde cholangiopancreatography catheter. The stricture site was marked with clips to identify the location prior to stent placement. The guidewire was then advanced through the stenosis to cover the entire length of the stenosis (using the scope method). After accurate positioning, the stent was deployed from the oral (proximal) to the anal (distal) side by releasing the sheath from the stent catheter. Proper positioning and expansion of the stent were confirmed both with radiological images and endoscopic views. In addition, abdominal radiographs were obtained at 24 and 48 h to rule out stent migration and poor or failed expansion.

Measurements of outcomes

The primary outcome was clinical success, defined as resolution of the obstructive symptoms confirmed by clinical and radiological assessment within 48 h. Clinical success was based on the ColoRectal Obstruction Scoring System (CROSS) score[8]. Adler *et al*[9,10] constructed this score to establish a scoring system similar to that used for assessing the condition of patients with malignant gastric outlet obstruction, and to assess oral intake and abdominal symptoms before and after treatment. CROSS is scored by oral intake ability and abdominal symptoms as follows: (1) Requiring continuous decompressive procedure, 0; (2) No oral intake, 1; (3) Liquid or enteral nutrient, 2; (4) Soft solids, low residue, 3; and (5) Full diet without symptoms of stricture, 4.

The secondary outcome was technical success, which was defined as accurate stent placement with adequate stricture coverage on the first attempt without any adverse events. Procedure-related adverse events recorded were as follows: Perforation, re-obstruction, stent migration, infection/fever, abdominal pain, and tenesmus. Adverse events that developed within and after 7 d, including the day of stenting, were defined as early and late adverse events. respectively[11].

Statistical analysis

Data are presented as mean ± SD or median (range). Fisher's exact test was used to compare qualitative variables, and Wilcoxon rank sum test was used to compare quantitative variables. A P value of < 0.05 was considered statistically significant. All statistical analyses were performed using JMP software (SAS Institute, Inc., Cary, NC, United States).

RESULTS

Patient flowchart

Figure 2 shows a flowchart of the patient allocation. The study participants included 105 patients (male/female: 58/47) with 110 lesions. No patients were excluded from the study during the study period. Among these, 35 patients (37 lesions) were treated with WallFlex colonic stents (Group W), 51 patients (53 lesions) with Niti-S D type colonic stents (Group N), and 19 patients (20 lesions) with the newly developed "Niti-S MD type" colonic stent (Group MD). In Group W, a SEMS was placed in 19 lesions (51.4%) as BTS and in 18 lesions (48.6%) as PAL; in Group N, a SEMS was placed in 32 lesions (60%) as BTS and in 21 lesions (40%) as PAL; and in Group MD, a SEMS was placed in 10 lesions (50%) as BTS and in 10 lesions (50%) as PAL.

Patient and tumor characteristics

Table 1 shows a summary of the clinical characteristics of the patients and tumors in this study. Among them, 18 men (48.6%) and 19 women (51.4%) comprised the Group W, while 28 men (52.8%) and 25 women (47.2%) comprised the Group N.

The mean patient age was 71.4 years ± 11.8 years in Group W (n = 37) and 74.3 years ± 13.6 years in Group N (n = 53). The stricture was located in the right colon (ileocecal, ascending colon, hepatic flexure, and transverse colon) in 8/37 (21.6%) of cases, in the left colon (rectosigmoid junction, sigmoid and descending colon, splenic flexure) in 27/37 (73.0%), and in the rectum in 2/37 (5.4%) in Group W *vs* 14/53 (26.4%), 38/53 (71.7%), and 1/53 (1.9%) in Group N, respectively. The stenosis was due to the primary tumor in 30/37 (81.1%) of cases and due to metastatic lesion in 7/37 (18.9%) in Group W *vs* 49/53 (92.5%) and 4/53 (7.5%) in Group N, respectively. The median length of the stenosis was 5.0 cm (range 2.0–13.0 cm) in Group W and 5.0 cm (range 2.0–11.0 cm) in Group N.

Group MD was composed of 15 (75%) men and 5 (25%) women, and the mean patient age was 73.7 years ± 9.6 years. The stricture was located in the right colon in 6/20 (30%), in the left colon in 10/20 (50%), and in the rectum in 4/20 (20%). The stenosis was due to the primary tumor in 13/20 (65%) of cases and 7/20 (35%) due to a metastatic lesion. The median length of the stenosis was 6.2 cm (range 2.5–11.5 cm).

Clinical outcomes in Group MD vs Groups W and N

Table 2 shows outcomes in each stent group and a summary of stent types with their sizes and diameters. Stents were placed successfully in all patients. The clinical success rate in Group MD was 100% (20/20). The average procedure time (± SD) was 31.3 min ± 11.2 min, and the mean CROSS score before/after stenting was 1.4 ± 0.9/3.8 ± 0.5.

The clinical success rate was 89.2% (33/37) in Group W and 96.2% (51/53) in Group N. The clinical success rate for BTS and PAL in Group W were 100% (19/19) and 77.8% (14/18), while 96.9% (31/32) and 95.2 % (20/21) in Group N, respectively. The average procedure times were 32.6 min ± 14.0 min and 33.6 min ± 23.7 min in Groups W and N, respectively. The mean CROSS score before/after stenting was 1.6 ± 1.2/3.8 ± 0.8 and 1.2 ± 1.0/3.8 ± 0.7 in Groups W and N, respectively. No significant difference in outcomes was found between Group MD and the other groups.

Adverse events in Group MD vs Groups W and N

Early and late adverse events are compared in Table 3. Despite the small number of cases, no adverse events occurred in the early or late stage in Group MD.

Early adverse events in Group W included abdominal pain (3/37, 8.1%, BTS 2/PAL 1), poor expansion (1/37, 2.7%, PAL 1), and fever (1/37, 2.7%, BTS 1), and late adverse events included stent-related perforations (4/36, 11.1%, PAL 4) and stent occlusion (1/36, 2.8%, PAL 1). On the contrary, the only early adverse event in Group N was perforation (2/53, 3.8%, BTS 1/PAL 1) caused by obstructive colitis, which was defined as "proximal ulceration related to unresolved colonic obstruction," and late adverse events included stent occlusion (2/51, 3.9%, PAL 2).

Although the proportion with each adverse event was not significantly different between Group MD and other groups, the stent-related perforation rate in Group W was significantly higher than that in Group N (P < 0.05), and perforation likely occurred because of obstructive colitis (due to unresolved obstruction) in Group N compared with Group W.

One case of BTS and one case of PAL are shown in Figures 3 and 4, respectively.

DISCUSSION

In our study, overall, endoscopic colorectal stenting was relatively safe and had a low incidence of complications, but the rate of stent-related perforation was significantly higher with the WallFlex stent than that with the Niti-S D type stent. We believe that this is likely caused by the lower axial force of the Niti-S D type stent. The newly

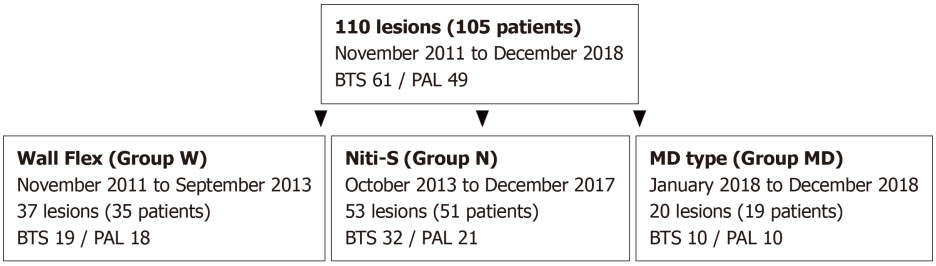

Figure 2 Flow chart of patient allocation. Of the 105 patients (110 lesions) who were enrolled in the study, 35 patients (37 lesions) were treated with WallFlex stents (Group W), 51 patients (53 lesions) with Niti-S stents (Group N), and 19 patients (20 lesions) with the newly developed Niti-S MD type stent (Group MD). BTS: Bridge-to-surgery; PAL: Palliative.

designed "Niti-S MD type" stent, with a 22 mm diameter, mounted to a 9-Fr delivery system not only allows increased radial force while maintaining the stent structure and low axial force but also permits delivery through highly flexible-tipped smaller-caliber colonoscope with a working channel of 3.2 mm. In this study, the technical and clinical success rate of the Niti-S MD type was 100%, and its perforation rate was 0%.

The real advantage of our newly designed "Niti-S MD type" stent is that it maintains the structure and low axial force of the conventional Niti-S D type, but its 22-mm diameter provides additional radial force. Another advantage is that it allows use of flexible smaller-caliber colonoscope as it has a 9-Fr catheter delivery system. It is the first 22-mm diameter colonic stent with 9-Fr delivery system that causes less damage on the intestinal wall and could reduce the risk of stent-related perforation. Cheung *et al*[12] reported the results of a multicenter randomized prospective trial of WallFlex and Niti-S D type stents. They reported a technical success rate of 100% in both groups, while the perforation rate with WallFlex was 3.6% (1/28) *vs* 0% (0/30) with the Niti-S D type in the PAL group. The clinical success rate was 86.0% and 90.1% in the WallFlex and Niti-S D type, respectively, and the perforation rate was 6.9% (3/43) and 4.5% (1/22) in the WallFlex and Niti-S D type in the BTS group, respectively.

In addition, in a multicenter prospective study (n = 513) in Japan, the technical success rates, clinical success rates, and perforation rates of WallFlex at 7 d were 97.9%, 95.5%, and 2.1%, respectively[10]. On the other hands in a multicenter study using Niti-S D type (n = 200) from the same group in Japan, the technical success rate at 7 d, the clinical success rate, and the perforation rates were 98.0%, 96.5%, and 0%, respectively[13], that considered to be lower than that of WallFlex. These perforation rates of the two studies were considerably lower than those in studies performed outside Japan. This probably occurred because the safety procedure was established and shared before the study, so the perforation rates during the procedure were low[10]. Therefore, this value was considered to represent the original rate of perforation by the stent itself, not including perforation during the procedure.

In our study, the technical success rate in both WallFlex and Niti-S stents was 100%, which was similar to the previously reported results[14-17]. The clinical success rates were 89.2% and 96.2% for WallFlex and Niti-S D type stents, respectively, which were also similar to previously reported data[14-17]. These previous studies, including our present study suggested that the Niti-S D type stent had a lower tendency to cause perforation than did the WallFlex stent. This raises the possibility of differences in stent characteristics: WallFlex stent has about three times stronger radial force and about two times stronger axial force than Niti-S D type stent[12], which may have influenced the perforation rate. Indeed, Yamao *et al*[18] proposed that perforation was more likely to occur when the gastroduodenal stent has higher axial force.

Our newly designed Niti-S MD type stent has another advantage, *i.e.*, it could be deployed with a smaller-caliber colonoscope using the through-the-scope technique, because it is the first 22-mm diameter colonic stent in the 9-Fr delivery system. In our previous study, we reported that risk factors related to prolonged and difficult SEMS placement were peritoneal carcinomatosis, CROSS score of 0, or extensive strictures[19]. These challenging situations could be overcome with higher scope operability by using a smaller-caliber colonoscope, such as a PCF colonoscope[7,20].

Despite the advantages of our newly designed Niti-S MD type stent, we encountered a few limitations. First, the visibility of the newly developed stent was not as good as that under fluoroscopy. Second, the Niti-S MD stent tended to be pulled toward the oral side during deployment; hence, determining the exact length of the stent compared with that of the WallFlex stent was difficult. Hence, the commonly used stent length was 6 cm for the WallFlex stent, whereas that for the

Table 1 Patients' demographics and clinical characteristics in each group

	Group W (*n* = 37)	Group N (*n* = 53)	Group MD (*n* = 20)	Total (*n* = 110)
Patients' characteristics				
Age (yr, mean ± SD)	71.4 ± 11.8	74.3 ± 13.6	73.7 ± 9.6	73.5 ± 12.5
Male/Female	18/19	28/25	15/5	61/49
PS score (mean ± SD)	1.6 ± 1.2	1.9 ± 1.2	2.3 ± 1.0	1.9 ± 1.2
Therapeutic intent				
BTS	19/37 (51.4%)	32/53 (60.4%)	10/20 (50%)	61/110 (55.5%)
PAL	18/37 (48.6%)	21/53 (39.6%)	10/20 (50%)	49/110 (44.5%)
Tumor characteristics				
Obstruction/tumor site				
Right colon	8/37 (21.6%)	14/53 (26.4%)	6/20 (30%)	28/110 (25.4%)
Left colon	27/37 (73.0%)	38/53 (71.7%)	10/20 (50%)	75/110 (68.2%)
Rectum	2/37 (5.4%)	1/53 (1.9%)	4/20 (20%)	7/110 (6.4%)
Etiology of colorectal obstruction				
Primary colorectal cancer	30/37 (81.1%)	49/53 (92.5%)	13/20 (65%)	92/110 (83.6%)
Metastatic lesion	7/37 (18.9%)	4/53 (7.5%)	7/20 (35%)	18/110 (16.4%)
Noncancerous stenosis	0/37 (0%)	0/53 (0%)	0/20 (0%)	0/110 (0%)
Stenosis length [cm, median (range)]	5.0 (2.0-13.0)	5.0 (2.0-11.0)	6.2 (2.5-11.5)	5.0 (2.0-13.0)

BTS: Bridge-to-surgery; PAL: Palliative.

Niti-S MD stent was 10 cm. Further improvement in design to overcome this weakness will improve the performance of this new stent.

This study has several limitations. First, this was a retrospective study from a single center. However, we included all cases to reduce the confounding factors. Second, as the Niti-S MD type stent was recently developed, the number of cases using this new stent was small. Thus, we think that a prospective study with a large number of cases is necessary to validate our results. Third, each stent was used sequentially. The WallFlex colonic stent was the first stent used from November 2011 to September 2013, followed by Niti-S D type stent since 2013 (became available since 2013 in Japan). We developed the new Niti-S MD type stent in 2018 and treated 19 consecutive patients from January 2018 to December 2018. This potentially introduces time bias, as the expertise of the operator may have improved over time. A good technical success rate of the WallFlex stent possibly negate any significant time bias. Lastly, we only focused on the important factors linked with perforation, such as axial and radial forces, and did not consider other factors, such as stenosis size and characteristics of stenosis.

In conclusion, our preliminary data suggested that the new "Niti-S MD type" stent with increased radial force while maintaining low axial force was feasible and safe with a lower perforation rate. Despite the small number of cases in our study, the clinical success in all cases with no perforation was promising; however, larger prospective studies and randomized comparison trials are required to completely evaluate and compare this new stent with other conventional colonic stents.

Table 2 Outcomes in each stent group, Group W, Group N, and Group MD

	Group W	Group N	Group MD	Total
Technical success rate	37/37 (100%)	53/53 (100%)	20/20 (100%)	110/110 (100%)
Stent length				
6 cm	24/37 (64.9%)	12/53 (22.6%)	3/20 (15%)	39/110 (35.5%)
8 cm	NA	17/53 (32.1%)	7/20 (35%)	24/110 (21.8%)
9 cm	11/37 (29.7%)	NA	NA	11/110 (10.0%)
10 cm	NA	18/53 (34.0%)	6/20 (30%)	24/110 (21.8%)
12 cm	2/37 (5.4%)	6/53 (11.3%)	4/20 (20%)	12/110 (10.9%)
Stent diameter				
18 mm	NA	6/53 (11.3%)	NA	6/110 (5.5%)
22 mm	30/37 (81.1%)	47/53 (88.7%)	20/20 (100%)	97/110 (88.2%)
25 mm	7/37 (18.9%)	NA	NA	7/110 (6.3%)
Procedure time (min, mean ± SD)	32.6 ± 14.0	33.6 ± 23.7	31.3 ± 11.2	33.0 ± 19.1
Clinical success rate	33/37 (89.2%)	51/53 (96.2%)	20/20 (100%)	104/110 (94.5%)
BTS	19/19 (100%)	31/32 (96.9%)	10/10 (100%)	60/61 (98.4%)
PAL	14/18 (77.8%)	20/21 (95.2%)	10/10 (100%)	44/49 (89.8%)
CROSS before stent placement (mean ± SD)	1.6 ± 1.3	1.2 ± 1.0	1.4 ± 0.9	1.4 ± 1.1
0	12/37 (32.5%)	10/53 (18.9%)	3/20 (15%)	25/110 (22.7%)
1	8/37 (21.6%)	32/53 (60.4%)	9/20 (45%)	49/110(44.6%)
2	3/37 (8.1%)	4/53 (7.5%)	5/20 (25%)	12/110 (10.9%)
3	13/37 (35.1%)	5/53 (9.4 %)	3/20 (15%)	21/110 (19.1%)
4	1/37 (2.7%)	2/53 (3.8%)	0/20 (0%)	3/110 (2.7%)
CROSS after stent placement (mean ± SD)	3.8 ± 0.8[a]	3.8 ± 0.7[a]	3.8 ± 0.5[a]	3.8 ± 0.7[a]
0	0/37 (0%)	0/53 (0%)	0/20 (0%)	0/110 (0%)
1	3/37 (8.1%)	2/53 (3.8%)	0/20 (0%)	5/110(4.6%)
2	0/37 (0%)	2/53 (3.8%)	1/20 (5.0%)	3/110 (2.7%)
3	0/37 (0%)	0/53 (0 %)	2/20 (10%)	2/110 (1.8%)
4	34/37 (91.9%)	49/53 (92.4%)	17/20 (85%)	110/110 (90.9%)

The CROSS score after stent placement was significantly higher than one before treatment,
[a]$P < 0.01$. BTS: Bridge-to-surgery; PAL: Palliative; CROSS: ColoRectal Obstruction Scoring System; NA: Not available.

Table 3 Early and late adverse events

	Group W	Group N	Group MD	Total
Early (≤ 7 d)				
Perforations	0/37 (0%)	2/53 (3.8%)[1]	0/20 (0%)	2/110 (1.8%)
Bleeding	0/37 (0%)	0/53 (0%)	0/20 (0%)	0/110 (0%)
Poor expansion	1/37 (2.7%)	0/53 (0%)	0/20 (0%)	1/110 (0.9%)
Abdominal pain	3/37 (8.1%)	0/53 (0%)	0/20 (0%)	3/110 (2.7%)
Stent occlusion	0/37 (0%)	0/53 (0%)	0/20 (0%)	0/110 (0%)
Fever	1/37 (2.7%)	0/53 (0%)	0/20 (0%)	1/110 (0.9%)
Late (> 7 d)				
Perforations	4/36 (11.1%)[a2]	0/51 (0%)[a]	0/20 (0%)	4/107 (3.7%)
Bleeding	0/36 (0%)	0/51 (0%)	0/20 (0%)	0/107 (0%)
Stent migration	0/36 (0%)	0/51 (0%)	0/20 (0%)	0/107 (0%)
Abdominal pain	0/36 (0%)	0/51 (0%)	0/20 (0%)	0/107 (0%)
Stent occlusion	1/36 (2.8%)	2/51 (3.9%)	0/20 (0%)	3/107 (2.8%)

[1]Perforation occurred due to obstructive colitis in all two cases;
[2]All four cases were stent-related perforation.
[a]$P < 0.05$.

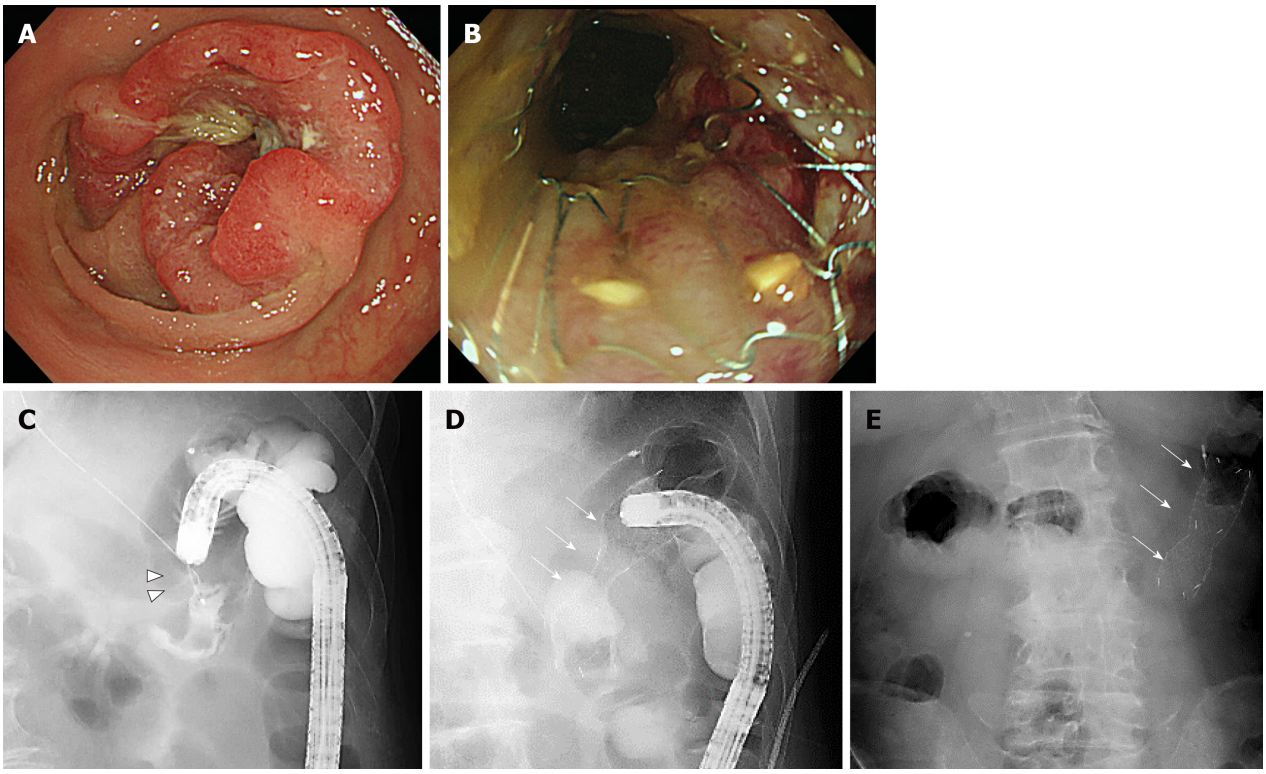

Figure 3 One of the bridge-to-surgery cases using the newly developed Niti-S MD type stent. A and C: The patient was an 83-year-old man with peritoneal type 2 advanced colorectal cancer (arrowhead) in the transverse colon; B and D: Using a smaller caliber colonoscope, we placed a 22 mm × 8 cm stent (arrow); E: Abdominal radiograph 2 d later shows firmly expanded stent successfully decompressing the acute obstruction. Tight stenosis is seen, and the enhanced expansible force of this stent enables successful decompression.

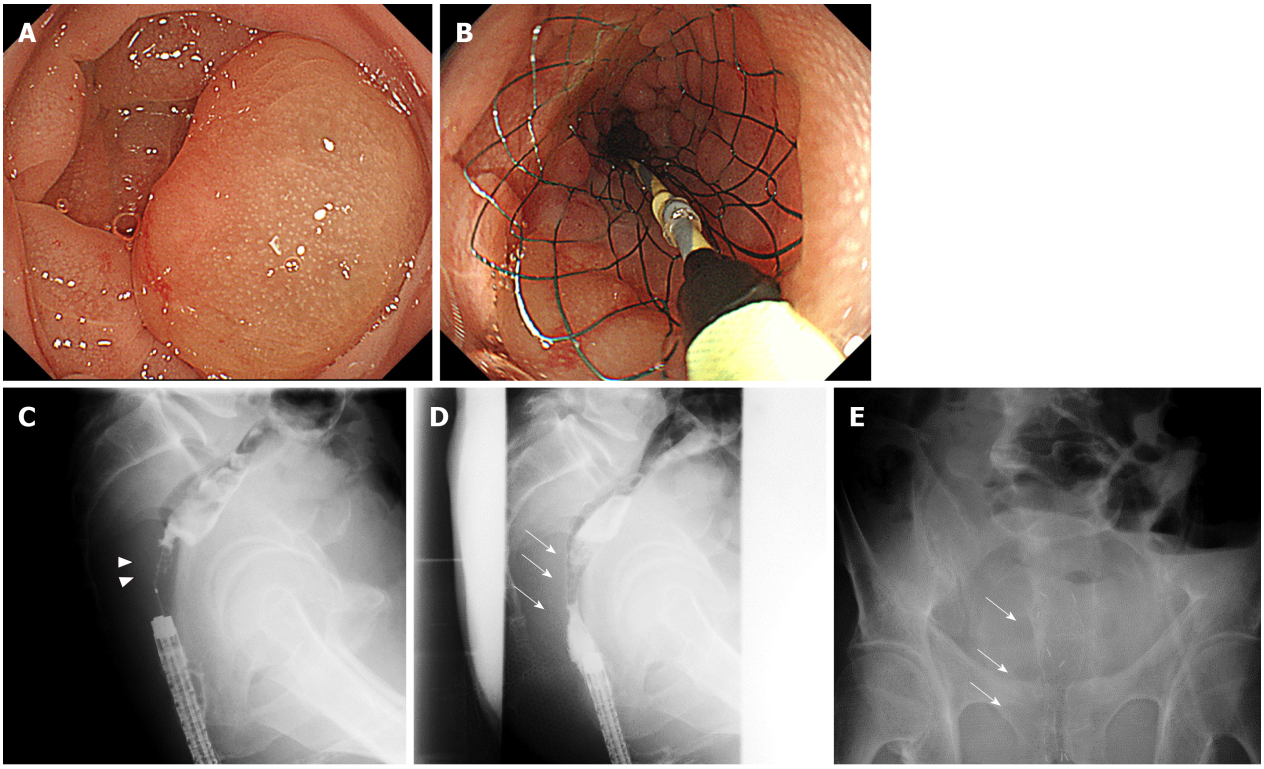

Figure 4 Palliative care using the newly developed Niti-S MD type colonic stent. A and C: The patient was a 65-year-old man who presented with obstructive lesion (arrowhead) in the rectum (Rb); B and D: The patient had rectal stenosis caused by peritoneal dissemination of gastric cancer. Using a smaller caliber colonoscope, we placed a 22 mm×8 cm stent (arrow) while paying attention not to cover the stent on the pectinate line; E: On the second day, the stent was fully expanded, decompressing the acute obstruction.

ARTICLE HIGHLIGHTS

Research background

The most serious adverse event of colonic stenting is perforation. The Niti-S D type stent could be ideal to reduce risk of perforation due to its structure with weaker axial force. Stents are deployed using a standard colonoscope, which can pose a challenge while overcoming sharp angles. Smaller caliber colonoscopes could be ideal for easy maneuverability, facilitating scope advancement and cecal intubation where the standard colonoscope has failed. The main drawback of using small caliber colonoscope is its small channel of 9.2 mm, that would only allow 9Fr delivery catheter available only with stents of diameter 18 mm that has less radial force to overcome obstruction. Stents with greater radial force are 22 mm that require larger channel standard colonoscope.

Research motivation

We would like to develop a new colonic stent that maintains the structure with low axial force of the conventional Niti-S D type and takes additional radial force with 22-mm diameter, but that requires 9Fr delivery system, hence can be deployed using smaller caliber colonoscope.

Research objectives

We evaluated the efficacy and safety of the newly developed "Niti-S MD type" colonic stent.

Research methods

This single-center retrospective observational study with endoscopic self-expandable metallic stents placed between November 2011 and December 2018, and we evaluated the short-term outcomes including success rates and adverse events.

Research results

The technical and clinical success rate of the Niti-S MD type was 100%, and its perforation rate was 0%.

Research conclusions

Our preliminary data suggested that the newly developed "Niti-S MD type" colonic stent was feasible and safe.

Research perspectives

The stent might have a potential to be an ideal one that offers high radial force and can be deployed with small caliber colonoscope. Larger prospective studies and randomized comparison trials are warranted to evaluate and compare this new stent with available conventional colonic stents.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Mammalian target of rapamycin inhibitors after post-transplant hepatocellular carcinoma recurrence: Is it too late?

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Abstract

BACKGROUND

Mammalian target of rapamycin (mTOR) inhibitors have been shown to reduce the risk of tumour recurrence after liver transplantation for hepatocellular carcinoma (HCC). However, their role in established post-transplant HCC recurrence is uncertain.

AIM

To investigate whether mTOR inhibitor offers a survival benefit in post-transplant HCC recurrence.

METHODS

A retrospective study of 143 patients who developed HCC recurrence after liver transplantation was performed. They were divided into 2 groups based on whether they had received mTOR inhibitor-based immunosuppression. The primary endpoint was post-recurrence survival.

RESULTS

Seventy-nine (55%) patients received an mTOR inhibitor-based immunosuppressive regime, while 64 (45%) patients did not. The mTOR inhibitor group had a lower number of recurrent tumours (2 *vs* 5, $P = 0.02$) and received more active treatments including radiotherapy (39 *vs* 22%, $P = 0.03$) and targeted therapy (59 *vs* 23%, $P < 0.001$). The median post-recurrence survival was 21.0 ± 4.1 mo in the mTOR inhibitor group and 11.2 ± 2.5 mo in the control group. Multivariate Cox regression analysis confirmed that mTOR inhibitor therapy was independently associated with improved post-recurrence survival ($P = 0.04$, OR = 0.482, 95%CI: 0.241-0.966). The number of recurrent tumours and use of other treatment modalities did not affect survival. No survival difference was observed between mTOR inhibitor monotherapy and combination therapy with calcineurin inhibitor.

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CONCLUSION
mTOR inhibitors prolonged survival after post-transplant HCC recurrence.

Key words: Mammalian target of rapamycin inhibitor; Hepatocellular carcinoma; Recurrence; Liver transplant; Survival; Outcomes

Core tip: Mammalian target of rapamycin (mTOR) inhibitors have been shown to reduce the risk of tumour recurrence after liver transplantation for hepatocellular carcinoma (HCC). However, their role in established post-transplant HCC recurrence is uncertain. A retrospective study of 143 patients who developed HCC recurrence after liver transplantation was performed. Seventy-nine (55%) patients received an mTOR inhibitor-based immunosuppressive regime, while 64 (45%) patients did not. The median post-recurrence survival was 21.0 ± 4.1 mo in the mTOR inhibitor group and 11.2 ± 2.5 mo in the control group. Multivariate Cox regression analysis confirmed that mTOR inhibitor therapy was independently associated with improved post-recurrence survival (P = 0.04, OR = 0.482, 95%CI: 0.241-0.966).

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INTRODUCTION

Calcineurin inhibitors (CNI) form the cornerstone of immunosuppressive therapy after liver transplantation. However, CNIs promote cancerous growth[1] and studies have demonstrated a dose-dependent relationship with tumour recurrence in patients transplanted for hepatocellular carcinoma (HCC)[2,3]. In contrast, mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, are suggested to have anti-tumour effects by suppressing angiogenesis[4] and cellular proliferation[5]. mTOR inhibitors have been given to patients engrafted for HCC with encouraging results. Their oncological benefits were supported by the findings in numerous retrospective[6-10] and prospective studies[11,12] showing a reduced risk of recurrence.

In theory, patients with established recurrence or at risk of recurrence *i.e.*, more advanced tumour at transplant benefit most from the oncological advantages offered by mTOR inhibitors. These patients are also candidates for mTOR inhibitor-based regimes in our centre. However, evidence supporting mTOR inhibitor therapy following HCC recurrence is limited. It is unknown whether mTOR inhibitors still confer survival benefits in this late course of the disease. Recommendations for mTOR inhibitors in this context are based on expert opinions[13]. To address this knowledge gap in the literature, the current study was undertaken to quantify survival following post-transplant HCC recurrence with regard to the administration of mTOR inhibitors.

MATERIALS AND METHODS

Patients

A retrospective study was conducted at Queen Mary Hospital, the University of Hong Kong, which is a tertiary referral centre and the only liver transplant centre in Hong Kong. Outpatient follow-up was arranged every 3 mo for patients transplanted for HCC, during which clinical examination and blood tests for liver function and alpha-fetoprotein (AFP) were performed. A contrast-enhanced computed tomography (CT) scan of the thorax and abdomen was performed at 6-month intervals. The diagnosis of recurrent HCC was primarily radiological. All consecutive patients diagnosed with recurrent HCC after liver transplantation between 2000 and 2019 were included in this study. The patients were divided into two groups based on whether they received an mTOR inhibitor (sirolimus or everolimus) after recurrence. Abnormal liver

function during follow-up was investigated with a CT scan and/or liver biopsy as appropriate. Clinical suspicion of acute rejection was confirmed by liver biopsy.

Treatment

Upon recurrence, immunosuppression was tapered to the lowest effective dose. Considerations were given to an mTOR-based regime, with or without a reduced dose of CNI (tacrolimus with trough level < 5 μg/L). The decision was individualized based on the patients' general status, liver function and tumour status. In this study, combination therapy was defined as patients receiving both mTOR inhibitor and CNI for more than 50% of the time.

Comprehensive staging was performed by dual-tracer positron emission tomography or a combination of contrast CT scan of the thorax and abdomen with a bone scan. Patients with disseminated recurrence were reviewed for targeted therapy *e.g*., sorafenib. Patients with oligo-recurrence *i.e*., recurrent disease limited in number and location were selected for loco-regional treatments including surgery, trans-arterial chemoembolization and radiotherapy[13]. The treatment decisions were discussed in a multidisciplinary tumour board among transplant surgeons, transplant hepatologists, radiation oncologists and medical oncologists.

Data collection, outcomes and statistics

Data were retrieved from a prospectively maintained database. Patients were compared in terms of pre-transplant status, characteristics of recurrence and the treatments they received. The characteristics of recurrence included pattern (intra-, extra-hepatic or both), location, tumour load (number and size) and serum level of AFP. The primary outcome was post-recurrence survival. Categorical variables were compared with the χ^2 test. Continuous variables are presented as median and interquartile range. Parametric and non-parametric variables were compared using the *t*-test and Mann-Whitney *U* test, respectively. Survival was assessed by the Kaplan-Meier method. Potential confounding factors were compared with univariate and multivariate Cox-regression analysis. Data were analyzed using the Statistical Package for the Social Sciences 16.0 (SPSS) for Windows (SPSS Inc., Chicago, IL, United States). Statistical significance was defined as a P value < 0.05.

RESULTS

During the study period from January 2000 to December 2019, 143 patients were diagnosed with post-transplant HCC recurrence and they formed the basis of this study. Of these patients, 59 (41%) received liver transplantation in our centre, while 84 (59%) underwent the procedure elsewhere. Following the diagnosis of recurrence, 79 (55%) patients received an mTOR inhibitor-based immunosuppressive regime, while 64 (45%) patients did not.

Pre-transplant characteristics

The pre-transplant characteristics were comparable between the two groups (Table 1). There was a male predominance and the subjects primarily had hepatitis B virus induced liver disease (95% and 89%, respectively). The number of salvage transplantations *i.e*., liver transplantation performed for recurrent HCC after primary liver resection was similar (38% *vs* 33%, P = 0.52). Tumour status at the time of transplant was comparable in terms of number of tumours (2 *vs* 2, P = 0.85), size of largest tumour (4.3 *vs* 4.0 cm, P = 0.68), and serum level of AFP (144 *vs* 111 ng/mL, P = 0.51). The proportion of patients compliant with Milan (27 *vs* 22%, P = 0.54) and UCSF criteria (33% *vs* 23%, P = 0.22) were similar.

Recurrence status and treatment

The recurrence status is summarized in Table 2. Recurrence occurred later in calendar years in the mTOR inhibitor group (7/2013 *vs* 3/2008, P < 0.001). However, the timing was similar in terms of age (58 *vs* 55, P = 0.06) and time from transplant (12 *vs* 12 mo, P = 0.73). The mTOR inhibitor group had a lower number of recurrent tumours (2 *vs* 5, P = 0.02). Otherwise the disease status upon recurrence was comparable in terms of numbers of involved organs (1 *vs* 1, P = 0.50) and size of largest tumour (2.0 *vs* 2.1 cm, P = 0.74). There were more bone recurrences in the mTOR inhibitor group (22 *vs* 9%, P = 0.049).

Fewer patients in the mTOR inhibitor group received supportive care (4% *vs* 36%, P < 0.001) and more active treatments were undertaken, including radiotherapy (39 *vs* 22%, P = 0.03) and targeted therapy (59 *vs* 23%, P < 0.001).

Immunosuppression after recurrence

Table 1 Baseline characteristics at the time of liver transplantation

	mTOR inhibitor (*n* = 79)	No mTOR inhibitor (*n* = 64)	*P* value
Age at transplant (years)	57 (50-62)	53 (46-59)	0.07
Gender (%M)	75 (95%)	57 (89%)	0.19
Etiology			0.28
Cryptogenic	1 (1%)	4 (6%)	
HBV	72 (91%)	59 (92%)	
HCV	4 (5%)	1 (2%)	
Alcoholic liver disease	3 (4%)	2 (3%)	
Primary/salvage transplant	49/30	43/21	0.52
Cadaveric/living related	53/26	47/17	0.41
Whole graft/partial graft	53/26	47/17	0.41
No. of tumours	2 (1-5)	2 (1-6)	0.85
Size of largest tumour (cm)	4.3 (2.9-6.6)	4.0 (2.5-6.5)	0.68
AFP (ng/mL)	144 (14-1388)	111 (19-817)	0.51
Within Milan criteria	21 (27%)	14 (22%)	0.54
Within UCSF criteria	26 (33%)	15 (23%)	0.22

AFP: Alpha-fetoprotein; HBV: Hepatitis B virus; HCV: Hepatitis C virus; mTOR: Mammalian target of rapamycin.

In the mTOR inhibitor group, 48 (61%) patients received sirolimus and 29 (37%) received everolimus. The remaining 2 patients (3%) were initially started on sirolimus but were subsequently converted to everolimus. The majority of them (80%, n = 63) were commenced on mTOR inhibitor after diagnosis of recurrence. Thirty-one of these patients (39%) were maintained on mTOR inhibitor only, while 48 (61%) received a combination of mTOR inhibitor and CNI. As a result, there was lower CNI usage (62 *vs* 97%, $P < 0.001$) and lower median tacrolimus levels (3.0 *vs* 5.2 μg/L, $P = 0.03$) in the mTOR inhibitor group.

Outcomes

The median follow-up time was 14.2 mo. Patients with an mTOR inhibitor included in the immunosuppressive regime survived significantly longer (21.0 ± 4.1 *vs* 11.2 ± 2.5 mo, $P = 0.04$) (Figure 1). There was no difference in survival outcomes between patients receiving sirolimus and everolimus (19.1 ± 5.7 *vs* 21.0 ± 4.4 mo, $P = 0.88$) (Figure 2). Single agent immunosuppression did not affect survival (single *vs* combination: 26.3 ± 8.0 *vs* 17.9 ± 5.3 mo, $P = 0.59$) (Figure 3) or rejection rate (0 *vs* 4.2%, $P = 0.25$).

As shown in Table 3, multivariate analysis confirmed that immunosuppression with mTOR inhibitor was independently associated with improved survival from recurrence ($P = 0.04$, OR = 0.482). Early recurrence ($P = 0.001$, OR = 0.977), liver recurrence ($P = 0.01$, OR = 1.92), larger tumour ($P = 0.02$, OR = 1.13), and higher AFP level ($P = 0.02$, OR = 1.00) were predictors of poor survival. The trough level of tacrolimus ($P = 0.16$), date of recurrence ($P = 0.79$) and number of recurrent tumours ($P = 0.33$) did not predict survival.

DISCUSSION

The results from our study suggested that incorporation of an mTOR inhibitor into the immunosuppressive regime of liver transplant recipients with recurrent HCC was associated with improved survival after recurrence (median survival 21.0 ± 4.1 *vs* 11.2 ± 2.5 mo, $P = 0.04$).

In this cohort, several differences in recurrence status were highlighted between both arms. Firstly, recurrence in the mTOR inhibitor group occurred later in calendar years (7/2013 *vs* 3/2008, $P < 0.001$). mTOR inhibitor was first administered in 2004 in our series and was only considered for patients from that time onwards. There was a fundamental time effect while improvements in medical and surgical treatment contributed to better survival outcomes[14-19]. Indeed, more patients in the mTOR inhibitor group received targeted therapy *e.g.*, sorafenib (59 *vs* 23%, $P < 0.001$) and radiotherapy (39 *vs* 22%, $P = 0.03$). Stereotactic body radiotherapy was applied for

Table 2 Recurrence characteristics

	mTOR inhibitor (*n* = 79)	No mTOR inhibitor (*n* = 64)	*P* value
Date of recurrence	7/2013	3/2008	< 0.001
Age at recurrence (years)	58 (52-64)	55 (46-61)	0.06
Time from transplant (mo)	12 (6-24)	12 (5-25)	0.73
Number of tumours	2 (1-5)	5 (1-9)	0.02
Size of largest tumour (cm)	2.0 (1.1-3.2)	2.1 (1.1-3.9)	0.74
Number of organs involved	1 (1-1)	1 (1-2)	0.50
Site of recurrence			
Liver	34 (43%)	28 (44%)	0.93
Lung	36 (46%)	35 (55%)	0.33
Bone	17 (22%)	6 (9%)	0.049
Peritoneum	4 (5%)	8 (13%)	0.11
Adrenal	5 (6%)	6 (9%)	0.50
Lymph node	6 (8%)	4 (6%)	0.75
AFP upon recurrence (ng/mL)	14 (4-139)	32 (6-855)	0.19
Immunosuppression			
Calcineurin Inhibitor	49 (62%)	62 (97%)	< 0.001
Tacrolimus level	3.0 (0-4.9)	5.2 (3.7-6.1)	0.03
Treatment			
Surgery	22 (28%)	11 (17%)	0.13
RFA	7 (9%)	6 (9%)	0.89
TACE	19 (24%)	10 (16%)	0.23
Radiotherapy	31 (39%)	14 (22%)	0.03
Targeted therapy	47 (59%)	15 (23%)	< 0.001
Immunotherapy	2 (3%)	0 (0%)	0.18
Supportive	3 (4%)	23 (36%)	< 0.001

AFP: Alpha-fetoprotein; RFA: Radiofrequency ablation; TACE: Trans-arterial chemoembolization; mTOR: Mammalian target of rapamycin.

patients with limited intrahepatic recurrence for local control.

Secondly, the mTOR inhibitor group had earlier disease with fewer tumours (2 *vs* 5, $P = 0.02$). This probably resulted due to selection bias. Clinicians could have avoided aggressive therapy in patients with widespread disease due to fear of futility. This also explained why more patients in the control group received supportive treatment (4 *vs* 36%, $P < 0.001$). Last but not least, mTOR inhibitors were used with reduced or spared CNI, which could have contributed to their protective effect[2,3]. Therefore, survival associations were estimated using multivariate Cox regression taking into account these potential confounders. Our results showed that mTOR inhibitor maintained a robust association with improved survival. Data suggested that the oncological advantages of mTOR inhibitors in patients with post-transplant HCC recurrence were independent of the CNI sparing effect. The other clinical differences, including date of recurrence, number of recurrent tumours, use of targeted therapy and decision for supportive treatment, did not contribute to the disparity in outcomes.

The prognosis after post-transplant HCC is dismal. The median survival after recurrence ranges from 8 to 19 mo[19-21]. Not surprisingly, most studies on mTOR inhibitors have focused on prevention rather than control of recurrence. The protective effects against recurrence have been illustrated by numerous retrospective[6-10] and prospective studies[11,12]. Interestingly, Geissler *et al*[12] pointed out from the SiLVER trial that survival benefits due to sirolimus were confined to low risk patients, as defined by those receiving a primary transplant for tumours within the Milan criteria[22]. Sirolimus was unable to alter the imminent disease course in patients with more advanced tumours. Along this line, the efficacy of mTOR inhibitor in established recurrence was questioned. This is the first report in the literature directed at this question. Apart from confirming the survival benefits, we reported a median post-recurrence survival of 21 mo associated with mTOR inhibitors. We did not manage all post-transplant HCC recurrences with palliative intent. We adapted the concept of oligo-recurrence[13,23], in which patients with recurrent disease limited in

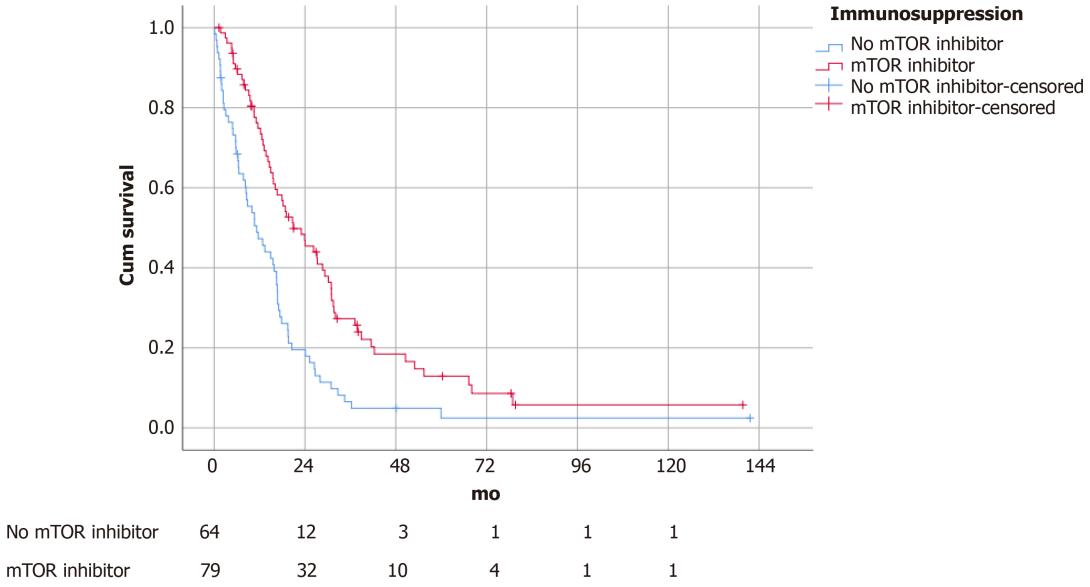

Figure 1 Survival of patients with mammalian target of rapamycin inhibitor *vs* no mammalian target of rapamycin inhibitor (survival 21.0 ± 4.1 *vs* 11.2 ± 2.5 mo, *P* = 0.04). mTOR: Mammalian target of rapamycin.

number and location were given the therapeutic opportunity of cure with a combination of systemic (including mTOR blockade) and loco-regional therapy. Twenty-seven patients (35%) in the study arm received curative treatment. The 3-year post-recurrence survival reached 27.1% in the entire mTOR inhibitor group. The results in this study indicate that long-term survival is not impossible and reinforces our treatment strategy.

Another consideration is whether mTOR inhibitor monotherapy offers superior survival outcomes over combination with CNI. Results from the SiLVER study revealed that patients receiving sirolimus monotherapy had fewer recurrences than those receiving combination therapy. The major concern with the CNI sparing regime is the risk of acute rejection. A previous study showed that mTOR inhibitor monotherapy was associated with a significantly higher rejection rate despite combination with CNI up to 4 mo after transplant[24]. Rejection might become less of a problem at the time of recurrence (median time from transplant 12 mo). Our study results were produced with a case mix of monotherapy and combination therapy. Two episodes of biopsy proven acute rejection occurred in the combination therapy group and none occurred in the monotherapy group. However, we did not perform protocol biopsy and mild episodes of rejection were not studied. Given the low incidence of acute rejection, the current study would be underpowered to detect any differences. The sample size might well be insufficient to study any differences in survival. We can not provide any recommendations regarding monotherapy versus combination therapy.

The current study was limited by its retrospective nature. Selection bias was inevitable. The non-mTOR inhibitor group had modestly more advanced disease. The performance status of our patients was not quantified in our pre-existing database. Patients with inferior performance status could be poorer candidates for mTOR inhibitor therapy due to potential side effects. The decision to administer mTOR inhibitor was primarily based on clinical judgement and was not protocol driven. Our data could not provide recommendations for patient selection. Results from previous studies showed that the mTOR pathway was not universally upregulated in all patients transplanted for HCC[25,26]. Whether a subgroup of patients benefit more from mTOR blockade remains to be answered by future studies. In summary, the current study adds to the literature confirming the clear survival benefits of mTOR inhibitor-based immunosuppression, and provides a foundation for this therapy in post-transplant HCC recurrence. It is not too late to offer mTOR blockade following the development of recurrence.

Table 3 Survival analysis

	Univariate		Multivariate	
	***P* value**	**OR (95%CI)**	***P* value**	**OR (95%CI)**
Date of recurrence	0.006	1.00 (1.00-1.00)	0.79	
Age at recurrence (years)	0.93			
Time from transplant	< 0.001	0.977 (0.966-0.988)	0.001	0.977 (0.963-0.991)
Number of tumours	< 0.001	1.01 (1.01-1.02)	0.33	
Size of largest tumour	0.02	1.11 (1.02-1.20)	0.02	1.13 (1.02-1.24)
Number of organs involved	0.01	1.14 (1.11-1.89)	0.27	
Site of recurrence				
Liver	0.01	1.62 (1.13-2.31)	0.01	1.92 (1.14-3.25)
Lung	0.43			
Bone	0.17			
Peritoneal	0.46			
Adrenal	0.52			
Lymph node	0.49			
AFP upon recurrence	0.02	1.00 (1.00-1.00)	0.02	1.00 (1.00-1.00)
Immunosuppression after recurrence				
mTOR inhibitor	< 0.001	0.485 (0.339-0.695)	0.04	0.482 (0.241-0.966)
Calcineurin Inhibitor	0.07			
Tacrolimus trough (μg/L)	0.002	1.13 (1.04-1.22)	0.16	
Treatment				
Surgery	< 0.001	0.380 (0.240-0.601)	0.22	
RFA	0.16			
TACE	0.32			
Radiotherapy	0.90			
Targeted therapy	0.97			
Immunotherapy	0.80			
Supportive	< 0.001	2.34 (1.49-3.67)	0.73	

AFP: Alpha-fetoprotein; RFA: Radiofrequency ablation; TACE: Trans-arterial chemoembolization; mTOR: Mammalian target of rapamycin.

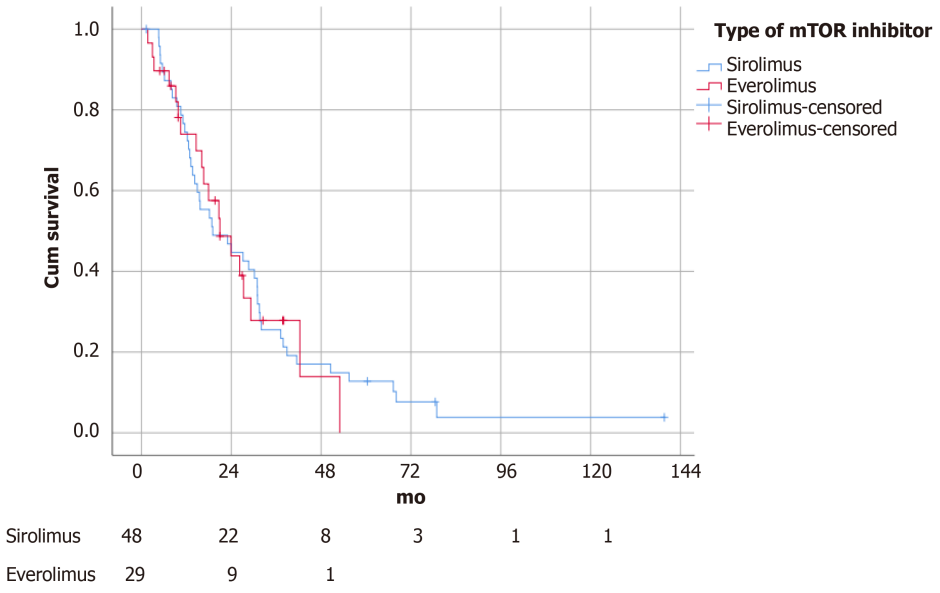

Figure 2 Survival of patients stratified by sirolimus *vs* everolimus (*P* = 0.88). mTOR: Mammalian target of rapamycin.

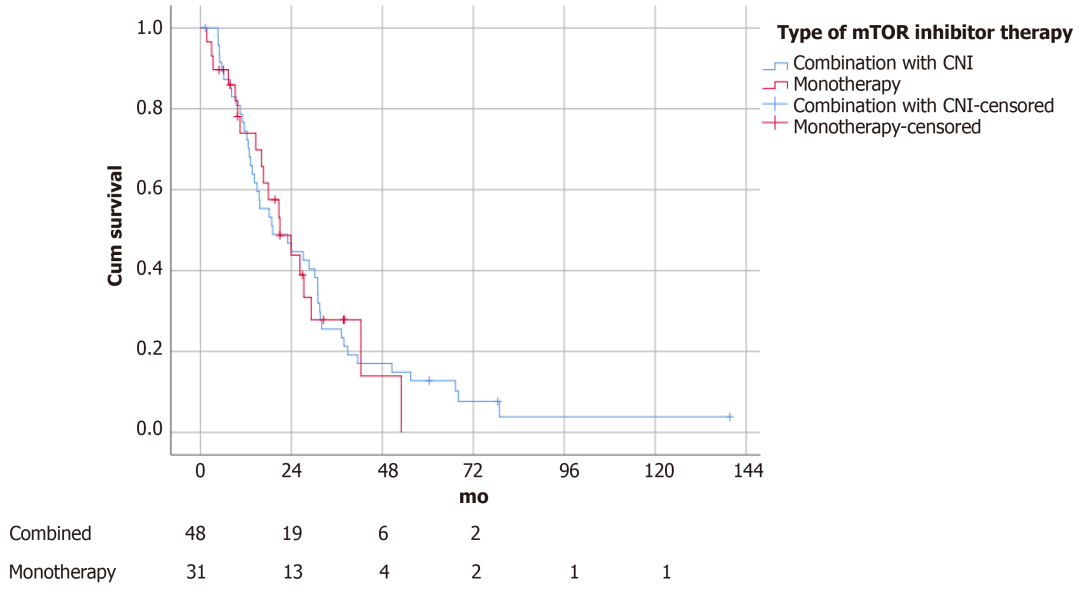

Figure 3 Survival of patients stratified by mammalian target of rapamycin inhibitor monotherapy *vs* combination therapy with calcineurin inhibitor (*P* = 0.59). mTOR: Mammalian target of rapamycin.

ARTICLE HIGHLIGHTS

Research background

Mammalian target of rapamycin (mTOR) inhibitors have been shown to reduce the risk of tumour recurrence after liver transplantation for hepatocellular carcinoma (HCC). However, their role in established post-transplant HCC recurrence is uncertain.

Research motivation

It is unknown whether mTOR inhibitor still confers survival benefits following HCC recurrence. Recommendations for mTOR inhibitor under this context are based on expert opinions. To address this knowledge gap in the literature, the current study was undertaken to quantify survival following post-transplant HCC recurrence with regard to the administration of mTOR inhibitors.

Research objectives

The objective was to ascertain any survival benefits conferred by mTOR inhibitors following HCC recurrence after liver transplantation.

Research methods

A retrospective study of 143 patients who developed HCC recurrence after liver transplantation was performed. The patients were divided into 2 groups based on whether they had received mTOR inhibitor-based immunosuppression. The primary endpoint was post-recurrence survival.

Research results

Seventy-nine (55%) patients received an mTOR inhibitor-based immunosuppressive regime, while 64 (45%) patients did not. The mTOR inhibitor group had a lower number of recurrent tumours (2 *vs* 5, $P = 0.02$) and received more active treatments including radiotherapy (39 *vs* 22%, $P = 0.03$) and targeted therapy (59 *vs* 23%, $P < 0.001$). The median post-recurrence survival was 21.0 ± 4.1 mo in the mTOR inhibitor group and 11.2 ± 2.5 mo in the control group. Multivariate Cox regression analysis confirmed that mTOR inhibitor therapy was independently associated with improved post-recurrence survival ($P = 0.04$, OR 0.482, 95%CI: 0.241-0.966). The number of recurrent tumours and use of other treatment modalities did not affect survival. There were no survival differences between patients treated with mTOR inhibitor monotherapy and combination therapy with calcineurin inhibitor.

Research conclusions

mTOR inhibitors prolonged survival after post-transplant HCC recurrence.

Research perspectives

The role of mTOR inhibitor therapy in post-transplant HCC recurrences should be confirmed with further prospective randomized studies. A further area of study should include patient selection for mTOR inhibitor treatment following HCC recurrence.

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ORIGINAL ARTICLE

Retrospective Study

Contemporary indications for and outcomes of hepatic resection for neuroendocrine liver metastases

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Abstract

BACKGROUND

Although surgical resection is associated with the best long-term outcomes for neuroendocrine liver metastases (NELM), the current indications for and outcomes of surgery for NELM from a population perspective are not well understood.

AIM

To determine the current indications for and outcomes of liver resection (LR) for NELM using a population-based cohort.

METHODS

A retrospective review of the 2014-2017 American College of Surgeons National Surgical Quality Improvement Program and targeted hepatectomy databases was performed to identify patients who underwent LR for NELM. Perioperative characteristics and 30-d morbidity and mortality were analyzed.

RESULTS

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Among 669 patients who underwent LR for NELM, the median age was 60 (interquartile range: 51-67) and 51% were male. While the number of metastases resected ranged from 1 to 9, the most common (45%) number of tumors resected was one. The majority (68%) of patients had a largest tumor size of < 5 cm. Most patients underwent partial hepatectomy (71%) while fewer underwent a right or left hepatectomy or trisectionectomy. The majority of operations were open (82%) versus laparoscopic (17%) or robotic (1%). In addition, 30% of patients underwent intraoperative ablation while 45% had another concomitant operation including cholecystectomy (28.8%), bowel resection (20.2%), or partial pancreatectomy (3.4%). Overall 30-d morbidity and mortality was 29% and 1.3%, respectively. On multivariate analysis, American Society of Anesthesiologists class ≥ 3 [odds ratios (OR), OR = 2.089, 95% confidence intervals (CI): 1.197-3.645], open approach (OR = 1.867, 95%CI: 1.148-3.036), right hepatectomy (OR = 1.618, 95%CI: 1.014-2.582), and prolonged operative time of > 230 min (OR = 1.731, 95%CI: 1.168-2.565) were associated with higher 30-d morbidity while intraoperative ablation and concomitant procedures were not.

CONCLUSION
LR for NELM was performed with relatively low postoperative morbidity and mortality. Concomitant procedures performed at the time of LR did not increase morbidity.

Key words: Carcinoid; Neuroendocrine tumor; Primary tumor resection; Intraoperative ablation; Cholecystectomy; Small bowel resection

Core tip: Surgical resection of neuroendocrine liver metastases is associated with the best long-term outcomes, however the current indications for and outcomes of surgery are not well understood. In this study, we performed a retrospective review of the 2014-2017 American College of Surgeons National Surgical Quality Improvement Program to identify 669 patients who underwent liver resection to define characteristics associated with increased 30-d postoperative morbidity and mortality. Overall morbidity and mortality were relatively low at 29% and 1.3% respectively. Factors associated with increased 30-d morbidity included open and prolonged cases (> 230 min), right hepatectomy, and American Society of Anesthesiologists class ≥ 3 while concomitant procedures including intraoperative ablation did not influence morbidity.

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INTRODUCTION

Neuroendocrine tumors (NET) are a heterogeneous group of neoplasms that can occur anywhere in the body but commonly arise from the gastrointestinal tract. While relatively rare, the incidence and prevalence of NETs are steadily increasing, at least in part due to improved imaging and diagnostic techniques[1,2]. Despite their low grade nature, a substantial proportion (60%-80%) of well-differentiated NETs are diagnosed with or will develop neuroendocrine liver metastases (NELM), which is one of the strongest prognostic factors among patients with NETs[3]. For example, the 5-year overall survival of patients with untreated NELM range from 13% to 54%, compared with 61% to 79% among individuals who undergo treatment[4-8].

Multiple treatments exist for patients with NELM including surgical resection, ablative techniques, transarterial therapies, somatostatin analogs, cytotoxic chemotherapy, targeted therapies, and peptide receptor radionuclide therapy[4]. Other novel systemic and targeted therapies are rapidly emerging[9,10]. Despite the absence of level I evidence, surgical resection is associated with the best long-term outcomes

based on retrospective cohort studies and meta-analyses[6,11,12]. Indeed, even cytoreductive surgery (*i.e.*, surgical debulking) of NELM has been associated with improved overall survival if residual disease less than 10%-30% can be achieved[5,13-15]. Based on these data, surgical resection of NELM has been recommended as the preferred initial approach, when feasible, by the European Neuroendocrine Tumors Society and North American Neuroendocrine Tumors Society[16,17].

Previous studies evaluating the short-term outcomes of surgery for NELM have frequently been limited by their retrospective, single-institution nature[18-22]. Other more recent multi-institutional studies have been limited to high-volume institutions and conducted over long study periods[6,14,23]. Thus, there is a need for an evaluation of contemporary practice patterns and outcomes from a population-based perspective. Such information would inform patient selection and facilitate patient education and the informed consent process. Therefore, we utilized the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) targeted hepatectomy database to analyze contemporary characteristics of patients with NELM who underwent liver resection (LR) in the United States and evaluate factors associated with postoperative morbidity and mortality.

MATERIALS AND METHODS

Data acquisition and study population

The ACS-NSQIP data set is a national validated and risk adjusted outcomes based database that includes demographic, clinical, perioperative, and 30-d postoperative details of patients undergoing surgery from 600 eligible hospitals across the United States. The ACS-NSQIP uses a systemic sampling process to ensure that each case has an equal chance of selection and it is frequently monitored to minimize sample bias. A retrospective review of the 2014-2017 ACS-NSQIP and targeted hepatectomy databases were performed and patients were matched based on case ID numbers. All adult patients undergoing LR were identified using Current Procedural Terminology codes 47120, 47122, 47125, and 47130.

Study variables and outcomes

Independent variables included demographic, preoperative health status, relevant comorbidities, operative, and postoperative outcomes. Demographics included age and gender. Preoperative health included American Society of Anesthesiologists (ASA) classification, body mass index, weight loss within 6 mo from surgery, smoking, chronic steroid use, preoperative sepsis (systemic inflammatory response syndrome or septic shock) and preoperative transfusion. Comorbidities included diabetes mellitus, chronic obstructive pulmonary disease, hypertension requiring medications, bleeding disorders, congestive heart failure. Targeted hepatectomy variables included neoadjuvant therapy within 90 d of surgery, ascites, viral hepatitis, and pre-operative biliary stent placement. Operative variables consisted of operative approach (open, laparoscopic, robotic), type of resection (trisegmentectomy, total right or left hemihepatectomy, or partial hepatectomy), concomitant procedures (cholecystectomy, intestinal resection, partial pancreatectomy), size of metastatic lesion (< 2, 2-5, or > 5 cm) number of metastatic lesions (1-2, 3-5, or > 5), number of concurrent partial hepatectomies (0, 1-5, 6-9, or > 10), liver texture (normal, congested, cirrhotic or fatty), operative time, pringle maneuver during resection, concomitant intraoperative ablation (IA), and biliary reconstruction.

Overall morbidity included each of the following within 30 d from the date of surgery: Superficial, deep and organ/space surgical site infection, sepsis, respiratory complications including pneumonia or reintubation, pulmonary embolism, deep vein thrombosis, myocardial infarct, cardiac arrest, stroke, renal complications such as renal insufficiency or urinary tract infection, hemorrhage requiring at least 4 U of packed red blood cells, bile leak, liver intervention post hepatectomy and postoperative liver failure. Perioperative mortality was also measured and defined as death within 30 d after LR. Length of stay, discharge disposition, 30-d readmission and reoperation were also among the postoperative measures assessed.

Statistical analysis

Descriptive statistics were reported as percentages of the total number of patients in the study. Univariate and multivariate analyses were used to identify factors associated with the development of overall morbidity and mortality within 30 d of surgery. Logistic regression analysis was used for univariate analysis. Stepwise logistic regression analysis was used for multivariable analysis and included all non-collinear variables. Results are reported as odds ratios (OR) and 95% confidence

intervals (CI). Analyses were performed using SAS 9.2 (SAS Institute, Inc., Cary, NC, United States). *P* values < 0.05 were considered statistically significant. All statistics were performed by an experienced biostatistician.

RESULTS

Patient characteristics

Between 2014-2017, 669 patients were identified within the ACS-NSQIP database who underwent LR for NELM. Complete demographic and clinicopathologic criteria of the cohort are listed in Table 1. The median age was 60 [interquartile range (IQR): 51-67], 51% were male and the mean body mass index was 27.4 (IQR: 24-32). Most patients underwent partial hepatectomy (71%) while fewer underwent hemihepatectomy (23%) or trisegmentectomy (6%). The majority of operations were open (82%); fewer were laparoscopic (17%) or robotic (1%). The mean number of lesions resected was 3.8 (range 1-9) and the most common size of the largest tumor was 2-5 cm (45%) (Figure 1A and B). Among all patients, 30.6% underwent concomitant IA in conjunction with a LR. In addition, 45.4% of patients underwent a combined resection in addition to the LR. The most common concomitant procedure was a cholecystectomy (28.8%), followed by intestinal resection (20.2%) and pancreatectomy (3.4%) (Figure 1C).

Perioperative outcomes

Table 2 reports the postoperative outcomes of patients undergoing resection of NELM. Median operative time was 232 min (IQR: 179-297) and the mean length of stay was 6 (IQR: 4-8) d. The overall 30-d complication rate was 29% with the most common perioperative complications being perioperative transfusion (15.5%), intraabdominal infection (7.3%), bile leakage (5.9%), sepsis (5.6%), surgical site infection (3.5%), reoperation (3.1%), pneumonia (2.9%), liver failure (2.6%), and pulmonary embolism (2%). Of note, serious adverse events such as stroke, cardiac arrest, and myocardial infarction occurred in less than 1% of all patients undergoing resection for NELM. Postoperative mortality occurred in 1.3%. The vast majority (95%) of patients were able to be discharged home and readmission was required in 11.2% of the patients.

Predictors of postoperative morbidity

Factors associated with 30-d morbidity on univariate analysis are reported in Table 3. ASA class of ≥ 3 (OR = 2.418, 95%CI: 1.422-4.113, *P* = 0.0011), open approach (OR = 1.943, 95%CI: 1.218-3.102, *P* = 0.0053), right, left or trisection hepatectomy (OR = 1.660, 95%CI 1.169-2.355, *P* = 0.0046), and operative time (> 230 min, OR = 2.403, 95%CI: 1.407-2.968, *P* = 0.0002) were all associated with increased morbidity while IA was associated with a decrease in perioperative morbidity (OR = 0.686, 95%CI: 0.476-0.988, *P* = 0.0431). Interestingly, the use of concomitant procedures (including bowel resections, cholecystectomy, or pancreatectomy), as well as the size or number of tumors were not associated with postoperative morbidity.

On multivariable logistic regression, ASA class of ≥ 3 (OR = 2.089, 95%CI: 1.197-3.645, *P* = 0.0095), open approach (OR = 1.867, 95%CI: 1.148-3.036, *P* = 0.0118), right, left or trisegmental hepatectomy (OR = 1.618, 95%CI: 1.014-2.582, *P* = 0.0437), and operative time > 230 min (OR = 1.731, 95%CI: 1.168-2.565, *P* = 0.0062) were independently associated with increased morbidity while normal liver texture was protective of overall morbidity (OR = 0.641, 95%CI: 0.433-0.950, *P* = 0.0266) (Table 4).

DISCUSSION

The incidence of NETs is increasing worldwide and a majority of patients will present with metastatic disease in their liver[1]. NELM is a strong negative prognostic factor for survival and is associated with significant reductions in patient quality of life[24]. While several systemic and liver-directed therapies are available, surgical resection is typically recommended when feasible[25]. In this paper, we used a contemporary, population-based, prospective database to define the characteristics and outcomes of patients undergoing surgery for NELM in the United States. These results highlight several important findings. First, the majority of operations are being performed for small tumors in the setting of multifocal disease and typically are minor resections. Second, a significant proportion of cases are being performed concomitant with another operation, either liver IA, cholecystectomy, or (presumably) primary tumor resection. Finally, modern surgery for NELM can be performed with relatively minimal postoperative morbidity (29%) and mortality (1.3%). These results are critical

Table 1 Demographic, clinical, and operative characteristics of patients with neuroendocrine liver metastases undergoing resection

	NELM (*n* = 669)
Median age in years, *n* (IQR)	60 (51-67)
Male gender, *n* (%)	341 (51)
ASA classification, *n* (%)	
I	2 (0.3)
II	143 (21)
III	459 (69)
IV	61 (9)
Median BMI (kg/m^2), *n* (IQR)	27.4 (24-32)
Comorbidities/preoperative	
> 10% loss body weight in last 6 mo, *n* (%)	30 (4.4)
Diabetes mellitus with oral agents or insulin, *n* (%)	115 (17)
Current smoker within one yr, *n* (%)	79 (12)
Severe chronic obstructive pulmonary disease, *n* (%)	9 (0.3)
Congestive heart failure in 30 d before surgery, *n* (%)	5 (0.7)
Hypertension requiring medications, *n* (%)	326 (49)
Viral hepatitis, *n* (%)	13 (1.9)
Preoperative biliary stent, *n* (%)	13 (1.9)
Ascites within 30 d, *n* (%)	3 (0.4)
Preoperative sepsis, *n* (%)	2 (0.3)
Steroid use for a chronic condition, *n* (%)	20 (3)
Bleeding disorders, *n* (%)	18 (2.6)
Preoperative transfusion, *n* (%)	3 (0.4)
Neoadjuvant therapy, *n* (%)	119 (17.7)
Patients with concomitant procedure (%)	304 (45.4)
Total number of cholecystectomy	193 (28.8)
Total number of small/large bowel resection	135 (20.2)
Total number of partial pancreatectomy	23 (3.4)
Operative approach, *n* (%)	
Open	546 (82)
Laparoscopic	113 (17)
Robotic	10 (1)
Liver resection type, *n* (%)	
Trisegmentectomy	42 (6)
Right hepatectomy	99 (15)
Left hepatectomy	52 (8)
Partial lobectomy	476 (71)
Size of metastatic lesion, *n* (%)	
< 2 cm	152 (23)
2-5 cm	303 (45)
> 5 cm	181 (27)
Unknown	33 (5)
Number of metastatic lesions, *n* (%)	
< 2	298 (45)
3-5	168 (26)
> 5	166 (27)
Unknown	37 (2)
Concurrent partial liver resections, *n* (%)	
0	205 (30.6)
1-5	385 (57.5)
6-9	44 (6.6)
> 10	5 (0.7)
Unknown	30 (4.5)

Liver texture, *n* (%)	
Normal	190 (28)
Congested	8 (1)
Cirrhotic	12 (2)
Fatty	57 (9)
Unknown	402 (60)
Median optime in minutes, *n* (IQR)	232 (179-297)
Pringle maneuver during resection, *n* (%)	161 (24)
Biliary reconstruction, *n* (%)	14 (2)
Intraoperative ablation, *n* (%)	205 (30)
Drain placement	253 (38)

NELM: Neuroendocrine liver metastases; IQR: Interquartile range; BMI: Body mass index; ASA: American Society of Anesthesiology.

for informed preoperative discussions with patients as well as future comparative effectiveness research with other liver-directed treatments.

Recent advances in the perioperative management of patients undergoing LR have improved the safety of hepatectomy and expanded criteria for selecting patients for surgery. Indeed, a recent study by Cloyd *et al*[26] evaluated nearly 4000 patients who underwent LR over two decades and noted steady improvements in postoperative morbidity despite increases in case complexity. Improvements in the outcomes of LR are likely multifactorial but improved patient selection, evaluation and optimization, are paramount. Accurate liver volumetry and future liver remnant augmentation have been important strategies for minimizing post hepatectomy and postoperative liver failure[27,28]. Improved perioperative and anesthetic care, including reduced intravenous fluid administration and less blood loss, have similarly been critical advances in contemporary hepatic surgery. The introduction of enhanced recovery after surgery processes have further contributed to reduced morbidity following surgery and are now commonly routinized at major medical centers[29]. Finally, implementation of laparoscopic and robotic approaches for surgery have led to reduced postoperative pain, blood loss, and length of hospital stay with similar outcomes compared with open approaches[30-33].

Prior studies evaluating the role of IA for NELM have demonstrated that this therapeutic approach is generally well tolerated and is indicated for patients whose tumors are not amenable to resection[6,34] though the safety of IA during surgery for NELM has not been thoroughly evaluated[34-36]. In this study, we noted that IA was associated with decreased 30-d morbidity in univariate analysis though this association did not persist on multivariate analysis. These findings are consistent with a recent study evaluating IA during resection of colorectal liver metastasis which found lower overall morbidity, hospital length of stay, and readmission rates in patients who underwent LR and IA compared to patients who underwent LR alone[37]. Based on these results and others, IA appears to be a safe and effective strategy to expand the surgical options for patients with multifocal NELM.

While the role of primary tumor resection in the setting of unresectable NELM remains controversial, resection of the primary NET is indicated when liver metastases are resectable[19,38-41]. The current study suggests that resection of the primary (*e.g.*, pancreatectomy, intestinal resection) can be performed safely and is not associated with increased postoperative morbidity. These findings are consistent with the large body of literature which suggests that most LRs for colorectal liver metastasis can be performed safely in a combined fashion with standard colorectal resections[42,43].

While the ACS-NSQIP targeted hepatectomy database has the advantage of containing hepatectomy-specific perioperative variables, a limitation of the current database was the lack of cancer- and patient-specific information. For example, the database lacked relevant information such as the symptomatic status of patients, functional status of tumors, tumor grade, or presence of extra-hepatic disease. In addition, it lacked Furthermore, as the study was limited to the 30-d postoperative period, we were unable to describe the long-term efficacy of LR for NELM. However, the purpose of the current study was to evaluate the indications for and short-term outcomes of surgery for NELM. Multiple prior studies have found that LR for NELM is associated with good long-term survival[4,6,44]. Similarly, the ACS-NSQIP database did not have information on carcinoid crisis, however, previous studies have shown this to be a relatively rare event[45,46]. This study had several other limitations,

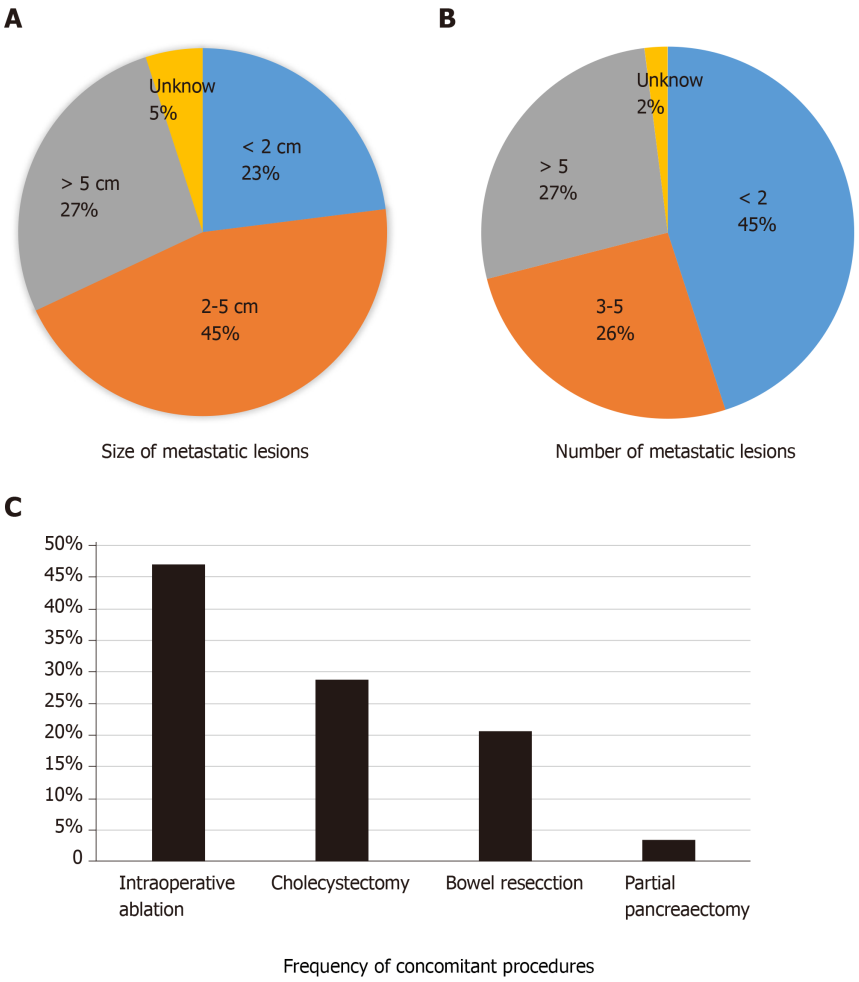

Figure 1 Indications for liver resection for neuroendocrine liver metastases. Overall size (A) and number (B) of neuroendocrine liver metastases and frequency of concomitant procedures including intraoperative ablation (C) among patients undergoing liver resection for neuroendocrine liver metastases.

primarily related to its retrospective nature and the fact that data were limited to the 30-d postoperative period which may be insufficient to capture all complications.

In conclusion, in this contemporary population-based analysis, we demonstrated that LR can be performed for NELM with relatively low postoperative morbidity and mortality. Concomitant operations such as cholecystectomy, bowel resection, pancreatectomy, and IA can safely be performed and do not contribute to increased morbidity. Careful patient selection, minimizing operative time, and utilizing minimally invasive surgical approaches may help reduce postoperative morbidity. While multiple therapeutic options exist for NELM, given the excellent long-term outcomes observed in the literature and the satisfactory short-term outcomes demonstrated herein, surgical resection should remain the standard of care when feasible.

Table 2 Postoperative outcomes of patients with neuroendocrine liver metastases undergoing liver resection

	NELM (*n* = 669)
Post-hepatectomy	
Bile leakage, *n* (%)	40 (5.9)
Post hepatectomy invasive intervention, *n* (%)	65 (9.7)
Post hepatectomy liver failure, *n* (%)	18 (2.6)
Specific complications	
Superficial surgical site infection, *n* (%)	24 (3.5)
Deep incisional surgical site infection, *n* (%)	4 (0.6)
Organ/space surgical site infection, *n* (%)	49 (7.3)
Bleeding requiring transfusion, *n* (%)	104 (15.5)
Unplanned re-intubation, *n* (%)	9 (1.3)
Pneumonia, *n* (%)	20 (2.9)
Pulmonary embolism, *n* (%)	14 (2)
Progressive renal insufficiency, *n* (%)	7 (1.1)
Urinary tract infection, *n* (%)	14 (2)
Stroke, *n* (%)	1 (0.1)
Cardiac arrest, *n* (%)	2 (0.3)
Myocardial infarction, *n* (%)	3 (0.4)
Deep venous thrombosis/thrombophlebitis, *n* (%)	9 (1.4)
Sepsis, *n* (%)	38 (5.6)
Overall	
Median length of hospital stay in days, *n* (IQR)	6 (4-8)
Discharge destination to home, *n* (%)	637 (95.2)
30-d readmission, *n* (%)	75 (11.2)
Reoperation, *n* (%)	21 (3.1)
30-d overall morbidity, *n* (%)	194 (29)
Mortality, *n* (%)	9 (1.3)

NELM: Neuroendocrine liver metastases; IQR: Interquartile range.

Table 3 Significant predictors of 30-d overall morbidity among patients undergoing hepatectomy for neuroendocrine liver metastases based on univariate logistic regression analysis

	OR	95%CI	*P* value
Age > 60	0.931	0.658-1.316	0.6835
Male gender	1.232	0.890-1.707	0.2092
ASA class ≥ 3	2.418	1.422-4.113	0.0011
BMI > 27	1.030	0.743-1.428	0.8596
Preop biliary stent	2.562	0.850-7.719	0.0946
Viral hepatitis	2.538	0.841-7.660	0.0983
Concomitant bowel resection	1.278	0.885-1.844	0.1906
Concomitant cholecystectomy	1.094	0.749-1.598	0.6431
Concomitant pancreatectomy	1.579	0.626-3.984	0.3335
Open approach	1.943	1.218-3.102	0.0053
Size < 2 cm (ref)			
Size 2-5 cm	0.989	0.645-1.516	0.9591
Size > 5 cm	1.397	0.882-2.215	0.1546
Number of tumors > 1	0.984	0.681-1.422	0.9317
Right/left/triseg hepatectomy	1.660	1.169-2.355	0.0046
Abnormal liver texture	1.340	0.818-2.193	0.2447
Intraoperative ablation	0.686	0.476-0.988	0.0431
Biliary reconstruction	3.979	1.317-12.023	0.0144
Operative time > 230 min	2.043	1.407-2.968	0.0002
Pringle	1.429	0.986-2.070	0.0593

OR: Odds ratio; CI: Confidence intervals; ASA: American Society of Anesthesiologists; BMI: Body mass index.

Table 4 Significant predictors of 30-d overall morbidity among patients undergoing hepatectomy for neuroendocrine liver metastases based on multivariate stepwise logistic regression analysis

	OR	95%CI	*P* value
ASA class ≥ 3	2.089	1.197-3.645	0.0095
Normal liver texture	0.641	0.433-0.950	0.0266
Open approach	1.867	1.148-3.036	0.0118
Right hepatectomy	1.618	1.014-2.582	0.0437
Intraoperative ablation	0.697	0.473-1.029	0.0697
Biliary reconstruction	2.802	0.870-9.021	0.0842
Operative time > 230 min	1.731	1.168-2.565	0.0062

OR: Odds ratio; CI: Confidence intervals; ASA: American Society of Anesthesiologists.

ARTICLE HIGHLIGHTS

Research background

Multiple liver-directed therapies, including hepatic resection, exist for patients with neuroendocrine liver metastases (NELM). While surgical resection is associated with the best long-term outcomes, the current indications for and outcomes of surgery for NELM from a population perspective are not well understood.

Research motivation

A better understanding of the frequency and predictors of postoperative complications will improve shared-decision making for patients with NELM, especially given the expanding number of liver-directed and systemic therapies available.

Research objectives

The purpose of the current study was to define the current indications for surgery for NELM, characterize the short-term outcomes of patients undergoing surgery, and evaluate predictors of complications using a population-based approach.

Research methods
A retrospective review of the 2014-2017 American College of Surgeons National Surgical Quality Improvement Program targeted hepatectomy database was performed to identify patients who underwent hepatic resection for NELM. Perioperative characteristics and 30-d morbidity and mortality were analyzed.

Research results
Among 669 patients who underwent liver resection for NELM, the number of metastases resected ranged from 1 to 9 though the most common (45%) number of tumors resected was one. The majority (68%) of patients had a largest tumor size of < 5 cm and most patients underwent partial hepatectomy (71%). The majority of operations were open (82%) versus laparoscopic (17%) or robotic (1%). In addition, 30% of patients underwent intraoperative ablation while 45% had another concomitant operation including cholecystectomy (28.8%), bowel resection (20.2%), or partial pancreatectomy (3.4%). Overall 30-d morbidity and mortality was 29% and 1.3%, respectively. On multivariate analysis, American Society of Anesthesiologists class ≥ 3, open approach, formal hemi-hepatectomy or trisectionectomy, and prolonged operative time were associated with higher 30-d morbidity. Concomitant procedures including intraoperative ablation, small bowel resection, or pancreatectomy were not independently associated with higher morbidity.

Research conclusions
In this contemporary population-based analysis, we demonstrated that hepatic resection can be performed with relatively low postoperative morbidity and mortality for patients with NELM. Concomitant operations such as cholecystectomy, bowel resection, pancreatectomy, and liver ablation can safely be performed and do not contribute to increased morbidity. Careful patient selection, minimizing operative time, and utilizing minimally invasive approaches may help reduce postoperative morbidity. While multiple therapeutic options exist for NELM, given the excellent long-term outcomes observed in the literature and the satisfactory short-term outcomes demonstrated in the current study, surgical resection should remain the standard of care when feasible.

Research perspectives
This study highlights the current population-based indications for liver resection for patients with neuroendocrine liver metastases and confirms satisfactory short-term outcomes. In light of these findings, future research should focus on expanding the indications for hepatic resection particularly given the increasing number of liver-directed and systemic therapy options available. Future prospective studies should evaluate the optimal sequencing of liver-directed therapies including neoadjuvant and adjuvant strategies to improve long-term outcomes.

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ORIGINAL ARTICLE

Retrospective Study

Clinical course of suspected small gastrointestinal stromal tumors in the stomach

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Abstract

BACKGROUND

Gastric subepithelial lesions are frequently encountered during endoscopic examinations, and the majority of them are small and asymptomatic. Among these lesions, gastrointestinal stromal tumors (GISTs) are the major concern for patients and clinicians owing to their malignant potentials. Although previous guidelines suggested periodic surveillance for such small (≤ 20 mm) lesions, several patients and clinicians have still requested or prescribed repeated examinations or radical resection, posing extra medical burdens and risks.

AIM

To describe the clinical course of suspected small gastric GISTs and provide further evidence for surveillance strategy for tumor therapy.

METHODS

This single-center, retrospective study was conducted at West China Hospital, Sichuan University. Consecutive patients with suspected small gastric GISTs were reviewed from November 2004 to November 2018. GIST was suspected according to endoscopic ultrasonography features: hypoechoic lesions from muscularis propria or muscularis mucosa. Eligible patients with suspected small (≤ 20 mm) GISTs were included for analysis. Patients' demographic data, lesions' characteristics, and follow-up medical records were collected.

RESULTS

A total of 383 patients (male/female, 121/262; mean age, 54 years) with 410 suspected small gastric GISTs (1 lesion in 362 patients, 2 lesions in 16, 3 lesions in 4, and 4 lesions in 1) were included for analysis. The most common location was gastric fundus (56.6%), followed by body (29.0%), cardia (12.2%), and antrum (2.2%). After a median follow-up of 28 mo (interquartile range, 16-48; range, 3-

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156), 402 lesions (98.0%) showed no changes in size, and size of 8 lesions (2.0%) was increased (mean increment, 10 mm). Of the 8 lesions with size increment, endoscopic or surgical resection was performed in 6 patients (5 GISTs and 1 leiomyoma). For other 2 remaining patients, unroofing biopsy or endoscopic ultrasound-guided fine-needle aspiration was carried out (2 GISTs), while no further change in size was noted over a period of 62-64 mo.

CONCLUSION
The majority of suspected small (≤ 20 mm) gastric GISTs had no size increment during follow-up. Regular endoscopic follow-up without pathological diagnosis may be highly helpful for such small gastric subepithelial lesions.

Key words: Endoscopic ultrasound-guided fine-needle aspiration; Gastrointestinal stromal tumor; Hypoechoic lesions; Stomach; Surveillance strategy; Unroofing biopsy

Core tip: This retrospective study submitted by Ye LS *et al* describes the clinical course of suspected small (≤ 20 mm) gastrointestinal stromal tumors in the stomach, in which the majority of lesions (98%, 402/410) had no size increment during a median follow-up of 28 mo (interquartile range, 16-48; range, 3-156), and the size of only 8 lesions (2.0%, 8/410) was increased (mean increment, 10 mm). Our findings may provide further evidence that surveillance strategy may be helpful for such small gastric subepithelial lesions.

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INTRODUCTION

Gastric subepithelial lesions are frequently encountered, with a frequency of about 0.36% during routine upper endoscopies[1]. With increased endoscopic and radiological utilization, such lesions are becoming increasingly prevalent. Although the majority of these lesions are small and asymptomatic, they can cause bleeding, obstructive symptoms, and also carry malignant potentials. The most common subepithelial lesions detected by endoscopists are gastrointestinal stromal tumors (GISTs), leiomyomas, lipomas, granular cell tumors, pancreatic rests, and carcinoid tumors. Among them, GISTs remain as one of the major concerns for patients and clinicians because of their potential malignancy. Although previous guidelines have recommended that periodic surveillance for small (less than 20 mm) GISTs without high-risk endoscopic ultrasound (EUS) features is reasonable since malignant evolution is uncommon[2-4], several patients remain extremely worried, and request repeated endoscopic examinations or radical resection for their accidentally detected small gastric subepithelial lesions, posing extra medical burdens and risks. In addition, several clinicians prefer to perform endoscopic or surgical resection for these patients because of patients' strong demands and the potential malignancy of lesions, which is blameless indeed, while may put those patients at great medical risks. Although several studies[5,6] demonstrated a low rate of size increment in patients with subepithelial lesions of the upper gastrointestinal tract, investigations involving only suspected gastric GISTs are limited; optimal follow-up interval for such lesions remained uncertain[2,4,7]. Therefore, in the present study, we described the clinical course of suspected small gastric GISTs, and our results may provide further evidence for surveillance strategy for tumor therapy.

MATERIALS AND METHODS

Study design

This is a single-center, retrospective study conducted at West China Hospital, Sichuan University (Chengdu, China). The study protocol was reviewed and approved by the Ethics Committee of West China Hospital, Sichuan University (Chengdu, China).

Patients

From November 2004 to November 2018, all patients with suspected small (≤ 20 mm) gastric GIST were retrospectively reviewed at West China Hospital, Sichuan University. The diagnosis of GIST was suspected according to EUS characteristics[8,9], which were hypoechoic lesions (with or without homogeneous echo and well-defined margins) from muscularis propria or muscularis mucosa. Patients who underwent endoscopic or surgical resection after initial assessment owing to patients' demands or high-risk EUS features, or patients who lost follow-up after initial endoscopic assessment were excluded.

Endoscopic assessment

All the examinations were performed by experienced endoscopists (each with experience of ≥ 1000 endoscopic examinations). Miniprobe EUS examination was performed on all patients to measure the exact size of lesions and for differential diagnosis. Radial or linear EUS was selected when miniprobe EUS could not clearly show the details of lesions. High-risk EUS features included irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity. Specimens were obtained by unroofing biopsy, EUS-guided fine needle aspiration (EUS-FNA), or resection, when lesions increased in size or patients strongly requested.

Follow-up

Patients with suspected GISTs less than 10 mm in size were recommended to receive endoscopic follow-up every 2 to 3 years, while patients with suspected GISTs of 10-20 mm in size were recommended to undergo endoscopic follow-up every 1 to 2 years. Endoscopic or surgical resection was planned if the lesion increased in size or became ulcerative, or when the patient strongly refused continual surveillance.

Statistical analysis

Statistical analysis was performed using SPSS 25.0 software (IBM, Armonk, NY, United States). Continuous data were described as mean ± SD; range or median [interquartile range (IQR); range] according to their distribution. Categorical data were described as rate or proportion. The Student's *t*-test, the Mann–Whitney *U* test, the χ^2 test, or Fisher's exact test was used accordingly. $P < 0.05$ was considered statistically significant.

RESULTS

Patients' baseline characteristics

A total of 448 patients with 475 suspected small (≤ 20 mm) gastric GISTs were retrospectively reviewed, and 383 patients with 410 lesions were eligible for final analysis (Figure 1 and Table 1). The mean age of the 383 patients was 54 years (SD, 10; range, 23-80), and the male-to-female ratio was 1:2.2 (121/262). The majority of patients (94.5%, 362/383) had a single lesion, 16 patients (4.2%) had 2 lesions, 4 patients (1.0%) had 3 lesions, and 1 patient (0.3%) had 4 lesions. The median initial size of these lesions was 7 mm (IQR, 6-10; range, 3-20). The most common location was gastric fundus [232 lesions (56.6%)], followed by body [119 lesions (29.0%)], cardia [50 lesions (12.2%)], and antrum [9 lesions (2.2%)].

Specimens were obtained from 45 of 410 lesions, by unroofing biopsy in 1 lesion, EUS-FNA in 1, endoscopic resection in 29, and surgical resection in 14.

Final diagnosis was made in all the 45 patients, including 39 GISTs and 6 leiomyomas.

Clinical course

During a median follow-up of 28 mo (IQR, 16-48; range, 3-156), 402 lesions (98.0%) showed no changes in size, and size of 8 lesions (2.0%) was increased (mean increment was 10 mm; SD, 3; range, 7-14) (Table 1).

Of these 8 lesions with increased size, endoscopic or surgical resection was performed in 6 patients, which revealed 5 GISTs (3 with low risk of malignancy, and 2 with intermediate risk of malignancy) and 1 leiomyoma. For other 2 remaining patients, unroofing biopsy or EUS-FNA was conducted, while no further change in size was noted over a period of 62-64 mo (Figure 2).

Table 1 Four hundred and ten suspected gastric gastrointestinal stromal tumors in 383 patients: Comparing demographic and lesion characteristics of lesions with or without size increment

	All lesions	Lesions without size increment	Lesions with size increment	*P* value
Patients, *n*[1]	383	375	8	-
Age, yr[2]	54 (10; 23-80)	54 (10; 23-80)	57 (16; 31-74)	0.572[4]
Sex, male/female, *n*	121/262	115/260	6/2	0.014[5]
Lesions, *n*[1]	410 (100%)	402 (98.0%)	8 (2.0%)	-
Distribution, *n*				0.366[5]
Single lesion	362 (94.5%)	355 (94.7%)	7 (87.5%)	
Two lesions	16 (4.2%)	15 (4.0%)	1 (12.5%)	
Three lesions	4 (1.0%)	4 (1.1%)	0 (0%)	
Four lesions	1 (0.3%)	1 (0.3%)	0 (0%)	
Location, *n*				0.139[5]
Cardia	50 (12.2%)	49 (12.2%)	1 (12.5%)	
Fundus	232 (56.6%)	230 (57.2%)	2 (25.0%)	
Body	119 (29.0%)	114 (28.4%)	5 (62.5%)	
Antrum	9 (2.2%)	9 (2.2%)	0 (0%)	
Initial size, mm[3]	7 (6-10; 3-20)	7 (6-10; 3-20)	12 (9-13; 4-15)	0.018[6]
Less than 10 mm, *n*	291 (71.0%)	289 (71.9%)	2 (25.0%)	0.009[5]
10-20 mm, *n*	119 (29.0%)	113 (28.1%)	6 (75.0%)	
Follow-up, mo[3]	28 (16-48; 3-156)	27 (15-47; 3-156)	60 (46-83; 41-146)	0.001[6]

[1]Sixteen patients had 2 lesions (one lesion in these patients increased in size during follow-up), 4 patients had 3 lesions, and 1 patient had 4 lesions.
[2]Age was expressed as mean (standard deviation; range).
[3]Initial size and follow-up were expressed as median (interquartile range; range).
[4]Student's *t*-test.
[5]Fisher's exact test.
[6]Mann–Whitney *U* test.

DISCUSSION

In the present study, we found that there was no size increment in the majority of small (≤ 20 mm) suspected gastric GISTs (98.0%, 402/410), and the size of only 8 lesions (2.0%) was increased during a median follow-up of 28 mo (IQR, 16-48; range, 3-156). Our findings are consistent with those reported previously[5,6,10]. Imaoka *et al*[5] showed that only 2 of 132 subepithelial lesions of the stomach (1.51%) had size increment during 5 years of endoscopic follow-up. Kim *et al*[6] followed-up 989 subepithelial lesions of the stomach (≤ 30 mm) over a median period of 24 mo (range, 3-123 mo), and noted that only 81 tumors (8.19%) had significant increment in size. Song *et al*[10] also reported no size increment in 613 of 640 small (≤ 35 mm) subepithelial lesions of the upper gastrointestinal tract (95.78%) over a mean follow-up of 47.3 mo (range, 6-118 mo). The difference between these reports and the present study is related to the definition of small lesions. We defined small lesions as lesions ≤ 20 mm in size, since lesions larger than 20 mm are commonly recommended to undergo resection, and lesions with size of ≤ 20 mm are taken as very low risk of recurrence[4], which seems to be more reasonable. The current study provided further evidence that the majority of small (≤ 20 mm in size) suspected gastric GISTs remained stable during follow-up, and periodic surveillance without pathological diagnosis was found to be reasonable.

It is also highly important to indicate optimal follow-up interval for such suspected small gastric GISTs. Recommendations from different countries and associations were found remarkably different[2,4,7]. The European Society for Medical Oncology and the European Society of Gastrointestinal Endoscopy suggested initial EUS after 3 mo of detection, and then annual follow-up; the National Comprehensive Cancer Network highly recommended 6-12 mo of follow-up interval; the Japan Gastroenterological Endoscopy Society demonstrated that 1-2 years of follow-up interval is enough for such small lesions; the recently published French guideline recommended EUS follow-up at 6 and 18 mo, and then every 2 years. However, as shown in Table 1, lesions with larger initial size may be more likely to increase during follow-up. Such phenomenon has already been reported by Kim *et al*[6] and Song *et al*[10]. Therefore, from economic point of view, we suggested that different follow-up intervals may be better for lesions with different initial sizes. Our strategy that 2- to 3-year interval for

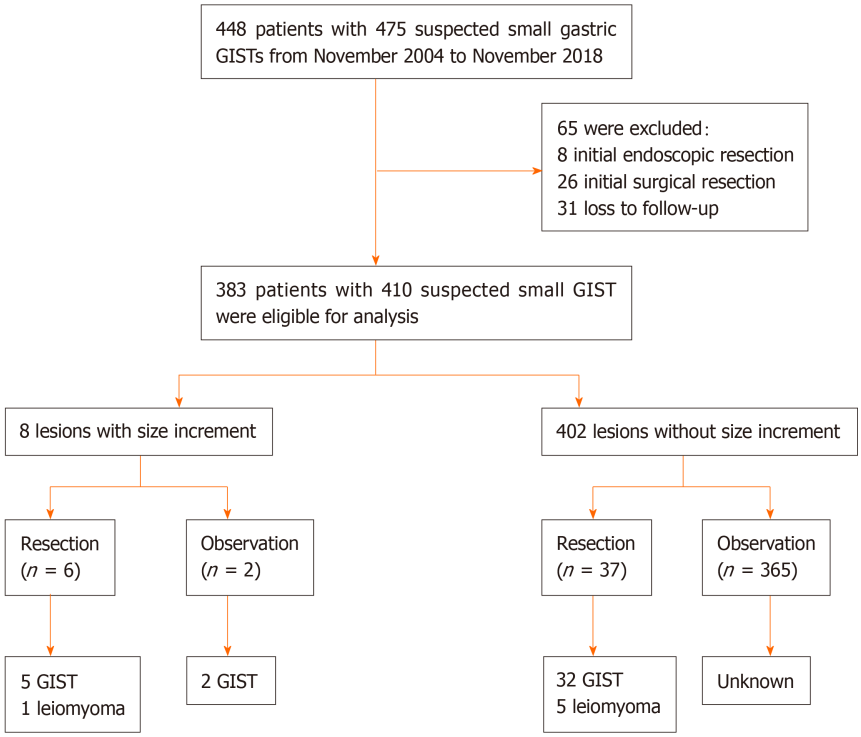

Figure 1 Study flowchart of patients' selection. GISTs: Gastrointestinal stromal tumors. ("small" was added in the first line of this Figure, and "unknow" in the last line was revised to "Unknown").

lesions less than 10 mm and 1- to 2-year interval for lesions with size of 10-20 mm, seems to be advisable.

In the present study, all the patients underwent initial and follow-up EUS for lesion assessment. Although EUS has been suggested as the gold-standard in distinguishing intramural lesions from extramural compression, its role in determining lesions with size of less than 10 mm is limited[11-13]. Considering that exophytic lesions may be underestimated under endoscopic view, initial EUS assessment regardless of lesion size seems to be reasonable, while routine EUS follow-up should not be used despite patients' preference.

We also demonstrated that lesions with size increment did not increase constantly over time (Figure 2). In 2010, Lim *et al*[14] reported that continual size increment was not detected in lesions with size increments. In addition, Kim *et al*[6] found no consistent growth patterns for small gastric subepithelial lesions. These results revealed that size increment during follow-up may not be taken as a catastrophe into consideration, and continual follow-up may also be an alternative for selective patients.

There were several limitations in this study. First, it was a retrospective study, thus the modality and interval of follow-up could not be standardized. Some patients with lesions less than 10 mm in size strongly requested repeated examinations or even radical resection although no size increment was noted. Second, underlying mucosal change was not discussed in this study although it has been reported to be a risk factor for size increment[10]. This is mainly because only 2 lesions had underlying mucosal ulceration during follow-up (1 lesion with size increment and 1 lesion without size increment, respectively). Since size of lesion is one of the most important factors (the other one is mitotic index) for prediction of the risk of recurrence for localized gastric GIST[4], assessment of only lesion size for suspected gastric GIST is reasonable.

In conclusion, the majority of small (≤ 20 mm) suspected gastric GISTs had no size increment during follow-up. Regular endoscopic follow-up may be therefore helpful for such small gastric subepithelial lesions. From economic point of view, different follow-up intervals should be proposed for lesions with size of less than 10 mm and those with size of 10-20 mm.

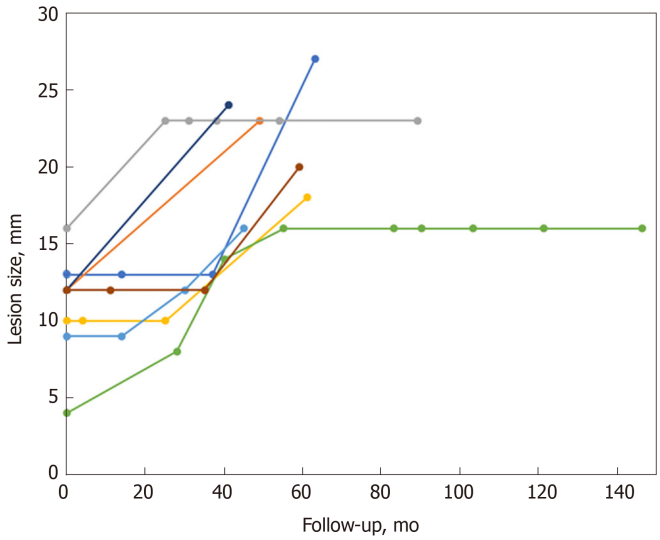

Figure 2 Changes in size of suspected small gastric gastrointestinal stromal tumors compared with follow-up interval.

ARTICLE HIGHLIGHTS

Research background

Gastric subepithelial lesions are frequently encountered during endoscopic examinations, and the majority of them are small and asymptomatic. Among these lesions, gastrointestinal stromal tumors (GISTs) are the major concern for patients and clinicians owing to their malignant potentials. Although previous guidelines suggested periodic surveillance for such small (≤ 20 mm) lesions, several patients and clinicians have still requested or prescribed repeated examinations or radical resection, posing extra medical burdens and risks.

Research motivation

Although several studies demonstrated a low rate of size increment in patients with gastric subepithelial lesions, there were limited investigations involving only suspected small gastric GISTs; the optimal follow-up interval for such lesions remains uncertain.

Research objectives

In this retrospective study, we aimed to describe the clinical course of suspected small gastric GISTs, and to provide further evidence for surveillance strategy for tumor therapy.

Research methods

Consecutive patients with suspected small (≤ 20 mm) gastric GISTs from November 2004 to November 2018 at West China Hospital were retrospectively reviewed. GIST was suspected according to endoscopic ultrasonography features: hypoechoic lesions from muscularis propria or muscularis mucosa. Eligible patients with suspected small GISTs were included for analysis. Patients' demographic data, lesions' characteristics, and follow-up medical records were collected.

Research results

A total of 383 patients (male/female, 121/262; mean age, 54 years) with 410 suspected small gastric GISTs (1 lesion in 362 patients, 2 lesions in 16, 3 lesions in 4, and 4 lesions in 1) were included for analysis. The most common location was gastric fundus (56.6%), followed by body (29.0%), cardia (12.2%), and antrum (2.2%). After a median follow-up of 28 mo (interquartile range, 16-48; range, 3-156), 402 lesions (98.0%) showed no changes in size, and 8 (2.0%) lesions increased in size (mean increment, 10 mm). Of the 8 lesions with size increment, endoscopic or surgical resection was performed in 6 patients (5 GISTs and 1 leiomyoma). For other 2 remaining patients, unroofing biopsy or endoscopic ultrasound-guided fine-needle aspiration was carried out (2 GISTs), while no further change in size was noted over a period of 62-64 mo.

Research conclusions

The majority of suspected small (≤ 20 mm) gastric GISTs had no size increment during follow-up. Regular endoscopic follow-up without pathological diagnosis may be highly helpful for such small gastric subepithelial lesions.

Research perspectives

Prospective study involving specific follow-up period for lesions with different initial size may be better to develop an economic strategy for surveillance.

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ORIGINAL ARTICLE

Observational Study

Short term outcomes of minimally invasive selective lateral pelvic lymph node dissection for low rectal cancer

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Author contributions: Wong KY designed the study, analyzed and interpreted the data, wrote and revised the final manuscript for submission; Tan AMN participated in the data collection and analysis, co-wrote and revised the final manuscript for submission.

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Abstract

BACKGROUND

Pelvic recurrence after rectal cancer surgery is still a significant problem despite the introduction of total mesorectal excision and chemoradiation treatment (CRT), and one of the most common areas of recurrence is in the lateral pelvic lymph nodes. Hence, there is a possible role for lateral pelvic lymph node dissection (LPND) in rectal cancer.

AIM

To evaluate the short-term outcomes of patients who underwent minimally invasive LPND during rectal cancer surgery. Secondary outcomes were to evaluate for any predictive factors to determine lymph node metastases based on pre-operative scans.

METHODS

From October 2016 to November 2019, 22 patients with stage II or III rectal cancer underwent minimally invasive rectal cancer surgery and LPND. These patients were all discussed at a multidisciplinary tumor board meeting and most of them received neoadjuvant chemoradiation prior to surgery. All patients had radiologically positive lateral pelvic lymph nodes on the initial staging scans, defined as lymph nodes larger than 7 mm in long axis measurement, or abnormal radiological morphology. LPND was only performed on the involved side.

RESULTS

Majority of the patients were male (18/22, 81.8%), with a median age of 65 years (44-81). Eighteen patients completed neoadjuvant CRT pre-operatively. 18 patients (81.8%) had unilateral LPND, with the others receiving bilateral surgery. The median number of lateral pelvic lymph nodes harvested was 10 (3-22) per pelvic side wall. 8 patients (36.4%) had positive metastases identified in the lymph nodes harvested. The median pre-CRT size of these positive lymph nodes was 10mm. Median length of stay was 7.5 d (3-76), and only 2 patients failed

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initial removal of their urinary catheter. Complication rates were low, with only 1 lymphocele and 1 anastomotic leak. There was only 1 mortality (4.5%). There have been no recurrences so far.

CONCLUSION
Chemoradiation is inadequate in completely eradicating lateral wall metastasis and there are still technical limitations in accurately diagnosing metastases in these areas. A pre-CRT lymph node size of ≥ 10 mm is suggestive of metastases. LPND may be performed safely with minimally invasive surgery.

Key words: Lateral pelvic lymph node dissection; Robotic rectal surgery; Locally advanced rectal cancer; Local recurrence; Pelvic side wall recurrence

Core tip: Lateral pelvic recurrence after rectal cancer surgery is still a major problem. There have been differences in the treatment of suspicious lateral pelvic lymph nodes between the East and West, treating this as either regional or systemic disease. Lateral pelvic lymph node dissection is a topic of debate in the treatment of these patients. In this study, we evaluate our single-center data, showing our short-term outcomes. Minimally invasive surgery, especially with the robotic platform is shown to be safe and feasible in lateral pelvic lymph node dissection.

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INTRODUCTION

Total mesorectal excision (TME) has been established as the gold standard for treatment of low rectal cancer. This technique, however, only removes the mesorectal lymph nodes. The incidence of lateral pelvic lymph nodes (LPLN) metastasis in locally advanced low rectal cancer has been shown to be as high as 18%. Pelvic recurrence after rectal cancer surgery is a major concern, and one of the most common types of recurrence after TME is from lateral pelvic lymph node metastasis[1,2].

In Western countries, lateral pelvic lymph node metastases have always been considered as systemic disease and treated as metastatic disease. Japanese surgeons, however, have a different approach and considered lateral pelvic disease as regional disease, with LPND being potentially curative. Some studies have reported improved local control and possibly survival benefits in patients undergoing LPND for metastatic LPLN after neoadjuvant CRT[3].

LPND is not routinely performed outside of Japan because of its associated morbidity. The procedure has been associated with urinary and sexual dysfunction, longer operative time and larger volume of blood loss. LPND has traditionally been performed via open surgery but recent small studies have reported the feasibility of laparoscopic surgery. Laparoscopic LPND is a technically challenging procedure and robotic surgery may have an advantage owing to the flexibility of the instrument, 3D stereoscopic visuals and its ability to work in a confined lateral pelvic space.

This study aims to share our experience in minimally invasive LPND in rectal cancer and reaffirm its safety and feasibility.

MATERIALS AND METHODS

This study was approved by the local ethics review board. Data was collected prospectively in a tertiary referral hospital, Tan Tock Seng Hospital from October 2016 to November 2019 and retrospectively reviewed.

Patients

A total of 22 patients were diagnosed with locally advanced low rectal cancer (T3+/N+) and underwent curative surgery during this period of time. Patients with radiologically positive LPLN were included in the study. Radiologically positive pelvic lymph node metastases were defined as lymph nodes larger than 7 mm in short axis measurement or had abnormal morphology on imaging studies. Patients with rectal neuroendocrine tumors were also included if they had suspicious LPLN as well. All patients underwent minimally invasive surgical approaches.

Clinical staging and treatment strategy

All cases were discussed in multidisciplinary tumor board meeting. Majority of the patients underwent long course neoadjuvant CRT according to multidisciplinary tumor board meeting recommendations. These patients received between 40-50 Gy in 25# for 5 wk with twice daily capecitabine. Repeat magnetic resonance imaging (MRI) was routinely performed 5 to 6 wk after completion of CRT for evaluation of tumor response and surgical planning. TME and LPND were performed regardless of the response and size of the LPLN after CRT (Figure 1 and Figure 2). All patients included in the study underwent TME and LPND, except 1 patient who had only the LPND performed for an isolated lateral pelvic lymph node recurrence a year after TME surgery. All cases were performed either laparoscopically or robotically. The decision for performing the surgery via laparoscopy or robotic surgery was based on availability and affordability of the robotic system. All patients who underwent CRT and low anterior resection had a diverting ileostomy performed together at the same time. End colostomy was formed for patients who had abdominoperineal resection or Hartmann's procedure respectively.

Surgical technique

The dissection of LPLN was performed after completion of TME and transection of the distal rectum. LPND for rectal cancer in our institution places emphasis on complete clearance of internal iliac and obturator compartments, as lymph nodes at these two compartments have the highest incidence of metastasis in low rectal cancer[4]. External iliac and common iliac lymph nodes were cleared only if pre-operative imaging showed disease involvement. This is to minimize the side effects of LPND, such as chronic lymphedema of the lower limb and injury to the genitofemoral nerve. In laparoscopic cases, dissection of the lateral sidewall was carried out using monopolar diathermy and an ultrasonic energy device. For robotic cases, a total robotic technique was used, including mobilization of colon, ligation of inferior mesenteric artery (IMA), TME and LPND. The Da Vinci S or Xi system was utilized for these robotic cases. LPND was only performed on the side of suspected metastatic LPLN seen on the pre-CRT MRI scan. Branches of the internal iliac artery were ligated if necessary, to allow access to the deep pelvic side wall or when metastatic lymph nodes were adhered to the vessel. The superior vesicle artery on either side was spared if bilateral LPND was performed. This was to preserve arterial perfusion to the bladder. The obturator nerve was not routinely sacrificed if there was no definite involvement by metastatic lymph nodes (Figure 3 and Figure 4). The ureterohypogastric fascia was preserved in all cases to preserve genitourinary function, and only sacrificed if there was tumor involvement (Figure 5). Lymphofatty tissues were excised en bloc as a whole and we do not practice cherry-picking of metastatic lymph nodes (Figure 6 and Figure 7).

Statistical analysis

Statistical analysis was performed using SPSS 24.0. Categorical data were expressed with numbers with percentages, and continuous data were expressed as medians with a range.

RESULTS

Overall patient characteristics

The median age of patients was 65 (44-81). Majority of these patients were male (18/22, 81.8%). The median distance of the tumor from the anal verge was 5 cm (2-7). Average body mass index of the patients included was 23.4 (14.2-34.3). 18 of the patients completed neoadjuvant CRT before surgery. Of the patients with adenocarcinoma, one patient already had previous pelvic radiation, and another patient was not suitable for pre-operative CRT in view of his poor performance status and lack of social support. There were two patients with neuroendocrine tumors and hence were not given neoadjuvant CRT (Table 1).

Operative data

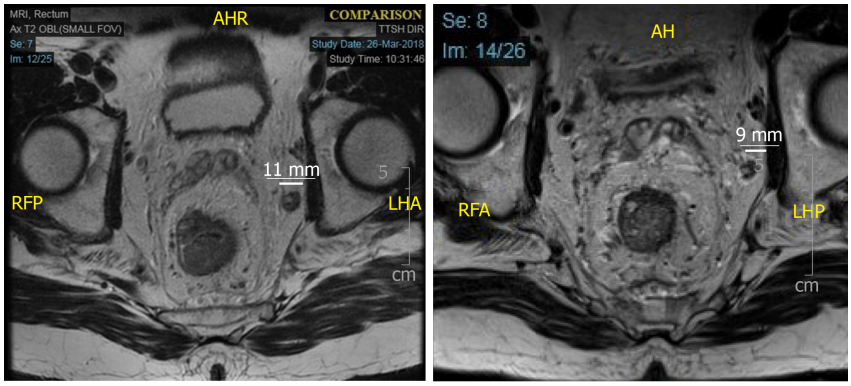

Figure 1 Magnetic resonance imaging rectum showing an enlarged, metastatic, left internal iliac node before (left, 11 mm) and after (right, 9 mm) neoadjuvant chemoradiation.

The 81.8% of patients had unilateral LPND whereas the remaining patients had bilateral LPND. The types of surgery performed included low anterior resection (72.7%, *n* = 16), inter-sphincteric resection (9.1%, *n* = 2), abdominoperineal resection (9.1%, *n* = 2), Hartmann's procedure (4.5%, *n* = 1) and only pelvic lymph node dissection (4.5%, *n* = 1). Mean operative time for LPND was 70 min (35-120) and median total blood loss (including TME) was 100 mL (50-500). Nineteen patients (86.4%) had the procedure performed robotically. There was only 1 conversion (4.5%) to open surgery due to involvement of main trunk of internal iliac vein by metastatic lateral lymph (Table 2).

Analysis of lymph nodes harvested

Most patients had a final pathological stage III tumor (63.6%, *n* = 14). Only one patient had a complete pathological response. The median number of LPLN harvested was 10 (3-22) per pelvic side wall. Eight patients (36.4%) had positive metastases identified in the lymph nodes harvested. The median pre-CRT size of these positive lymph nodes was 10 mm (Table 3).

On further analysis of patients with positive lymph nodes, 6 out of 8 patients (75%) had a pre-CRT lymph node size of ≥ 10 mm. There were 10 patients with a pre-CRT lymph node size of ≥ 10 mm, and 60% of them eventually had LPLN metastases on final histology.

Post-operative outcomes

The median length of stay was 7.5 d (3-76), with a median follow up of 18 mo (1-36). The median number of days which a urinary catheter was kept was 3 d (1-37). Only 2 patients had re-insertion of their urinary catheter after failure to void, but these were still eventually removed at 20 and 37 d respectively (Table 4).

Morbidity was generally low in this analysis, with only 1 lymphocele (4.5%) requiring radiological guided drainage, and 1 anastomotic leak (4.5%). There was only one mortality (4.5%), which was the patient who developed the anastomotic leak requiring repeat surgical intervention, and eventually demised from pneumonia after a prolonged hospital stay. None of the patients have developed any local recurrence during their follow up within the time frame of this study.

DISCUSSION

TME is the gold standard treatment for rectal cancer and has successfully reduced local recurrence and improved survival since its introduction in 1990s. However, local recurrence in the lateral compartment can still occur after TME because of the lateral lymphatic drainage of low rectum. It is reported that lateral pelvic nodal metastasis ranges from 14% to 22% and the incidence of LPLN metastasis increases with a lower location of rectal cancer[5-7].

The use of multimodal treatments has reduced the rate of local recurrence but cannot completely eliminate lateral pelvic disease. In a series of 366 patients who underwent chemoradiotherapy and TME for T3/N+ locally advanced rectal cancer, lateral recurrence occurred in 8% of the patients[2]. Most of these were isolated lateral lymph node recurrences and almost half of them did not have distant metastasis. These studies show the inadequacies of CRT in eliminating lateral pelvic metastasis and raise the question on whether extended lymphadenectomy of the lateral

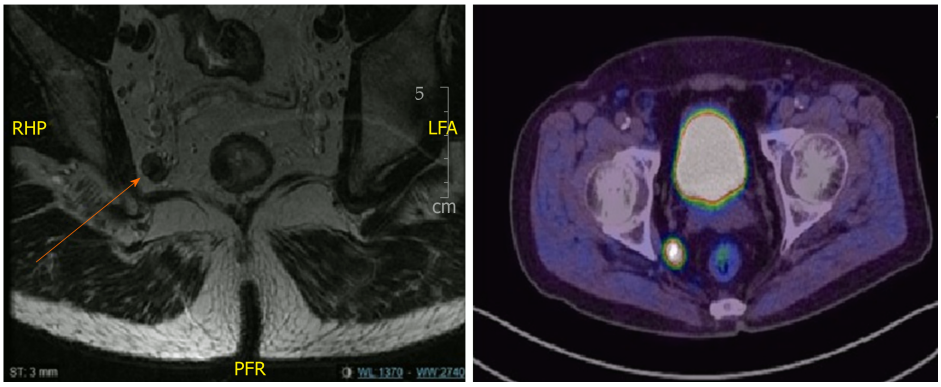

Figure 2 Metastatic lateral pelvic lymph node seen on magnetic resonance imaging rectum and positron emission tomography scan.

compartment during the index surgery could have prevented recurrence in these patients. Similarly, Kusters *et al*[8] also reported a lateral local recurrence rate of 33.3% in patients who had lateral nodes larger than 1cm despite receiving radiotherapy.

Local recurrence is associated with significant morbidity from local compression effects and pain, and salvage surgery is not always possible. Data from the Dutch TME trial showed that lateral recurrences made up 25% of all pattern of recurrences and survival is poor especially for patients who previously received radiotherapy[9].

There is still no consensus on the treatment of clinically overt lateral lymph node metastasis. LPND in rectal cancer is not performed routinely because it is widely held that lateral nodal metastasis is a systemic disease. However, a nationwide multicenter study in Japan evaluating LPND showed that the survival of patients with LPLN confined to the internal iliac region had a survival comparable to that of patients with a mesorectal N2a disease[10]. If the LPLN metastases extended past the internal iliac region, the survival was comparable to that of N2b disease, but still better than stage IV disease. The results suggested that LPLN metastasis, especially those from the internal iliac region should be considered as regional disease.

Most western surgeons have refrained from performing LPND because of the lack of evidence on survival benefit and also the perceived side effects of prolonged operative time, increased blood loss and genitourinary dysfunction[11]. Japanese surgeons on the other hand, have been advocating either prophylactic or therapeutic LPND in low rectal cancer without CRT. LPND has been the standard surgical procedure for locally advanced low rectal cancer, and it has been suggested that this may reduce local recurrence and improve survival outcome[12,13].

In the recently published multicenter randomized controlled non-inferiority JCOG0212 trial, it compared patients who had TME against patients who had TME plus LPND without any overt lateral pelvic node metastasis, defined by authors as LPLN less than 1 cm in size[1]. There was a slightly longer operative time and blood loss in the TME plus LPND group. However, there was no significant difference in terms of post-operative complications, anastomotic leak or urinary dysfunction. It showed that LPND can be performed safely with no significant morbidities if performed in high volume centers. The Japanese Society of Cancer of Colon and Rectum strongly recommends LPND in patients with clinically suspicious lateral nodes, with a weaker recommendation for prophylactic LPND[1]. Prophylactic LPND however, does carry a risk of overtreatment. The JCOG 0212 trial showed a 7% rate of lateral pelvic local recurrence for the TME-only group, of which a significant portion of these could possibly have been treated with pre-op CRT. Thus, the important question is how to identify LPLN that are involved with residual disease after CRT and selecting them for LPND.

Accurate diagnosis of lateral lymph node metastasis based on imaging is challenging, and the size of the lymph node has been shown to be the most useful compared to other diagnostic criteria. Various size criteria have been proposed with variable sensitivities and specificities, ranging from 5 mm to 10 mm. Ogura *et al*[14] reported a high local recurrence rate when suspected LPLN exceeded 7 mm on short axis diameter. The authors reported a 5-year local recurrence rate of 5.7% for patients who underwent CRT, TME and LPND compared to 19.5% in patients with CRT and TME only. Akasu *et al*[15] evaluated the accuracy of MRI in pre-operative staging and found it to be highly predictive of lateral pelvic node involvement. They found that size criteria was the most accurate in diagnosing metastatic lymph node, and this concurs with our findings too that a large LPLN is associated with a higher rate of positive lymph node metastases.

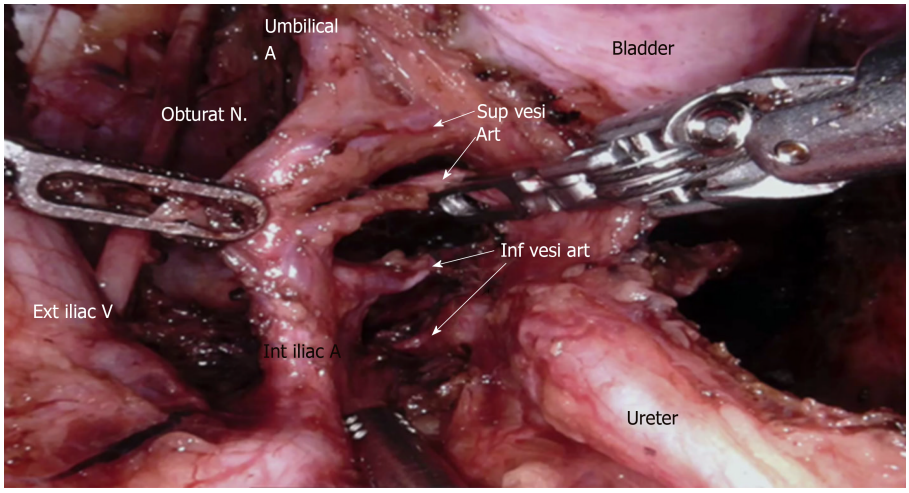

Figure 3 Branches of the internal iliac artery during lateral pelvic lymph node dissection.

Recently, selective LPND is gaining recognition and has been adopted by certain centers in the East to completely eliminate of the possibility of residual metastasis in the lateral node after CRT, in contrast to prophylactic LPND which has been traditionally practiced. Akiyoshi *et al*[3] reported a retrospective study of 127 patients, of which 38 patients underwent selective LPND after CRT if there were suspicious LPLN > 7 mm on the initial staging scan. 66% of LPLN that were suspicious on pre-operative imaging had persistent disease on histology after LPND despite undergoing CRT. They did not find any difference in survival between patients who underwent TME only compared to those who underwent TME with LPND. The latter group is theoretically supposed to have more advanced disease due to the presence of lateral pelvic metastasis. Upon further subgroup analysis of patients who underwent TME and LPND, patients with pathological proven LPLN metastasis had a similar survival and local recurrence rate compared to patients with negative lateral LN metastasis. This suggests that LPND after CRT may confer a survival benefit in patients with LPLN metastasis.

Similarly, another study from Korea suggested clearance of all enlarged lateral nodes seen on initial imaging, regardless of its response to CRT[16]. The authors found that enlarged LPLN which showed good response to CRT (< 5 mm) may still develop local lateral recurrence in up to 22% of cases. All patients with enlarged pre-CRT lymph nodes were subjected to TME and LPND and subsequently, no lateral recurrence was reported in their follow up.

Our results show that a pre-CRT LPLN size of > 10 mm is highly predictive of metastatic disease. Even if some of these lymph nodes responded to CRT and shrank in size, final histology after LPND still showed persistent malignancy in these nodes. If these were left alone without surgery, a lateral recurrence is almost inevitable, and subsequent LPND in a previously irradiated field and presence of the neorectum in the pelvis will surely be technically challenging.

LPND is usually performed as part of the surgery after completion of TME. But even as minimal invasive surgery becomes routine in rectal cancer surgery, it is necessary to evaluate whether LPND is safe and effective via these approaches. We had one case of lymphocele requiring percutaneous drainage in the third patient of our series, early on in our experience with MIS LPND. We have mitigated the risk of lymphatic leakage by securing large lymphatic channel with clips and leaving surgical drain in the post dissection lateral pelvic space. By doing do, we have not encountered further clinically evident lymphocele in our subsequent cases (Figure 8).

Neuroendocrine tumors were also included as the objective of the study was to demonstrate the safety and feasibility of minimally invasive approaches for LPND. Robotic and laparoscopic approaches are the standard techniques in our institution for the treatment of rectal cancer. Most of the LPND in our study were performed robotically. The robotic platform provides an advantage over conventional laparoscopic surgery because of the flexibility of its endo-wrist in a tight lateral pelvic space. 3D visualization and a stable operating platform allows precise dissection with preservation of neurovascular structures. There was one conversion to open surgery from laparoscopic surgery due to direct invasion of a metastatic lateral lymph node into the main trunk of the internal iliac vein, requiring conversion in order to gain vascular control before dissection.

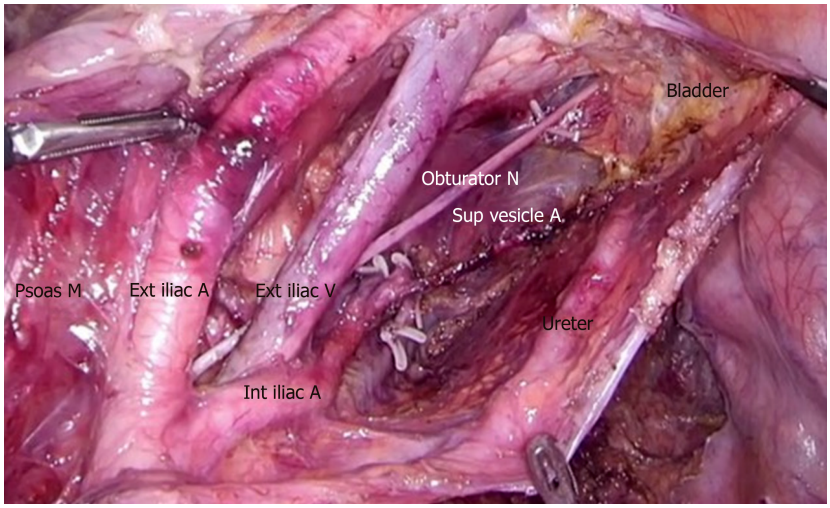

Figure 4 After completion of lateral pelvic lymph node dissection with clearance of external iliac, internal iliac and obturator compartments.

The main limitation of our study is our small sample size. However, we have shown that minimal invasive techniques for LPND are safe, feasible and able to achieve adequate nodal clearance with no local recurrence in our short term follow up. CRT is inadequate in completely eradicating lateral metastasis and there are still technical limitations in accurately diagnosing persistent disease post CRT. Pre-CRT lymph node size is a reliable predictor of metastasis, and a nodal size of 1cm or more is highly suggestive of metastasis. LPND in such cases may confer a benefit in local control or even survival outcome. Treatment of lateral pelvic lymph node disease in low rectal cancer is still a subject of debate but a combination of CRT and LPND may be the optimal option. Further randomized control trials are needed to evaluate and answer this question.

Table 1 Clinicopathological characteristics of the patients (*n* = 22)

Sex (*n*)	
Male	18
Female	4
Age (yr, mean, range)	65 (44–81)
ASA grade (%)	
1	1 (4.5)
2	19 (86.4)
3	2 (9.1)
Histology (%)	
Adenocarcinoma	20 (90.9)
Neuroendocrine	2 (9.1)
Distance from anal verge (cm)	5 (2–7)
BMI (kg/m^2, mean, range)	23.4 (14.2–34.3)
Pre-op chemoradiation (%)	18(81.8)
Final TNM stage (%)	
I	1 (4.5)
II	4 (18.2)
III	14 (63.6)
IV	1 (4.5)
Pathological complete response	1 (4.5)
Isolated LN recurrence	1 (4.5)
No. of lymph nodes harvested per side (median, range)	10 (3-22)
Patients with positive LPLN metastases on final histology (%)	8 (36.4)
Median size pretreatment LPLN (mm)	10

BMI: Body mass index; LN: Lymph nodes; LPLN: Lateral pelvic lymph nodes.

Table 2 Perioperative variables

Access (%)	
Robotic	19 (86.4)
Laparoscopic	3 (13.6)
Type of surgery (%)	
Low anterior resection	16 (72.7)
Low anterior resection with intersphincteric resection	2 (9.1)
APR	2 (9.1)
Hartmann's procedure	1 (4.5)
Isolated LPND	1 (4.5)
Laterality of LPND (%)	
Unilateral	18 (81.8)
Bilateral	4 (18.2)
Operative time for LPND (min, median, range)	70 (35-120)
Total blood loss (mL, median, range)	100 (50-500)
Conversion to open surgery (%)	1 (4.5)

LPND: Lateral pelvic lymph node dissection.

Table 3 Post-operative variables

Length of stay (d, median, range)	7.5 (3-76)
Day to removal of urinary catheter (median, range)	3 (1-37)
Complications (%)	
Lymphocele requiring drainage	1 (4.5)
Anastomotic leak	1 (4.5)
Follow up duration (mo, median, range)	18(1-36)
Local recurrence during follow up	0

Table 4 Analysis of lymph node size and response to neoadjuvant treatment

No.	Pre-op CRT	Pre-CRT Size(mm)	Post-CRT Size(mm)	LN positivity	Remarks
1	Yes	6	6	No	
2	Yes	8	5	No	
3	No	7	NA	No	Previous radiation for prostate cancer
4	Yes	8	0	No	Enlarged LPLN resolved after CRT
5	Yes	7/7 (L/R)	4/6 (L/R)	No	
6	Yes	11	10	No	
7	Yes	8	5	No	
8	No	15	NA	Yes	Neuroendocrine tumor
9	Yes	10	8	No	
10	Yes	11/8 (L/R)	7/8 (L/R)	Yes	Only the left side was positive for metastases
11	Yes	10	8	Yes	
12	No	6	NA	No	Not suitable for CRT in view of performance status and poor social support
13	Yes	5	5	Yes	
14	Yes	9	7	No	
15	Yes	10	NA	Yes	Isolated LPLN recurrence after TME surgery 1 yr ago
16	No	10	NA	Yes	Neuroendocrine tumor
17	Yes	11	11	No	
18	Yes	11	5	No	
19	Yes	14	10	Yes	
20	Yes	6	6	No	
21	Yes	7	7	No	
22	Yes	7	6	Yes	

CRT: Chemoradiation treatment; LN: Lymph nodes; NA: Not available; LPLN: Lateral pelvic lymph nodes; TME: Total mesorectal excision.

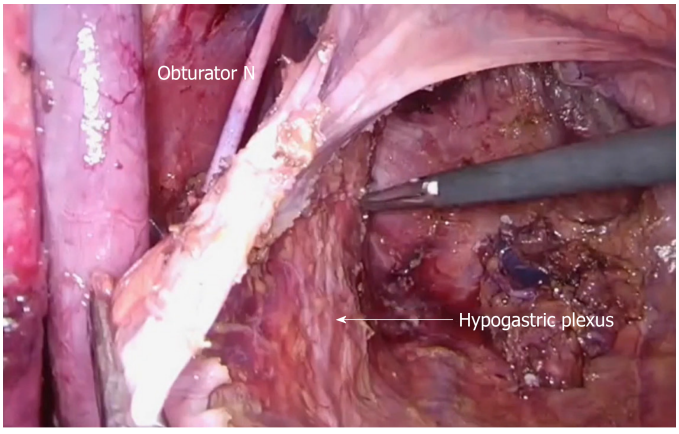

Figure 5 Preservation of ureterohypogastric fascia after lateral pelvic lymph node dissection.

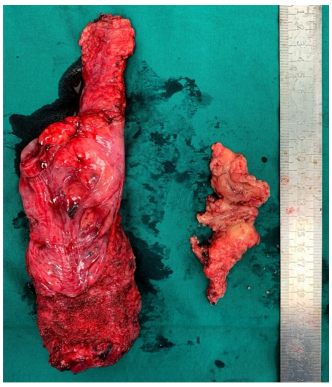

Figure 6 ***En bloc*** **lymphofatty tissue from lateral pelvic lymph node dissection.**

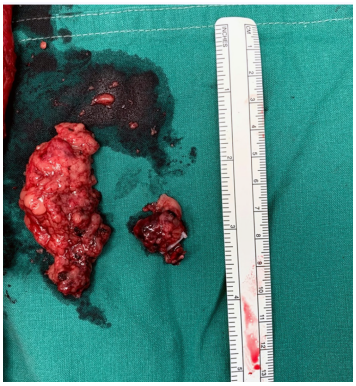

Figure 7 ***En bloc*** **lymphofatty tissue and metastatic lateral pelvic lymph node.**

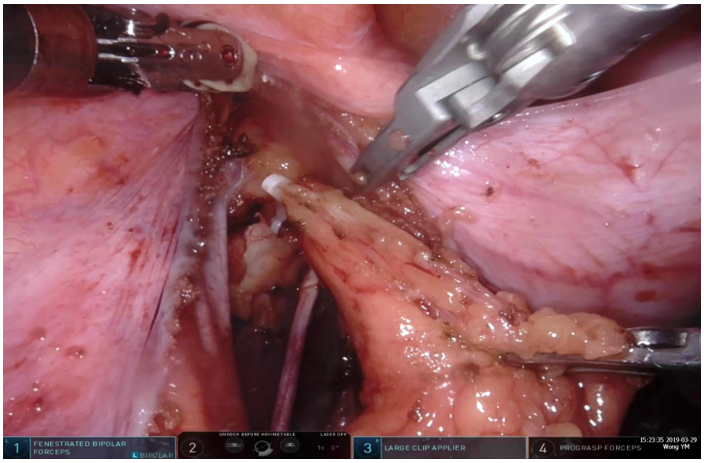

Figure 8 Clipping of a lymphatic channel.

ARTICLE HIGHLIGHTS

Research background

Despite chemoradiation, pelvic lymph node recurrence rates are still significant. Performing lateral pelvic lymph node dissection (LPND) is increasingly being acknowledged to be able to reduce pelvic recurrence rates in patients with rectal cancer. However, it is difficult to select and predict which patients have metastatic disease in their lateral pelvic lymph nodes (LPLN).

Research motivation

LPND has an important role in complete oncological clearance to improve outcomes for patients with rectal cancer. Performing it safely using minimally invasive techniques(MIS) has further benefits for patients.

Research objectives
To present the characteristics and outcomes of our patients who underwent LPND, including lymph node characteristics which may help to predict lymph node involvement. Also, to demonstrate the safety and feasibility of performing the procedure using minimally invasive techniques.

Research methods
Ethics approval was sought for this study. Clinico-pathological characteristics, perioperative variables and post-operative outcomes were analyzed retrospectively. Further analysis of the LPLN was performed, comparing their size against the final pathological outcomes.

Research results
Our findings show that there is minimal morbidity despite all procedures being performed using minimally invasive techniques. A lateral pelvic lymph node size of 1cm or more has a higher probability of metastasis. However, more research and data are needed to be analyzed to evaluate this size criterion for accuracy in predicting lymph node metastases.

Research conclusions
In conclusion, lateral pelvic lymph node disease was shown to be inadequately treated with neoadjuvant therapy. LPND using MIS techniques is safe and feasible. LPLN that are 10mm or larger have a significant chance of having metastatic disease. However, this is a small series and further data is needed to improve the selection of patients for LPND.

Research perspectives
Further research into this field should include larger and more extensive data sets to evaluate the size criteria that most accurately predicts lateral pelvic lymph node positivity. It may also reveal other variables that may assist in selecting patients that require LPND. We also wish to highlight the benefits of using the DaVinci Robot platform for this procedure, given its stability and maneuverability in a narrow space.

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ORIGINAL ARTICLE

Observational Study

Feasibility of robotic assisted bladder sparing pelvic exenteration for locally advanced rectal cancer: A single institution case series

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ORCID number: Nathaniel H Heah (0000-0001-2345-6789); Kar Yong Wong (0000-0003-4759-0979).

Author contributions: Wong KY and Heah NH all designed and performed research, analysed data, and wrote the paper.

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Informed consent statement: Patients were not required to give informed consent to the study because analysis used anonymous data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: The authors have no conflicts of interests to declare.

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Abstract

BACKGROUND

Pelvic exenteration for locally advanced rectal cancer involving prostate has been performed *via* open surgery. Robotic pelvic exenteration offers benefits of better pelvic visualisation and dissection for bladder preserving prostatectomy with vesicourethral anastomosis, while achieving clear margins.

AIM

To determine the feasibility of robotic assisted bladder sparing pelvic exenteration.

METHODS

We describe robotic assisted pelvic exenteration in three cases of locally advanced rectal cancer involving prostate and seminal vesicles (SV). The da Vinci S robotic system was used. Robotic console was docked at left oblique position for abdominal phase and redocked to between the patient's legs for pelvic phase. All three cases were performed fully robotically at Tan Tock Seng Hospital by colorectal and urological teams.

RESULTS

Case 1: 67-year-old with low rectal tumour 3cm from anal verge involving the prostate. He underwent neo-adjuvant chemoradiotherapy and robotic abdominoperineal resection with *en-bloc* prostatectomy. Case 2: 66-year-old with low rectal tumour 3cm from anal verge involving prostate and bilateral SV. He underwent neo-adjuvant chemoradiotherapy and robot assisted ultra-low anterior resection with coloanal anastomosis and *en-bloc* prostatectomy. Case 3: 57-year-old with metachronous rectal tumour in the rectovesical pouch inseparable from the anterior mid rectum, prostate and bilateral SV. He underwent robot assisted ultra-low anterior resection with *en-bloc* prostatectomy.

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Bladder neck margin revealed cauterized tumour cells, and he underwent total cystectomy and ileal conduit creation. Histology revealed no residual tumour. All patients are currently disease free

CONCLUSION
Robot assisted bladder sparing pelvic exenteration can be safely performed in locally advanced rectal cancer with acceptable surgical outcome while preserving benefits of minimally invasive surgery.

Key words: Rectal cancer; Robot surgery; Pelvic exenteration; Anterior resection; Prostatectomy; Minimal invasive surgery

Core tip: This paper adds on to the current evidence on feasibility of robotic surgery in pelvic exenteration for locally advanced rectal cancer. Studies on minimal invasive surgery for bladder sparing prostatectomy in rectal cancer scarce. Such extensive disease frequently requires total pelvic exenteration with ileal conduit formation. Our experience shows that minimal invasive surgery pelvic exenteration can be achieved using robotic surgery with good oncological outcome while at the same time, allows preservation of urinary and bowel function. This will encourage surgeons to consider the usage of robotic surgery in pelvic exenteration for rectal cancer.

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INTRODUCTION

Up to 10% of rectal cancers are locally advanced and many involve surrounding organs[1] necessitating extensive surgery for complete resection[2]. It is known that completeness of resection and clear resection margins (CRM) is a key factor in overall survival, disease free survival and is a predictor of local recurrence. In selected cases where rectal cancers are inseparable from other pelvic organs, *en-bloc* resection of urogenital organs are needed to achieve clear resection margin[3].

Traditionally, such complex operations have required open surgery. Even with the increasing adoption of minimally invasive surgery (MIS) for colorectal cancer, laparoscopic surgery in such large extirpative surgery is unquestionably challenging due to rigid laparoscopic instruments and narrow working space of the pelvis. It also involves a steep learning curve for surgeons, making it difficult to adopt this as a routine practice. With the adoption of robot in rectal cancer surgery in recent years, we see a role of robot in tackling difficult rectal cancer surgery. DaVinci© robotic system, with its 3-dimensional (3D) vision, enhanced ergonomics and elimination of tremor, has been shown to be non-inferior to laparoscopic surgery, in both short and medium-term outcomes. In locally advanced rectal cancer where the prostate is involved, robotic surgery enables preservation of the bladder after central exenteration by simplifying control of the dorsal venous complex (DVC) as well as performing an intracorporal anastomosis. The aim of our study is to describe three cases of advanced rectal cancer that used the DaVinci system to perform bladder sparing MIS pelvic exenteration and to demonstrate the feasibility of this procedure.

MATERIALS AND METHODS

We present 3 cases of patients with locally advanced rectal cancers. All cases were treated in the same centre, Tan Tock Seng Hospital, Singapore, by a combination of colorectal and urological teams with the aid of the DaVinci S Robot system to perform fully robotic-assisted surgery. Patients were placed in modified Lloyd-Davis position after general anaesthesia. The surgery was divided into 2 phases; abdominal phase

and pelvic phase. During the abdominal phase, the inferior mesenteric artery is ligated and left sided colon is mobilised. The splenic flexure is not routinely taken down unless there is concern of bowel length to anastomosis. The robot is docked from the patient left and ports placement as shown in Figure 1.

The pelvic phase requires the robot to be redocked in between the patient legs to facilitate total mesorectal excision (TME) and prostatectomy (We have since purchased the DaVinci Xi system after the publication of this paper and only single docking is required for the whole surgery). One assistant port is placed at right upper quadrant to assist in retraction and suction. After redocking, the pelvic phase begins with posterior dissection of the TME plane down till the pelvic floor. Lateral dissection was performed bilaterally as distal as possible, preserving lateral hypogastric nerve plexus. Anterior dissection and mobilisation of the rectum was not performed to avoid breaching the Denonvillier's fascia thus causing tumour spillage.

Dissection began posteriorly with mobilisation of bilateral seminal vesicles (SV) and vas. The bladder was dropped anteriorly and the bladder neck transected in usual fashion before the lateral prostatic pedicles were divided bilaterally. After the DVC was divided and over sewn, the urethra was divided sharply and prostatectomy was completed after division of rectourethralis.

Following resection of prostate, distal rectal dissection is continued to pelvic floor until full TME is achieved. Distal transection is performed using laparoscopic stapler for intended ultralow anterior resection. Otherwise, perineal excision is performed for abdomino-perineal resection.

The rectal tumour is removed *en-bloc* with prostate either *via* a pfannenstiel incision or the perineal wound. Coloanal anastomosis is performed if restoration of bowel continuity is possible. After completion of coloanal anastomosis, the vesicourethral anastomosis was performed by the urology team in a continuous fashion and a fresh indwelling urinary catheter was inserted. A leak test was performed to ensure the anastomosis was watertight. A diverting ileostomy is created at the end of the surgery.

Statistical analysis was performed with Stata 13.0 (StatCorp LLC, Texas, United States) using paired *t*-tests for dependent quantitative dependent variables.

This study received ethics approval from the local ethics board.

RESULTS

The average distance from the AV was 4.6 cm. Our series had a mean estimated blood loss of 700 mL, and average length of stay was 12.6 d. Average time to flatus was 3.3 d and average time to stoma functioning was 4.6 d. Average Hb drop was 2.3 (95%CI: -4.31 to -0.28, $P = 0.01$) and no patients required any transfusion in the intra-operative or immediate peri-operative period (first 24 h) (Table 1).

Patient 1

A 67-year-old man presented with per-rectal bleeding. He was diagnosed to have a low rectal tumour 3cm from the anal verge (AV) on colonoscopy. Staging computed tomography scans showed no evidence of metastatic disease. Magnetic resonance imaging (MRI) rectum done for local staging showed a clinical T4 tumour involving the prostate gland, with prominent peri-rectal lymph nodes. He underwent long course neo-adjuvant (NA) chemoradiotherapy and subsequently underwent a robot-assisted abdominoperineal resection with *en-bloc* prostatectomy with vesico-urethral anastomosis. His final histology was ypT3N1 disease, with clear margins. He was discharged well on post op day 4 and is currently disease free.

Patient 2

A 66-year-old man presented with change in bowel habits as well as tenesmus. He complained of reduced calibre of his stool with per-rectal bleeding mixed with his stools. He was found to have a low rectal tumour 3 cm from the AV on colonoscopy. Staging computed tomography scans did not show any distant metastases. MRI rectum showed a T4 low rectal tumour with invasion into the prostate and bilateral SV (Figure 2). Enlarged superior rectal nodes were seen on the MRI scan. He underwent long course NA chemoradiotherapy before undergoing a robot-assisted ultra-low anterior resection with J-pouch coloanal anastomosis and *en-bloc* prostatectomy with vesico-urethral anastomosis. Final histology showed ypT3N0 disease with clear margins (Figure 3). He completed adjuvant chemotherapy. His latest low anterior resection syndrome score is 18 (No low anterior resection syndrome) and his international prostate symptom score is 11.

Patient 3

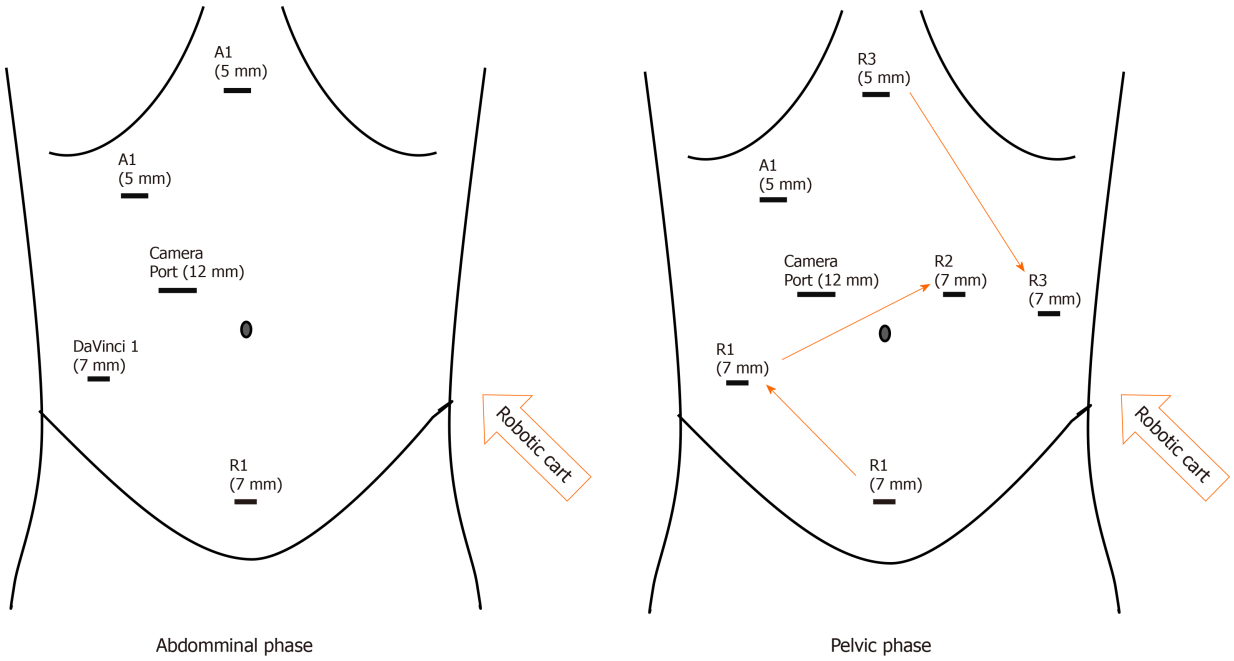

Figure 1 Port placement for robotic docking in both the pelvic and robotic phases.

A 57-year-old male with known previous pT4aN1b descending colon adenocarcinoma post left hemicolectomy, was diagnosed with recurrence in the rectovesical pouch on surveillance scans 3 year after his initial surgery. MRI rectum done for local staging showed an infiltrative soft tissue mass in the rectovesical pouch that was inseparable from the anterior mid rectum, prostate and bilateral SV. Radiological guided biopsy was performed and confirmed invasive adenocarcinoma with immunohistochemistry consistent with his previous biopsy. He underwent long course NA chemoradiotherapy before we performed a robot-assisted anterior resection with *en-bloc* prostatectomy and defunctioning ileostomy. Final histology confirmed the presence of recurrent colorectal adenocarcinoma. Cauterized tumour cells were seen at the bladder neck margin, while the rest of the margins were clear. His case was discussed at a multi-disciplinary team meeting and he underwent subsequent radical cystectomy and creation of ileal conduit. Subsequent histology from the radical cystectomy demonstrated no residual tumour.

DISCUSSION

Robot assisted exenteration was first reported in 2012[4] and subsequently the first case series was reported in 2014[5]. Another case series[6] published reported experience in multivisceral resection with robot assistance in, which the vagina and prostate were the most common organs resected. However, in these series, partial prostatic resection was performed without subsequent vesicourethral anastomosis or other forms of urinary diversion. Our study represents the first case series that reports on bladder sparing pelvic exenteration with vesicourethral anastomosis.

The DaVinci Robot system allows complex dissection and difficult anastomoses to be performed within the confines of the pelvis, with several advantages, including range of motion, reduction of tremor, binocular 3D vision, and magnification of field. These advantages are even more marked when operating within the tight confines of the male pelvis. This makes MIS more feasible with the aid of robot assistance and may result in less blood loss, lower transfusion requirements, decreased length of stay, with similar oncological outcomes.

Up to 10% of rectal cancers are locally advanced and pelvic exenteration is one of the few treatment modalities which offer potential survival gain and locoregional control[7]. However, the trade-off is that the peri-operative morbidity and mortality for such extensive surgery is high. In an era when laparoscopic surgery and robot assisted surgery are becoming common-place, the pelvic exenteration remains a procedure that is largely performed as open surgery. However, with the advancement of MIS in gynaecology and urology, acceptance for the suitability for MIS for pelvic exenteration is slowly gaining traction.

Table 1 Results for robotic bladder sparing exenteration

Patient	Age (yr)	Distance from AV (cm)	Pre-op Hb	Post-op Hb	Estimated blood loss (mL)	Margins	Underwent neo-adjuvant chemoradio-therapy
1	67	3	13.4	12.6	800	Negative	Yes
2	57	8	14.6	11.2	600	Cauterised edge	Yes
3	68	3	13.3	10.6	700	Negative	Yes
Average	64	4.6	13.7	11.5	700		

AV: Anal verge.

While laparoscopic exenteration in gynae-oncology[8] has been widely reported, there are only a few reports of laparoscopic exenteration in rectal surgery, and many of these have been reported to be extremely difficult, with a steep learning curve. The unique challenge of rectal surgery when compared to urological and gynaecological surgery in mainly due to the deeper pelvic dissection necessary, as well as the need for a low rectal anastomosis. This means that totally laparoscopic pelvic exenteration is extremely challenging due to technical difficulties[9], making this approach untenable for most, save for a few highly experienced laparoscopic surgeons. Our series has intra-operative blood loss ranging from 600-800mls, which is markedly less that what has been reported by other case series involving laparoscopic pelvic exenteration[10] and comparable to Shin *et al*[5].

Furthermore, the addition of bladder sparing *en-bloc* prostatectomy represents even more challenges, requiring an intra-corporeal vesico-urethral anastomosis. While there are several case reports for *en-bloc* bladder sparing pelvic exenterations, these were performed with open technique, with significant blood loss and prolonged post operatives stays[3]. The addition of a bladder sparing radical prostatectomy increases the risk of blood loss, especially during control of the DVC. Robot assisted surgery offers clear advantages to the surgeon, allowing quick ligation of the DVC intracorporeally. It also allows for complete prostatectomy to be performed, as opposed to partial prostatectomy as studies have shown that clear margins are associated with decreased rates of local recurrence, and it can be difficult to determine clear margins intra-operatively when performing a partial prostatectomy.

In our centre, robot assisted multivisceral resection is performed when adjacent organs are involved. Our case series reports only rectal cancers with prostate invasion because bladder sparing exenteration is rare. The bladder is usually routinely removed in open exenterations to do the difficulty of the vesicourethral anastomosis as well as questions regarding urinary control and function after bladder preservation. While mild incontinence is expected in up to 50% of patients in the immediate 12-18 mo following surgery, 5%-10% of patients may continue to have severe incontinence 12 mo after surgery regardless of the surgical approach. When extrapolated to include resection of the rectum, although we hope for similar urinary function most likely urinary function may be worse due to the close proximity of the hypogastric nerve during TME dissection. Use of the DaVinci robot system allows better 3D visualisation of the anatomy and precise dissection, reducing the risk of injury to the hypogastric nerve, and studies have shown that precise TME can be achieved using the robot with preservation of the pelvic autonomic nerves. This is reflected in our results, as patient 2 has been able to live on without the burden of a stoma. He has acceptable bowel and urinary function and has been able to maintain his premorbid quality of life.

In conclusion, our single centre early experience shows that robot assisted pelvic exenteration is feasible and safe in selected patient with locally advanced rectal cancers. The robotic approach can be applied to help patient's immediate post op recovery, retaining the benefits of MIS, while allowing the surgeon to perform multi-visceral surgery in the pelvis. Although there are still challenges in multidisciplinary robotic surgery as well as limited expertise and a continued learning curve, this minimally invasive methodology of pelvic exenteration with significant functional advantages shows much promise. Further studies are needed to demonstrate its superiority over standard open exenteration.

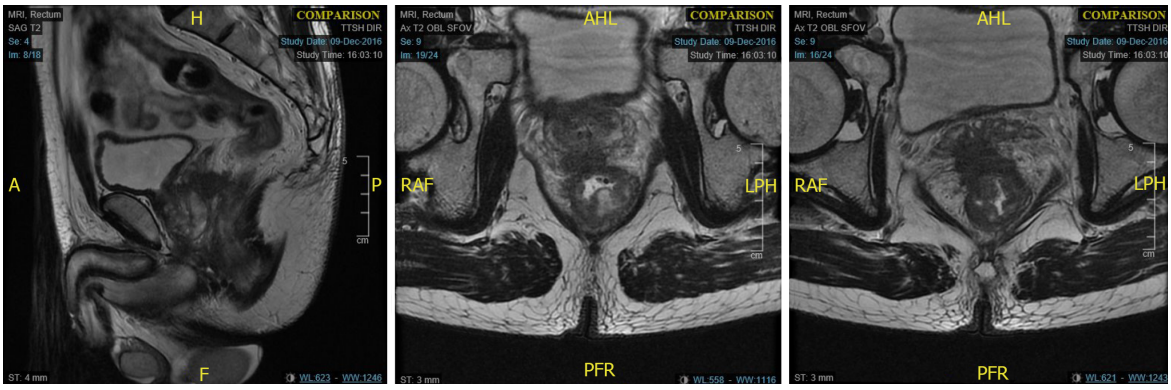

Figure 2 Magnetic resonance imaging demonstrating T4 low rectal tumour with prostate and bilateral seminal vesicle invasion.

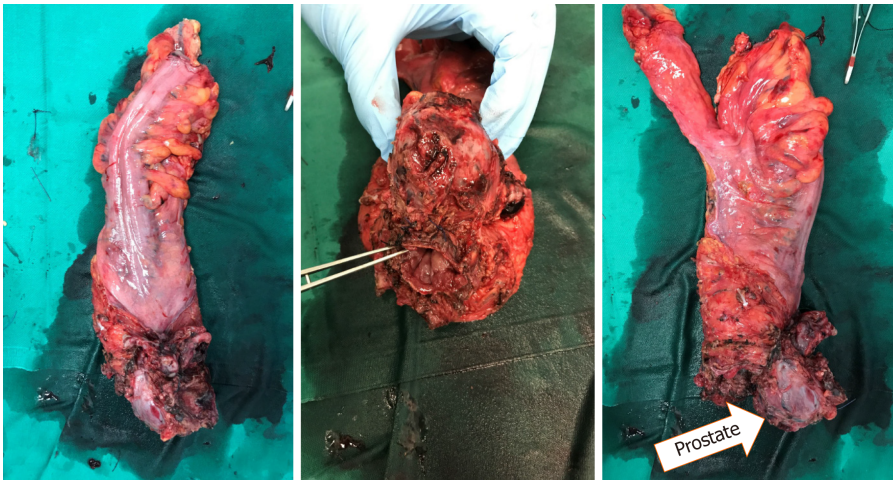

Figure 3 Histological specimen featuring 3 cm rectal tumour.

ARTICLE HIGHLIGHTS

Research background

Locally advanced rectal cancers can involve adjacent organs. In male, rectal cancers frequently involves seminal vesicles and prostate. Complete *en-bloc* removal of rectal cancer and adjacent organs with clear margin is key to successful oncological surgery, and this commonly requires a total pelvic exenteration with removal of urological and intestinal organ. Such extensive surgeries are usually performed *via* open technique. Majority of patients have a prolonged hospital stay due to wound pain and a decreased quality of life because of presence of permanent stomas.

Research motivation

Robotic surgery may have a role in introducing minimal invasive surgery to pelvic exenteration surgery for locally advanced rectal cancer. Robotic surgery allows anastomosis of bladder and urethra in the deep pelvis and can potentially reduce the rate of permanent stoma formation for patient in the future requiring total pelvic exenteration surgery.

Research objectives

To explore and demonstrate the benefits of robotic surgery as a form of minimal invasive surgery in total pelvic exenteration. To show the feasibility of minimally invasive surgery bladder preservation prostatectomy with total mesorectal excision. Patients are able to avoid a permanent ileal conduit and also maintain continuity of bowel when anal sphincter is spared.

Research methods

Ethics approval was sought for this study. The data for 3 patients were included in the analysis and statistics including mean and paired *t*-tests for dependent variables with Stata 13.0 software. Parameters gathered included patient demographics, tumour characteristics such as distance from anal verge, peri-operative data including estimated blood loss and peri-operative haemoglobin, and margin status.

Research results

Our research showed that robot assisted bladder sparing pelvic exenteration is feasible. Although the safety and oncological outcomes for the procedure appears to be acceptable, more research and data is needed to confirm this early finding.

Research conclusions

In conclusion, this pilot study of 3 patients using a novel technique of robot assisted bladder sparing pelvic exenterations is both feasible and safe. The advent of the DaVinci Robot allows complex pelvic surgery to be performed in a minimally invasive manner and the advantages of such an approach is clear, and performing such complex surgeries are pushing the boundaries of minimally invasive surgery. However, this is a small series and further data is needed to confirm the safety and oncological outcomes of this technique. Until then, patients need to be carefully selected before undergoing such a complex and challenging surgery from the minimally invasive approach.

Research perspectives

Future research in this field will involve not just confirmation of the findings from this initial case series, but also the extent and limitations of the DaVinci Robot system. 3D vision and increased magnification in the pelvis are crucial to ensuring clear margin status as well as good functional outcomes for the patients. Complex reconstructive surgery such as bowel anastomoses and urethrovesical anastomoses highlight the advantages of the DaVinci Robot system but direct comparison between robot assisted laparoscopic cases and open cases may prove to be challenging due to the rare and unique nature of these patients and their locally advanced disease.

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