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World Journal of Gastrointestinal Surgery

Contents

Monthly Volume 7 Number 11 November 27, 2015

EDITORIAL

279 Pelvic radiation therapy: Between delight and disaster

Morris KAL, Haboubi NY

289 Anastomotic leakage in rectal cancer surgery: The role of blood perfusion

Rutegård M, Rutegård J

REVIEW

293 Evolution and advances in laparoscopic ventral and incisional hernia repair

Vorst AL, Kaoutzanis C, Carbonell AM, Franz MG

MINIREVIEWS

306 Watch and wait approach to rectal cancer: A review

Pozo ME, Fang SH

313 Natural history of uncomplicated sigmoid diverticulitis

Buchs NC, Mortensen NJ, Ris F, Morel P, Gervaz P

319 Role of laryngeal mask airway in laparoscopic cholecystectomy

Beleña JM, Ochoa EJ, Núñez M, Gilsanz C, Vidal A

326 Endoscopic surgery - exploring the modalities

Lee DJK, Tan KY

ORIGINAL ARTICLE

Retrospective Study

335 Application of single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy

Hu BY, Leng JJ, Wan T, Zhang WZ

CASE REPORT

345 Gastric remnant twist in the immediate post-operative period following laparoscopic sleeve gastrectomy

Subhas G, Gupta A, Sabir M, Mittal VK

Contents

World Journal of Gastrointestinal Surgery
Volume 7 Number 11 November 27, 2015

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

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

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EDITORIAL

Pelvic radiation therapy: Between delight and disaster

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Abstract

In the last few decades radiotherapy was established as one of the best and most widely used treatment modalities for certain tumours. Unfortunately that came with a price. As more people with cancer survive longer an ever increasing number of patients are living with the complications of radiotherapy and have become, in certain cases, difficult to manage. Pelvic radiation disease (PRD) can result from ionising radiation-induced damage to surrounding non-cancerous tissues resulting in disruption of normal physiological functions and symptoms such as diarrhoea, tenesmus, incontinence and rectal bleeding. The burden of PRD-related symptoms, which impact on a patient's quality of life, has been under appreciated and sub-optimally managed. This article serves to promote awareness of PRD and the vast potential there is to improve current service provision and research activities.

Key words: Pelvic radiotherapy; Radiation; Toxicity

Core tip: Radical cancer treatments have come at a price. Radiotherapy carries the risk of pelvic radiation disease (PRD), a condition that can significantly reduce a patient's quality of life. We argue that PRD is a neglected problem that requires investment in service provision and research studies.

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INTRODUCTION

The last four decades have been a golden era for improving cancer survivorship. Three times as many people survive cancer than 30 years ago largely as a result of the increasingly potent, multi-modality treatment regimes[1]. Yet 20%-25% of cancer survivors

report a decline in quality of life secondary to the physical consequences of treatment[2]. A sinister side to cancer research studies is the fixation on survival statistics and prevention of disease recurrence. Patient quality of life has been unacceptably neglected. Toxicity and debilitating short- and long-term complications are inevitable consequences of radical treatments. Patients who receive radiotherapy form a large cohort of patients who report side effects leading to a reduced quality of life[1]. Radiotherapy is a cornerstone treatment for pelvic tumours which includes those of gastrointestinal, gynaecological or urological systems[3].

Radiotherapy to organs of the pelvis renders the bowel at risk of radiation induced injury, a condition recently coined pelvic radiation disease (PRD)[4,5]. This term encapsulates conditions including radiation enteritis, radiation proctitis and radiation cystitis[6] which inaccurately depict the condition as an ongoing inflammatory process. In fact, after the initial three months the inflammation is largely replaced by progressive ischaemia and fibrosis of tissues. This radiation induced damage to healthy tissue around the tumour could be a major limiting factor to curative treatment of localised cancer as treatment regimes may be interrupted.

This editorial outlines the clinical presentation, pathophysiology, histopathological features, prevention and management of PRD and aims to shed light on the future direction of much needed research in this field.

THE MAGNITUDE OF THE PROBLEM

It is truly remarkable how common PRD is. Yet should we be surprised? More people with pelvic tumours are treated with radiotherapy than any other anatomical site and as more people live longer with cancer or indeed survive it the burden of PRD increases. A questionnaire investigating the opinion of clinical oncologists in the United Kingdom reveals that most believe it is a significant problem that is under recognised and inadequately managed[7]. An impasse has been reached: The magnitude of the problem significantly exceeds clinical and research provisions. In fact, the annual incidence of patients adversely affected by PRD with symptoms of gastrointestinal disturbance eclipses the number of patients diagnosed with Crohn's disease[8]. Numerous large studies have documented the rates of complications in patients with pelvic tumours treated with surgery alone or surgery combined with either preoperative or postoperative radiotherapy[9-19]. Yet the funding and service provisions for PRD are a fraction of those for Crohn's disease[8].

A remarkable nine out of ten patients who received pelvic radiotherapy experience chronic change to bowel habit with five out of ten reporting a significant change to their quality of life[20]. Despite this only one fifth of patients with PRD in the United Kingdom are reviewed by a gastroenterologist[2]. This figure is even more remarkable given the fact that the onset of PRD, unlike inflammatory bowel disease (IBD), is relatively predictable. Acutely PRD occurs simultaneously or within three months of radiotherapy. There should be a low threshold for suspecting chronic PRD in patients previously treated with pelvic radiotherapy. PRD thus represents a model of disease with a predictable onset and a large patient cohort.

Not all patients who receive radiotherapy directed at tumours within the pelvis develop PRD. The reason for this is unclear however evidence suggests it may be a multifactorial process involving patient-related and treatment-related factors. Indeed, there is still uncertainty regarding who are the most susceptible patients, even those that fall into similar cohorts. Consequently, there is major scope for future research to exploit this disease model to shed light on the pathogenesis, preventative measures and management of PRD[21].

THE CLINICAL PRESENTATION

There is a vast spectrum of clinical presentations of PRD owing to numerous influential variables such as timing since radiotherapy, site of the tissue damage, severity of tissue damage, side effects of medications, coexisting medical conditions and psychological issues. The clinical presentations can be crudely classified into three clinical phases: Acute, chronic and delayed (latent)[22]. The timing of gastrointestinal complications of PRD follows a relatively predictable pattern (Table 1). Within these groups the symptoms of PRD may manifest as a result of direct damage to pelvic structures or as secondary phenomena triggered by the radiotherapy. These include small bowel bacterial overgrowth, bile salt malabsorption, malabsorption of lactose and similar fermentable sugars[23].

The acute phase

Acute PRD is defined as an acute inflammatory reaction to radiation treatment that can occur during, immediately after or within the first three months of radiotherapy. It occurs in 60%-80% of patients treated with abdominal or pelvic radiotherapy and is a major risk factor for modification of the planned treatment regime. Such changes could have ramifications on local tumour control[3]. Common symptoms include nausea, diarrhoea, tenesmus, abdominal cramps, urgency, mucus discharge, faecal urgency, loss of appetite and bleeding. Such non-specific symptoms can overlap with differential diagnoses such as infection, which needs to be excluded. Bleeding occurs in 50% of patients who receive pelvic radiotherapy as a consequence of radiation induced telangectasia which usually form on the anterior rectal wall[5]. Symptoms of acute PRD most commonly manifest in the second week post-radiotherapy and peak in week four or five and resolve within two to six months[23]. Importantly, the occurrence of acute PRD does not increase the risk of developing chronic PRD later on and patients can be reassured that resolution of symptoms generally occurs with cessation

Table 1 The timing of gastrointestinal complications of pelvic radiation disease in relation to tissue type damage

Complication	Primary tissue type damage	Timing
Acute proctitis	Epithelial	0-4 wk
Acute enteritis	Epithelial	0-4 wk
Rectal bleeding	Vascular	4-12 mo
Anal/perianal pain	Stromal	6-9 mo
Chronic abscess	Stromal	9-15 mo
Fistula	Stromal	18-24 mo
Stricture/malabsorption	Stromal	2-20 yr
Rectal malignancy	Epithelial	5-30 yr

of radiotherapy[24].

The chronic phase

Chronic PRD is a progressive condition and major source of morbidity for cancer survivors. Symptoms of chronic PRD begin to develop after a period of 6 mo to 3 years but can occur up to three decades following treatment. Occasionally the onset of symptoms crosses over with the acute phase of PRD. Clinically the signs of chronic PRD are symptoms of bowel dysmotility such as urgency. Altered transit of faeces and malabsorption are other prominent features[3]. In fact, when treating rectal cancer with radiation, it has been estimated that the majority will suffer from faecal incontinence[25]. Vascular telangectasia often lead to bleeding in the chronic phase. The bowel has a limited range of symptoms and therefore PRD manifests similarly to other bowel conditions including celiac disease, IBD, infection, malignancy, diverticular disease. The timing of radiotherapy in relationship to symptom manifestation is key to raising clinical suspicion and providing tailored support for PRD.

Patients that experience long standing chronic PRD can also experience sudden complications. Radiotherapy increases the risk of bowel wall stricture formation, adhesions, fissures, severe bleeding and bowel wall perforation. Surgeons should be alert to the fact that PRD may be the cause of acute or sub-acute small bowel obstruction.

The latent phase

A third stage of the clinical pathological presentation of PRD is well recognised. Latent clinical symptoms first arise years or decades after the initial radiotherapy treatment. Latent phase symptoms are in fact those of secondary malignancies, which can arise within or outside of the irradiation field. Radiotherapy used to treat the first malignancy can induce minor alterations to the nuclear DNA that predispose the cellular DNA to novel mutations, carcinogenesis and teratogenesis[22]. Studies have shown patients treated with radiotherapy for cervical or ovarian cancer developed endometrial cancer between approximately 15 years later[26,27]. Importantly there was a preponderance for high-risk histological sub-types in endometrial cancers that develop after pelvic radiotherapy[27]. Prostate cacner not treated with RT is not associated with an increased risk of other malignancies. Bostrom and Soloway[28] (2007) showed that there is a slight increase in radiation-induced secondary malignancies after prostate radiotherapy. Approximately one in seventy of such patients who survive longer than ten years will develop a secondary malignancy. There is a predilection for secondary rectal or bladder tumours[28]. Despite the association between radiotherapy and secondary malignancies there is a lack of definitive evidence for a direct relationship.

Clinicians should be suspicious of a primary tumour in any patient who has received pelvic radiotherapy and has new onset red flag symptoms of cancer, such as *per rectum* bleeding. Furthermore, although the risk of secondary malignancies after pelvic radiotherapy is modestly above the overall population patients should be informed about the risk.

THE PATHOPHYSIOLOGY OF PRD

Cells exposed to ionising radiation experience oxidative stress injuries. The damage is widespread however the principle sub-cellular target is the nuclear DNA[29]. Both direct and indirect mechanisms inhibit DNA from fulfilling its function as a template for DNA transcription. The nuclear chromatin is directly targeted, causing DNA damage through the generation of inter- and intra-strand cross-linkages, breaks and mutations. The plasma membrane is directly affected as radiotherapy disrupts the rigidity of the phospholipid bilayer and electric gradient; injuries which challenge integrity of the cell. Indirect damage occurs secondary to the formation of free radicals from the ionisation of water molecules[22].

Intricate and coordinated DNA repair mechanisms have evolved to fix damage induced by ionising radiation, including strand breaks and replication errors. At low levels of radiation repair mechanisms in the cell can resolve injuries such as double strand breaks. With increasing amounts of radiation the damage inflicted overwhelms these systems and the cell either enters programmed cell death (apoptosis) or mitosis is inhibited. The amount of ionising radiation required to inflict cell inactivation and cell death varies between each tumour and its surrounding tissues[30]. A further variable that influences a cell's response to radiotherapy is whether adjuvant chemotherapy features in the treatment regime. Concomitant chemotherapy often leads to delay or prevention of the reparative process thus aggravating the disease. Chemotherapeutic agents may help to accumulate cells in the more radiosensitive stages of the cell cycle. Timing of radiotherapy in relation to chemotherapy is an essential consideration[31].

The damaging affect of radiotherapy is most potent against tissues with a high turnover, making it an ideal modality to treat typically rapidly proliferating tumour cells. This is because the potential cell injury is dependent not only upon the cellular repair processes but also the stage of the cell cycle that the cell is in. Certain stages within the cell cycle optimise the

opportunity to repair damage. For example, ionising radiation damage results in cell cycle arrest and initiation of a temporary cell cycle check point. This aims to provide time to conduct repairs. A crucial protein in the checkpoint machinery is the tumour suppressor gene *p53*. Highly proliferative cells, such as those residing in the crypt epithelium of the bowel, are frequently in the more radiosensitive G_2-M phase[31]. Crypt cell death results in insufficient renewal of the villous epithelium. The mucosa and lamina propria become inflamed and the mucosal barrier breaks down[3]. In comparison slowly dividing tissues, such as those in vascular or fibrous tissue, spend more time in the less radiosensitive G_1 and S phases and damage to these tissues are usually not responsible for acute clinical presentations[22].

Impaired anorectal functionality

Maintenance of faecal continence is regulated by the tonic contractions of the internal and external anal sphincters. The former is a smooth muscle and is supplied by intrinsic myenteric innervation and has the chief role of maintaining a tonic contraction and thus continence whilst at rest. Comparatively the external sphincter is composed of striated muscle and is innervated by an extrinsic supply. In health these work together to provide an effective seal to solids, liquids and flatus. The anorectum has a rich nervous supply, which includes pain, temperature and touch sensory components, each of which aid the maintenance of continence through the ability to differentiate between solids and flatus. Impaired anal functioning can result from damage to the nerves of the pelvis including the pudendal nerve, the lumbo-sacral plexus and the myenteric plexus. The external anal sphincter is relatively radioresistant and it is postulated that faecal incontinence is strongly influenced by nerve damage. Case reports demonstrate that damage to the pudendal nerve may lead to morphological changes in the muscle. Some case reports have proposed that injury to the lumbo-sacral plexus can indirectly affect the external anal sphincter by causing perianal anaesthesia[32].

MICROSCOPIC CHANGES TO THE BOWEL MUCOSA

An appreciation of the radiation induced microscopic changes observed in patients with PRD is a window to understanding the clinical symptoms, stages of the disease and how best to manage the condition. The epithelial cells within the bowel wall, particularly those in the small bowel, have a high turnover rate which renders them vulnerable to ionising radiation. A fine balance lies between the dose tolerated by the epithelium and the dose that destroys the neoplasm. Histologically the damage inflicted upon surrounding healthy tissues has characteristic appearances depending upon the time interval since the radiotherapy. There are three main histological phases depending upon the tissue type that is predominantly affected. The epithelial phase generally correlates with acute phase clinical symptoms with vascular and stromal changes commence several weeks later (Table 1)[33].

In the epithelial phase damage to the epithelium, seen as sloughing of epithelial cells into crypt lumina, can be observed within eight hours of exposure to ionising radiation. Other characteristic acute phase histological changes include patchy fibroblastic changes to the submucosa, epithelial meganucleosis and significant eosinophilic infiltrate with formation of eosinophilic microabscesses. Caution and experience is required to interpret these morphological changes as they can resemble dysplasia. Nuclear and cytoplasmic early phase changes are usually reversible[33]. Mitosis is inhibited preventing epithelial re-growth and causing denudation of the underlying structures. Importantly, during the acute phase the vasculature appears normal[33,34].

Severe fibrovascular changes, depletion of goblet cells and atrophy are core features of chronic PRD and the vascular phase. Extensive fibrosis can be seen in submucosal arterioles and the lamina propria, which contributes to deformed architecture such as crypt distortion. Characteristic changes during the vascular are telangectasia of capillaries and post-capillary venules, fibrin deposition, subendothelial odema and platelet thrombi formation that can cause *per rectum* bleeding[33]. Ultimately there is significant narrowing of the vascular lumina that leads to ischaemia and further fibrosis. Macroscopically these microscopic changes correlate with a pale, non-compliant bowel wall with telangectasia[24]. The reversibility of the vascular phase morphological changes is unclear however the stromal phase which includes mesenchymal and stomal fibrosis is irreversible[33].

Despite these distinctions the bowel has a limited array of modifications in response to damage. In fact under a microscope a canny mimic of chronic PRD is the quiescent phase of IBD. Since chronic PRD can take months, if not years to develop, is quite possible that PRD is overlooked as a differential diagnosis and the histopathologist could remain oblivious to the patient's history of irradiation. Relevant clinical information is therefore essential for the histopathologist. As they trawl through mounds of rectal biopsies labelled with minimal clinical information the biopsy from the patient with chronic PRD could be mistaken for chronic IBD[35].

Importantly, a study profiling the time patterns of histological mucosal changes in relation to the clinical manifestation of PRD indicated that they do not always coincide. Microscopic evidence of inflammation in rectal biopsies precedes the onset of symptoms. Thus pathological changes do not always cause the symptoms but it is the disruption to normal physiological processes that results in the symptoms such as diarrhoea. These findings suggest that pre-emptive, prophylactic treatment that tries to prevent PRD may be a prudent way to tackle the condition[36].

HOW TO PREVENT PRD

Preventing the adverse impact of radiotherapy and development of PRD is a multi-disciplinary responsibility. Prior to receiving radiotherapy the patient should be optimised for treatment by attempting to control and treat pre-existing co-morbidities, such as hypertension and diabetes, and making lifestyle modifications like smoking cessation. Clinical oncologists have, over the decades, honed the radiotherapy regimes to try to reduce damage from too high doses or too large field sizes. Medical oncologists should liase closely with surgeons and clinical oncologists to attempt to minimise the increased toxic effects of concurrent chemotherapy.

Factors related to the host

Hypertension, arterial disease, IBD and diabetes mellitus are co-morbidities that predispose a patient to PRD. Previous abdominal surgery also increases the likehood of PRD owing to the tethering effect of adhesions that reduce bowel motility out of the radiation field[22]. Tobacco smoking is an independent risk factor for predicting the development of complications to radiotherapy. A body mass index greater than 30 is found to be protective against pelvic and abdominal radiotherapy whereas low body mass increase the risk of toxicity. Genetic predisposition is thought to explain the varying level of complications observed between patients who receive the same radiotherapy regime[3].

Factors related to therapy

When radiotherapy was initially used against tumours within the pelvis the development of resistance to the radiation was a common set back. This was especially problematic in patients with rectal cancer. Higher doses were discovered to overcome the resistance but are associated with higher collateral damage to surrounding healthy tissue in the radiotherapy beam[24].

High doses and large field sizes are associated with increased radiotherapy toxicity. Large doses per fraction facilitate a quicker completion of the radiotherapy regime and progression to surgery. Larger doses are believed to increase the chronic complications of radiotherapy as increase the safety problems of concurrent chemotherapy. These observations were particularly pertinent in the 1970s when patients with carcinoma of the uterine cervix were treated with > 1000 cGy/min over 2-3 min resulting in irreparable tissue damage. Modifications to radiotherapy doses have since resolved this risk[22]. Dose-volume histograms are routinely used by clinical oncologists to plot cumulative dose-volume frequency to help safeguard against toxicity and PRD[37].

Radiation therapy can be administered to a patient in two main ways: *Via* external beam radiation or brachytherapy (radioactive implants). The field size used in external beam radiotherapy is crucial to the level of exposure that surrounding healthy tissues receives. Large field sizes increase the acute side effects, in particular diarrhoea. Radiotherapy is delivered using an external photon generator that exposes the patient to X-rays, electron beams and gamma rays in a four beam approach which results in significant exposure to surrounding tissues[24]. Development of three dimensional conformal radiation therapy and intensity-modulated radiation therapy attempts to minimise the field size thus sparing non-cancerous tissue. Large field exposure can be avoided by limiting the field to 2-3 cm beyond the tumour margin on computed tomography (CT) or magnetic resonance imaging scans. This strategy accounts for natural bowel motility and infiltration of metastatic cells beyond tumour margins. Alternatively, surgical clips at sites of residual disease can be used as landmarks for post-operative radiotherapy although they are less reliable indicators than scans. Consequently, post-operative radiotherapy often utilises larger field sizes in comparison to pre-operative fields[22].

Post-operative radiotherapy is more toxic than preoperative radiotherapy due to disturbance to the natural reflections of the perineum and allowing it to enter the pelvis. Following surgery adhesions form around the bowel limiting its movement and tethering it in potential radiation fields. The Swedish rectal cancer trial involving 1168 patients randomly assigned to surgery alone or surgery with neoadjuvant radiotherapy showed five year survival rates as 48% and 58% (P = 0.004), respectively[38]. Studies comparing surgery with either pre-operative or post-operative radiotherapy for rectal cancer showed significant differences between the incidence of bowel habit disturbance (minimal *vs* 90% respectively)[11,39].

A retrospective study explored the use of non-absorbable mesh implanted during surgery which would act to protect the small bowel from radiation injury and suggests a reduction in chronic PRD from 90% to 3%[40]. Prophylactic surgical techniques such as pelvic reconstruction, omentoplasty and transposition of the large bowel can reduce the volume of bowel at risk of radiation exposure by 60%. Additionally clinical oncologists have developed a range of techniques to reduce PRD. Image guidance techniques such as megavoltage and kilovoltage cone beam CT performed immediately before radiotherapy can accurately assess location and mobility of the bowel. Manoeuvring the patient into the supine position during the radiotherapy has significantly reduced the incidence of PRD in patients treated for prostate, rectal, small bowel and bladder cancer[37].

MANAGEMENT

How to manage patients with PRD is a contentious subject. It was largely believed to be untreatable until a better understanding of the aetiology and pathogenesis paved the way for a paradigm shift in treatment. Medicines, dietary modifications and supportive measures are some of the components of current guidelines. In the

majority of cases the cornerstone of management after prevention is symptom control. Symptoms can originate from a variety of affected sites therefore a crucial step in PRD management is the understanding that urological, gastrointestinal, gynaecological, dermatological, lymphatic, nervous, vascular structures and sexual organs can be involved. The severity of damage and whether the patient is in the acute or chronic phase of PRD are additional variables that make each patients case unique. A degree of flexibility is essential when approaching PRD to cater for this wide spectrum of clinical presentations. Several scoring systems have been developed or adopted from elsewhere to quantify and categorise a patient's symptoms and quality of life. The inflammatory bowel disease questionnaire-bowel subset score[2] and the Franco-Italian glossary which classifies symptom severity 0 to 4[41] are two such examples.

Additionally, the psychological impact of PRD should never be underestimated. Evidence shows that 24 mo after radiotherapy for cervical cancer disease-free patients have a reduced quality of life and experience psychological reactions such as inability to perform daily household tasks and making plans for the future[42]. Sexual functioning in both males and females, ejaculation disorders and erectile dysfunction are significantly more common in patients who have received pelvic radiation when compared to surgery alone[17]. Although the bowel is the most affected site radiotherapy to the pelvis can cause complications such as vaginal stenosis. The pathogenesis of this condition is akin to that in the bowel; inflammation within the connective tissues and blood vessels leads to fibrosis and a reduced blood supply. Consequently, the hypoxic conditions encourage loss of elastin, atrophy and collagen deposition[43]. A holistic approach addressing the physical, psychological, social and emotional hurdles of PRD is thus gold standard management.

Management during the acute phase

Treatment of acute PRD can take the form of supportive and/or dietary modifications. To tackle the problem of diarrhoea bulking agents and anti-kinetic drugs, such as fybogel, codeine and loperamide, are commonly prescribed to increase excess fluid absorption in the bowel and to reduce the peristaltic activity, respectively. Anti-cholinergic anti-spasmodics, anti-emetics and analgesia are other agents offering effective symptom control. Most patients respond to this regime however patients with profuse diarrhoea leading to malabsorption and dehydration require more intensive supportive measures with fluids and electrolyte balance support. The use of these measures is generally based on anecdotal evidence and experience of the attending healthcare professionals. A salient point about acute PRD is that symptoms often recede once the radiotherapy regime has ceased[23]. Transparency about the potential for chronic manifestations of PRD through education and counselling can encourage patients to seek medical attention if needed.

Management during the chronic phase

Making the diagnosis of chronic PRD can be a convoluted process. Irritable bowel syndrome is a common misdiagnosis. Once the diagnosis is made many patients symptoms improve with modification of their diet. Ionising radiation can cause damaged intestinal villi and insufficient enzyme production leading to malabsorption of nutrients. Low fat, low roughage and low residue diets are encouraged and adequate calorific and fluid intake is essential. Dietetic input can provided structured and targeted advice[23]. Should symptoms persist, medical management can be added to this conservative approach through the addition of anti-inflammatory agents. Steroid enemas or suppositories and oral 5 acetyl salicylic acid preparations may offer symptomatic relief of *per rectum* bleeding, tenesmus or urgency[22].

In 2010, the United Kingdom national cancer survivorship initiative vision was launched. Its aims were to stimulate development of new models of care to manage patients with chronic cancer related symptoms. The initiative came into being after the recognition that surviving cancer does not equate to a good quality of life. The consequences of cancer treatment can result in debilitating chronic symptoms[2]. In total 23 different gastrointestinal symptoms have been associated with chronic PRD. The cluster of symptoms, severity, frequency of symptoms all vary between individual patients making chronic PRD a highly heterogenous condition. Andreyev *et al*[1] (2013) devised an investigative and management algorithm to help improve the gastrointestinal symptoms of chronic PRD. Results of the randomised control trial showed that use of the algorithm-based care improved symptoms in patients with PRD. Additionally, the study indicated that nurse-led care is sufficient for the majority of patients with PRD[2].

Malabsorption of bile acids is believed to be the cause diarrheal symptoms in between 35%-72% of patients with chronic PRD[23]. Ninety-five percent of all bile acid salts are absorbed in the terminal ileum which means that damage to this area or decreased transit time leads to bile acid malabsorption[44]. The terminal ileum is the most commonly affected portion of small bowel affected by PRD. An important factor which determines the risk of radiation induced damage to the bowel is its mobility. An area that is not tethered and therefore mobile has a chance of migrating into areas outside the radiation field in the weeks between radiation fractions. The entire duodenum, the jejunum at the ligament of trietz and the terminal ileum are tethered in place making them vulnerable for repeated radiation exposure[34]. Cholestyramine, colestipol and colesevelam bind bile salts and have been administered to patients with PRD[23]. There is evidence that patients with PRD respond well to the former agent but palatability is an issue[45].

LATEST DEVELOPMENTS AND FUTURE RESEARCH PRIORITIES

Rather disturbingly, although there have been a plethora of expensive multi-centre studies into the treatment of cancer, there is scant evidence of how to optimally manage the debilitating consequences of treatment. Several strategies of PRD management are being researched and are potential avenues for future PRD management.

Antibiotics vs probiotics

As outlined above, ionising radiation modifies the intestinal muscosa, inducing changes to the vascular permeability of the mucosa and overall motility. These changes directly impact on the natural bacteria that colonise the bowel[46]. Specifically, dysmotility and stasis encourages bacterial overgrowth in the small bowel. In comparison to the colon the small bowel usually harbours few microorganisms. Jejunal cultures from one in three people detect no bacteria. Ionising radiation disturbs the homeostasis of indigenous intestinal microflora which directly influences bowel functions. For example, they have a role in processing unabsorbed dietary carbohydrates and converting them into fatty acids: An energy source for the colonic mucosa. Enteric bacteria contribute to their host's health by synthesising essential molecules such as vitamin K and folate. Commensal bacteria also interact with the host immune response inducing a state of controlled inflammation which maintains a fine homeostasis between protection against disease and chronic inflammation[47].

There is contradictory evidence of how to combat this radiotherapy - induced pathophysiological change. Broad spectrum antibiotics including co-amoxiclav, ciprofloxacin, tetracycline and rifaximim are frequently used but some patients require repeated courses or low dose, long-term maintenance therapy[48]. Understanding the pathophysiology led to studies into the use of probiotics which aim to restore the balance of the commensal microbiota. Trials have yielded mixed results with some heralding lactobacilli probiotics as a cheap, safe and feasible method of reducing diarrhoea in the acute phase[46,49] with others finding no significant reduction in diarrhoeal symptoms[50]. There is currently no evidence supporting their use in the prevention of chronic PRD. This remains an area for future research studies[51].

Medications

Patients who take angiotensin I-converting enzyme inhibitors (ACEi) and the cholesterol lowering statins have been observed to have fewer gastrointestinal complications from radiotherapy to the pelvis. *In vitro* studies have supported this by showing the anti-inflammatory, anti-thrombotic and anti-fibrotic properties of statins when administered to human cells treated with ionising radiation[52]. The mechanism of action of statins is to inhibit 3-hydroxymethylglutaryl co-enzyme A reductase whilst ACEi block the conversion of angiotensin Ⅰ to angiotensin Ⅱ, which influences blood pressure homeostasis. These drug-induced physiological changes have recently been shown to have a protective effect on the bowel when it is exposed to ionising radiation. Wedlake *et al*[53] (2012) showed that in a study of 308 patients the use of a statin or stain with an ACEi significantly reduced the incidence of gastrointestinal symptoms following radiotherapy. Further prospective, randomised, blinded, adequately powered and stratified by disease stage trials with adequate follow up are required to support the use of statins and ACEi in PRD management.

Hyperbaric oxygen

Hyperbaric oxygen (HBO) therapy has been utilised to treat chronic PRD for several decades[54] but with insufficient evidence of its exact mechanism of action or to support its use in clinical practice. More recently HBO has been found to decrease tissue hypoxia by inducing angiogenesis in bowel affected by the ischaemic and fibrotic changes associated with chronic PRD changes[55]. Clarke *et al*[56] (2008) conducted the first randomised control trial and provided support for its use in refractory PRD. Specifically, HBO induced healing responses and was associated with an absolute risk reduction of 32%. Furthermore, bowel specific quality of life was improved. HBO treatment does require a significant time commitment, logistical hurdles and is expensive to fund. A complete regime consists of eight weeks of daily treatment in a specialist unit that typically have vast catchment areas[5].

Argon plasma coagulation

Three main strategies for managing PRD exist: Medical, surgical and endoscopic. New techniques are emerging in the endoscopy arena, such as argon plasma coagulation (APC) therapy, which followed the limited success of treating vascular telangiectasia with locally applied formaline solution. APC therapy is a noncontact thermal coagulation technique on a probe that can be passed through the scope during endoscopy. The probe delivers argon gas to bowel mucosa targeted by the endoscopist. A high voltage filament then ionises the gas which heats the mucosa and results in coagulation of tissues damaged by PRD and aims to prevent them from bleeding. So far, several case series have shown that APC reduces rectal bleeding in 80%-90% of treated patients[57]. APC should be used with caution as serious complications have been documented in as high as 26% of patients[58]. A case series of 16 patients states that it is a safe, well tolerated treatment for rectal bleeding in PRD and should be considered as first line treatment[59]. However, currently the evidence for its use in clinical practice is insufficient. There is a need for large, prospective, blinded, randomised control trials to explore the use of APC in PRD management and to explore its safety and outcomes in the short- and long-term[12].

Key research priorities

An area that requires serious consideration is clarification of the most effective - by considering both survival and quality of life parameters - radiotherapy regime for mid and lower rectal carcinomas. There is wide variation between treatment centres across the world. Short course with immediate surgery, short course with delayed surgery, long course with neoadjuvant chemotherapy then surgery and chemoradiotherapy without surgery are some of the approaches utilised to treat patients with the same stage of disease. It is concerning that without a unified approach that some centres or clinicians may be basing their clinical decisions on anecdotal evidence. A consensus meeting to address the application and modality of radiotherapy to low and mid rectal cancers could be a key step in reducing the incidence of future PRD cases.

Key research priorities revolve around the need for randomised trials of best supportative care *vs* hyperbaric oxygen or argon plasma coagulation or intrarectal formalin for bleeding associated with PRD. A large multi-centre phase three study in the United Kingdom, the Hyperbaric Oxygen Therapy (HOT-Ⅱ) study is completed, the results of which are eagerly awaited.

Further research into service provision would shed light on how best to use the resources that are currently in place. Simple amendments and interventions have the potential to improve patient care. The findings of a trial conducted by Andreyev *et al*[1] (2013) provided evidence that the use of an investigative and management algorithm for practitioners to follow improves patient symptoms when compared to current care.

CONCLUSION

A crucial step in management planning for patients with cancer is consideration of the risk-benefit ratio. Clinicians are faced with the task of weighing up the benefit of prolonged survival following surgery and radiotherapy *vs* the risks of treatment related complications such as PRD. As the number of cancer survivors continues to increase the long-term outcomes related to health and well-being, exemplified by those patients who develop PRD, becomes an ever more significant health issue. However, striving to improve cancer survivorship has meant that the recognition and management of treatment associated complications has not been prioritised. Thousands of patients with PRD are poorly managed and denied a service that is tailored to meet their needs. Although it is an uncomfortable notion we must not shy away from iatrogenic causes of patient debility[4]. Effective methods to prevent PRD and an optimal, unified strategy to manage affected patients remain elusive making PRD a well-placed focus for future research[3].

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EDITORIAL

Anastomotic leakage in rectal cancer surgery: The role of blood perfusion

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Abstract

Anastomotic leakage after anterior resection for rectal cancer remains a common and often devastating complication. Preoperative risk factors for anastomotic leakage have been studied extensively and are used for patient selection, especially whether to perform a diverting stoma or not. From the current literature, data suggest that perfusion in the rectal stump rather than in the colonic limb may be more important for the integrity of the colorectal anastomosis. Moreover, available research suggests that the mid and upper rectum is considerably more vascularized than the lower part, in which the posterior compartment seems most vulnerable. These data fit neatly with the observation that anastomotic leaks are far more frequent in patients undergoing total compared to partial mesorectal excision, and also that most leaks occur dorsally. Clinical judgment has been shown to ineffectively assess anastomotic viability, while promising methods to measure blood perfusion are evolving. Much interest has recently been turned to near-infrared light technology, enhanced with fluorescent agents, which enables intraoperative perfusion assessment. Preliminary data are promising, but large-scale controlled trials are lacking. With maturation of such technology, perfusion measurements may in the future inform the surgeon whether anastomoses are at risk. In high colorectal anastomoses, anastomotic revision might be feasible, while a diverting stoma could be fashioned selectively instead of routinely for low anastomoses.

Key words: Anastomotic leakage; Blood perfusion; Rectal cancer; Anterior resection; Diverting stoma

Core tip: Anastomotic leakage after anterior resection for rectal cancer is still common. Several preoperative risk factors may inform the surgeon of the leakage risk. The surgeon might choose to perform a diverting stoma to mitigate this risk, or to construct an end colostomy and thus avoid an anastomosis altogether. Intraoperatively, clinical judgment of the viability of the anastomosis is not reliable. However, research using blood perfusion measurement technology has evolved in recent years; technology using near-infra red light seems to be promising, allowing assessment

of the bowel perfusion. In the future, such technology may aid in the decision-making concerning colorectal anastomoses.

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INTRODUCTION

Anterior resection is considered standard procedure for patients with cancer in the mid and high rectum. With the advent of the total mesorectal excision (TME) technique, complications such as anastomotic leakage have been increasing in frequency[1]; current population-based studies indicate rates of around 10%-11%[2,3]. The impact of anastomotic leakage is considerable, leading to major morbidity and mortality[4]. Anastomotic breakdown is a multifactorial event, influenced by patient factors as well as surgical technique[5,6], although the pathogenesis has not been clearly elucidated. Axiomatically, the fundamental principles of a successful anastomosis entail anastomosing two ends of healthy bowel with adequate blood supply and lack of tension after union. The former aspect has been the subject of considerable debate but perhaps less investigation. Surgeons' ability to predict anastomotic leakage by judging the appearance of the serosa has been shown to be highly unreliable[7]; in current practice, only risk factor appraisal is available to guide the surgeon when making decisions whether to, *e.g.*, perform a diverting stoma, revise the anastomosis, or fashion an end colostomy. However, the advent of new studies and technologies may soon provide surgeons with effective means of assessing anastomotic viability.

Blood flow measurement technology

A plethora of methods has been used to determine blood flow or oxygenation in general surgery[8]. The most commonly used method has been laser-Doppler flowmetry (LDF), the principle of which is to measure the Doppler shift - the frequency change that light waves undergo when reflected by moving objects, *e.g.*, red blood cells. Laser light is emitted and the backscattered light is collected, producing an output signal that is proportional to the number and velocity of the moving blood cells in the measured volume. The method has proven to be reproducible and has been correlated with other flow measurements, but LDF measurements are easily perturbed by motion artefacts and require direct tissue contact, which may disturb local blood flow. In order to measure oxygenation, visible light spectrophotometry offers shallow penetration of tissue at the capillary level, while near-infrared (NIR) light goes deeper and allows for a global oxygenation assessment. Spectrophotometry systems employ devices that emit light on or near the bowel wall - this light penetrates, diffuses and is subsequently analysed as it re-emerges variably coloured, according to the oxygenation level. In combination with injection of fluorescent agents, perfusion may also be evaluated by the NIR technique, which has lately been introduced into clinical studies[8].

Vascular anatomy and the anastomosis

The importance of the knowledge of gross vascular anatomy cannot be overstated. Much attention has been directed at the colonic limb of the colorectal anastomosis, as evidenced by the controversy surrounding high ligation of the inferior mesenteric artery - high arterial ligation may compromise blood supply to the oral part of the anastomosis, if the sigmoid or descending colon is used and the marginal artery is not present or patent.

A Japanese group performed LDF on patients operated for cancer of the rectum and the sigmoid colon; colonic measurements were made before and after clamping, and showed marked reductions in perfusion after clamping, particularly for high tie patients[9]. Similar methodology was used by a Dutch group, but these authors compared measurements made immediately after laparotomy to measurements made before fashioning the anastomosis, and found that there were blood flow reductions in high tie patients; however, low tie patients displayed an increase in blood flow, a difference between groups that was statistically significant[10].

Observational studies on the clinical impact of high ligation have not consistently shown that this is a risk factor for anastomotic leakage[3,11,12], while no randomized clinical trial data are available. It is entirely possible that any perfusion compromise is uncommon due to collateral networks and also that surgeons adjust the colonic resection margins when faced with perfusion loss; thus, any perfusion disadvantage rendered by the high tie on the oral part of the anastomosis might be mitigated.

Using the TME technique, dissection at the level of the pelvic floor is sometimes extensive. The rectal blood supply after anterior resection is dependent on the inferior and the variable medial rectal arteries, but perfusion to the different parts of the rectum is not equally distributed. Angiographic findings suggest that the lower rectum has a sparse network of intramural collaterals, in contrast to the more vascularized upper and mid rectum[13]; this might explain the lower leak rate when performing partial mesorectal excision (PME), an oncologically feasible alternative for tumours in the upper rectum[14]. Moreover, the dorsocaudal aspect of the rectum is sparsely perfused[15], lending biological rationale to the clinical experience that most anastomotic leaks are located in the posterior aspect of the rectum[16]. Furthermore, laser-Doppler blood flow measurements recently made by our group have indicated that TME surgery, as compared to PME, markedly reduces perfusion in the posterior quadrant of the rectum[17].

An Italian group considered both the proximal and distal circulations in surgery for rectosigmoid cancers, where TME surgery was performed for cancers in the middle and lower rectum. Low tie was routinely performed, and measurements were made at the colonic serosa in and at the rectal mucosa, after division of the artery and before fashioning the anastomosis. The authors noted that most patients displayed colonic as well as rectal blood flow reduction, but the latter was more predictive of anastomotic leaks[18].

More recently, there have been several studies on NIR with fluorescent agents in the setting of colorectal surgery in general, including anterior resection. In a large series of open colorectal procedures, imaging of the bowel serosa prompted surgeons to revise transection margins in 16% of cases; reoperation for anastomotic leakage was decidedly less common in the group using this technique, compared to matched but historical controls[19]. As the bowel wall is difficult to assess aborally to the anastomosis in particularly low anterior resection, mucosal evaluation might be more important. Initial experiences have shown that reliable imaging of the perianastomotic region could be achieved[20], and suggested that revision of anastomoses, which displayed questionable perfusion, decreased leak rates[21]; in another study on NIR, the perceived imaging results provided confidence to avoid a diverting stoma in low anterior resection cases[22]. These studies all share small sample sizes and results cannot be validly extrapolated. However, the largest and most recent study to date on NIR included 139 laparoscopic colorectal resections, where all anastomoses were evaluated; in eleven patients, poor perfusion changed operative strategy, in most cases leading to an altered transection margin. In these patients, no leaks were detected[23]. However, no control group was enrolled and most anastomoses were high, making even this study difficult to apply to low rectal cancer. Arguably, the very low anastomoses may be challenging to revise, as any attempt may lead to a short and possibly damaged rectal stump; this would subsequently demand a purse string suture, hand-sewn under pressure, in order to be able to insert another circular stapler.

Future implications

Preoperative risk factors for anastomotic leakage have been identified[24], and serve as a means to select patients to either anterior resection or operation with end colostomy. The unselected use of a diverting stoma in low anterior resections seem to reduce anastomotic leakage in a trial setting[25], while recent audits provide data that favour more selective use, tailored to the individual patient risk factor profile[26].

Ideally, the experimental data on rectal perfusion above could be translated into clinical practice. First, the anatomical knowledge on rectal vasculature may inform the surgeon that deep extensive dissection in the posterior aspect of the rectal stump may be potentially harmful. Second, blood flow measurements before and after the construction of the anastomosis could inform the surgeon that this particular anastomosis is at risk, and subsequently the case for anastomotic revision (for high anastomoses) or a diverting stoma (for low anastomoses) could be stronger. Presently, it seems that the evolving NIR methodology may offer such an opportunity in the near future. Naturally, such a strategy would need extensive support from more experimental and clinical data, but would provide a valuable tool for the colorectal surgeon.

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REVIEW

Evolution and advances in laparoscopic ventral and incisional hernia repair

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Abstract

Primary ventral hernias and ventral incisional hernias have been a challenge for surgeons throughout the ages. In the current era, incisional hernias have increased in prevalence due to the very high number of laparotomies performed in the 20th century. Even though minimally invasive surgery and hernia repair have evolved rapidly, general surgeons have yet to develop the ideal, standardized method that adequately decreases common postoperative complications, such as wound failure, hernia recurrence and pain. The evolution of laparoscopy and ventral hernia repair will be reviewed, from the rectoscopy of the 4th century to the advent of laparoscopy, from suture repair to the evolution of mesh reinforcement. The nuances of minimally invasive ventral and incisional hernia repair will be summarized, from preoperative considerations to variations in intraoperative practice. New techniques have become increasingly popular, such as primary defect closure, retrorectus mesh placement, and concomitant component separation. The advent of robotics has made some of these repairs more feasible, but only time and well-designed clinical studies will tell if this will be a durable modality for ventral and incisional hernia repair.

Key words: Evolution; Advances; Laparoscopic ventral hernia repair; Laparoscopic incisional hernia repair; Laparoscopic ventral incisional hernia repair; Ventral hernia repair; Incisional hernia repair; Ventral hernia; Incisional hernia

Core tip: This manuscript reviews the evolution and advances of laparoscopic ventral and incisional hernia repair. We discuss preoperative considerations,

intraoperative factors including the type of mesh in conjunction with placement and fixation of the mesh, as well as postoperative issues such as complications, recurrence and quality of life. New evolving techniques such as minimally invasive components separation and robotic surgery are reviewed. In addition, some of the future directions of this exciting and rapidly developing field are explored. We hope you find this review helpful in summarizing the past advances in hopes that it may illuminate new avenues of research in minimally invasive ventral and incisional hernia repair.

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BRIEF HISTORY ON THE EVOLUTION OF LAPAROSCOPY

The concept of minimally invasive surgery has been present for millennia, and started with the advent of endoscopy of the rectum, vagina, ear, and nose. Hippocrates first described a rectoscope in the 4th century[1]. Later in the 10th century, Albukasim, an Arab physician, developed methods of speculum illumination with candlelight and mirrors. In the early 19th century, Phillipp Bozzini utilized the centrally bored mirror for his cystoscope. In 1879, Maximilian Nitze improved the cystoscope, adding a platinum wire electric light source and developing the first endoscopic photographs[2].

In 1901, the German surgeon George Kelling insufflated a dog's abdomen and viewed the viscera with the Nitze style cystoscope. A Swedish surgeon, Hans Christian Jacobaeus, performed the same procedure that year and coined the term laparoscopy. The new procedure of diagnostic laparoscopy then spread around the world. Innovations were rapidly added, such as needle induced pneumoperitoneum, 45-degree laparoscopes, trocar insertion, and insufflation machines. In 1933, Heinz Kalk, a German gastroenterologist, pioneered many of these techniques. He developed a dual trocar technique and a wide-angle scope to obtain biopsies. Visualization improved remarkably in the 1950's with the Hopkins lens and fiberoptic cold illumination; however, interest in these techniques waned for several decades. Gynecologists began experimenting again in the 1970's with tubal ligation, oocyte harvesting, and tumor biopsies[3]. In 1971, Harrith Hasson developed a technique to safely enter the abdomen with his new trocar. Kurt Semm performed the first laparoscopic appendectomy in 1983, and went on to perform a total of 20000 procedures. The German surgeon Erich Muhe performed the first laparoscopic cholecystectomy in 1985, but was not initially received well by his peers. This was followed by an explosion of laparoscopic procedures, including the first laparoscopic ventral hernia repair done by LeBlanc and Booth[4] in 1993.

TRANSLATION TO HERNIA REPAIR

While the incidence of primary ventral hernias has been relatively static, the incidence of incisional ventral hernias has increased as abdominal surgery has become more prevalent. In the United States, 4 to 5 million laparotomies are performed each year, and it is estimated that three to as high as fifty percent of these patients develop incisional hernias, although the exact incidence is unknown[5-8].

Prior to 1993, all ventral and incisional hernias were repaired with open exposure. Primary suture repair remains one of the oldest techniques, but it has been shown to have a high recurrence rate with wide variability, ranging from 8% to 63%[8-10]. The invention of prosthetics has revolutionized ventral hernia repair, leading to a significant reduction in the recurrence rates, ranging as low as 1% to 14% in some studies[8,9]. In the best prospective, randomized controlled trial of mesh based ventral incisional hernia repair, the recurrence rate was 24% with an appropriate follow-up period of 3 years[10]. The gold standard repair widely reinforces or bridges the defect, with mesh placed posterior to the fascia either in a retrorectus, preperitoneal, or intraperitoneal anatomic space. This takes advantage of LaPlace's Law, distributing intra-abdominal pressure across the overlapping mesh instead of only at the hernia defect[7]. However, the need for an extensive dissection, which was associated with postoperative wound-related complications, has driven surgeons to search for new techniques. This was translated to laparoscopic surgery in hopes of decreasing the morbidity of open surgery, including wound complications, postoperative pain, hernia recurrence, and delayed return to normal function[7,11]. Nowadays, about 20% to 27% of repairs are performed laparoscopically[11,12]. One challenge for the minimally invasive approach has been creating a more anatomic, physiologic abdominal wall reconstruction.

The general steps in laparoscopic ventral and incisional hernia repair include safe entry into the peritoneum, insufflation, careful lysis of intra-abdominal adhesions, reduction of the hernia contents, wide, typically intraperitoneal mesh coverage of the defect, and mesh fixation[8,11]. Primary defect closure or concomitant component separation can be performed in selected patients[13,14]. There is wide surgeon variability in preoperative selection of patients for open *vs* laparoscopic repair. These clinical decisions are based on patient factors such as obesity, previous operative history, and size and location of the hernia defect. Furthermore, there are surgeon specific variations in mesh fixation techniques, and differences in the type and size of mesh used[8,11].

PREOPERATIVE CONSIDERATIONS

Any given patient with a ventral or incisional hernia must be evaluated for open *vs* laparoscopic repair. Past data has pooled primary ventral hernias with ventral incisional hernias; however, the behavior of these two types of hernias is most likely different, and should not be overlooked during preoperative assessment. For example, Stirler *et al*[15] showed that laparoscopic repair of incisional hernias on average results in more adhesiolysis, a higher conversion to open, longer operative times, and a higher recurrence rate when compared to primary ventral hernias.

For the majority of surgical specialties, it is well established that patients' preoperative health status can significantly impact postoperative outcomes. Laparoscopic ventral and incisional hernia repairs are not an exception to this principle. Known risk factors for incisional hernia include male sex, advanced age, obesity, tobacco use, chronic obstructive pulmonary disease, immunosuppression, diabetes mellitus, and history of an emergent operation[7,8,16]. All these factors should be addressed during preoperative counseling. Postoperative wound-related complications have also been identified as a major risk factor for recurrence after laparoscopic ventral hernia repairs[7]. Wound infections may increase the incidence of incisional hernias up to 80%[10,17]. Our institution has previously identified predictive factors for postoperative wound infections after ventral and incisional hernia repairs using the American College of surgeons national surgical quality improvement program (NSQIP) database[18]. We found several risk factors for postoperative wound infections after ventral/incisional hernia repair including high body mass index (*i.e.*, greater than 30 kg/m^2), tobacco use, high American Society of anesthesiologists class (*i.e.*, 3 or 4), open surgical approach, prolonged operative times, recurrent hernias, and inpatient status. In addition, with the widespread use of smartphones, other investigators created a smartphone application, which uses an externally validated formula to calculate the risk of wound related complications and the associated cost of care after ventral hernia repairs[19]. These novel methods of patient education may provide motivation to modify these risk factors.

Martindale and Deveney[20] provide an extensive review of perioperative interventions aimed at decreasing wound infection and recurrence. Smoking cessation, blood glucose control, and obesity are again reviewed. Smoking cessation for 4 wk is associated with a decrease in complication rate from 41% to 21%. Preoperative blood glucose control with hemoglobin A1c less than 7% is desired, and perioperative blood glucose should be between 140-160 mg/dL. Obesity is more difficult to control; however, body mass index correlates strongly with recurrence. Many surgeons will not electively repair ventral hernias in patients with a body mass index over 50. In this setting, it has been suggested that aggressive attempts at weight loss including weight loss surgery should precede a futile attempt at ventral hernia repair. Other interventions include preoperative antibiotics and optimizing nutrition. Ríos *et al*[21] showed prophylactic antibiotics decrease wound infection rates in incisional hernia repair from 26.3% to 13.6%. Nutrition is a vital part of healing, and preoperative nutrition may decrease recurrence. Arginine and fatty acid mixtures have been shown to decrease perioperative complications, infection related morbidity, and length of hospital stay[20].

INTRAOPERATIVE CONSIDERATIONS

Selection of mesh

An ideal mesh has sufficient strength, is chemically stable, is easily sterilized, resists infection, is non-carcinogenic, limits inflammatory foreign body reactions, and incorporates (heals) well into the abdominal wall[22]. The latter point is important as many ventral hernia recurrences occur at the interface of the mesh and the wounded abdominal wall, a form of acute wound failure[23,24]. Materials fitting these prerequisites were not developed until the 1900s. Silver was used first, followed by stainless steel and other metals[22]. Polypropylene mesh was not created until 1959. Since then, several categories have been produced: Non-absorbable synthetic meshes, composite meshes, absorbable meshes and tissue-based biologic implants.

Permanent meshes, such as polypropylene and polyester, were use when laparoscopic hernia repairs were first started. However, uncoated meshes were soon abandoned due to the large number of visceral adhesion related complications, such as fistula, bowel obstruction, and complications during re-operative adhesiolysis[24]. Table 1 summarizes some of the main advantages and disadvantages of these meshes.

Composite meshes were developed for laparoscopic intraperitoneal onlay placement, and are the ones usually used for laparoscopic hernia repair[24]. They combine the strength of permanent mesh with a bowel-protective anti-adhesion barrier. The parietal peritoneum side is composed of permanent mesh, usually polypropylene or polyester, which provides structural strength and promotes tissue inflammation and ingrowth. The visceral facing side of the mesh requires an anti-adhesion barrier. Most of these barriers are absorbable, with the exception of expanded polytetrafluoroethylene[25]. Table 2 provides a general overview of the most common composite meshes used for laparoscopic ventral and incisional hernia repair and relevant research. Unfortunately, there is a lack of high-level clinical evidence to direct surgeons and patients as to the safest and most effective material.

New meshes are being developed for potential use in laparoscopic ventral and incisional hernia repair (Table 3). Recently, absorbable synthetic meshes were developed to have a better infection resistance profile, but risk recurrence by weakening during the resorption process[37]. To date, at least 3 new, slow resorbing meshes have been developed, including

Table 1 Advantages and disadvantages of permanent synthetic mesh materials (polyester and polypropylene)

Advantages	Disadvantages
Permanent synthetic mesh, either woven or knit	Risk contraction, chronic inflammation, stiff abdominal wall, chronic pain especially with heavy weight PP
Provides strength by stimulating inflammation and abdominal wall ingrowth	PE with possible higher infection and recurrence *vs* PP
PE has less contraction than PP	Should not be placed in contact with bowel as inflammatory response increases adhesions to viscera
Lightweight PP has less foreign body response, more pliable, more ingrowth[25]	Increased risk of fistula, bowel obstruction, and re-operative complications[26]
Sometimes able to salvage lightweight mesh after infection due to improved antibiotic penetration[25]	Enterotomy and/or bowel resection upon re-operation are almost four times greater with prior use of mesh, with most of these being uncoated mesh[27]

PE: Polyester; PP: Polypropylene.

Table 2 Advantages and disadvantages of commonly used composite meshes

Mesh	Abdominal wall side/visceral side	Advantages	Disadvantages
Composite meshes[24]	Permanent mesh/anti-adhesion barrier	Permanent mesh for inflammation, fibrosis, and abdominal wall ingrowth and strength Visceral side designed to prevent adhesion related complications	No level I evidence of the superiority of one mesh over another. Some differences have been noted in animal models, although adhesion prevention is similar for most[28]. A multi-center, human study is underway to better determine the characteristics of these composite meshes (NCT01355939)[29]
Dualmesh[25]	Micropore ePTFE/Macropore ePTFE	Minimal inflammatory reaction[22] Adhesions less tenacious than all other meshes[24,30] Less adhesiolysis time/mesh surface area compared to composix[24]	PTFE has higher rates of bacterial adherence and less resistant to colonization[31,32] Higher risk of explantation in open cases (14.2%), but not laparoscopic cases (4.6%)[32] Limited fibrous tissue ingrowth and incorporation[22]
Composix™[25]	PP/ePTFE	PP thought to promote better ingrowth and inflammation	Adhesions predominately found due to mesh eversion at periphery[24] Possible increased infection risk (8% in one series)[33]
Parietex[30]	PET/type I collagen, polyethylene glycol, and glycerol	United States evaluation showed adhesions in 18% of patients, *vs* 77% when uncoated PE was used	Collagen film absorbed quickly (20 d)[34]
Proceed[30]	PP encapsulated by PDS/oxidized regenerated cellulose	Lightweight, macro-porous mesh[34]	Incomplete peritoneal mesothelialization over graft Induced dense adhesions in rabbit models[35]
C-QUR[30]	PP/omega 3 fatty acid gel	Less contracture in rabbit model[30]	Poor incorporation strength in rat model[28]
Sepramesh[25]	PP/sodium haluronate and carboxy - methylcellulose	Low adhesion coverage and good incorporation[28]	Inflammation induces breakdown of the coating, resulting in delayed adhesion formation[28]

ePTFE: Expanded polytetrafluoroethylene; PDS: Polydioxanone; PE: Polyester; PET: Polyethylene terephthalate; PP: Polypropylene.

BioA® tissue reinforcement by Gore®, TIGR® Matrix by Novus Scientific[38], and Phasix™ mesh by Bard[39]. These meshes might be used for laparoscopic repair in contaminated fields, including parastomal hernia repair.

Titanized mesh might help reduce inflammatory, foreign body reactions and reduce pain after laparoscopic repair, although results have yet to be confirmed in randomized or comparative studies[42]. A third kind of mesh helps prevent migration and reduces the amount of mesh fixation needed. Covidien created a new, self-gripping mesh currently being used in laparoscopic inguinal, as well as open ventral and incisional hernia repairs. ProGrip™ is a polyethylene mesh that includes small absorbable "hooks" designed to promote abdominal wall adhesion, prevent migration, and decrease the number of fixation points needed. One study asserts less postoperative pain after inguinal hernia repair, but this has not been observed in other studies[43,44]. This mesh might be used in order to decrease the number of tacks and sutures needed for fixation.

Placement and fixation of mesh

Laparoscopic lysis of adhesions is performed prior to mesh placement. Multiple instruments exist for this application, including newly developed ultrasonic shears and bipolar devices. However, there is currently no level I data on the superiority of one over the other. Intraperitoneal mesh is placed once the hernia defect is identified and prepared, and there are many variations

Table 3 Advantages and disadvantages of newly developed meshes

Name	Materials	Properties	Current research
BioA® Tissue Reinforcement by Gore®[36,37]	3D matrix copolymer of polyglycolic acid and trimethyl carbonate	Absorbed in 6 mo	Prospective, observational study (NCT01325792) to evaluate single-staged open ventral incisional hernia repair with midline reinforcement in clean contaminated and contaminated wounds. Early one-year results demonstrated a hernia recurrence rate of 14% and an 18% infection rate[36]
TIGR® Matrix by Novus Scientific[38]	Knit mesh of fast absorbing and slow absorbing glycolide, lactide, and trimethylene carbonate fibers	First fiber retains strength for 1-2 wk Second fiber retains strength for 6-9 mo Stimulates neovascularization and a high level of type I collagen ingrowth Absorbed in 3 yr	One case report of onlay use for open ventral hernia repair[38] Currently three-year safety and performance study showing use for inguinal hernia repairs in humans[40]
Phasix™ mesh by Bard[39]	Monofilament, knit mesh of poly-4-hydroxybutyrate	Minimal absorption in 12-26 wk Porcine model shows 18% strength than natural abdominal wall at 48 wk Manufacturer claims hernia repair support for 12-18 mo	Launched in 2013 and currently there are no published results in human subjects
Titanized mesh[41]	PP mesh with relatively inert titanium coating	Retains strength of PP mesh Titanium retards inflammation and decreases foreign body reaction[42]	Lower analgesic use (1.6 d *vs* 6.1 d, $P < 0.001$) and a quicker return to baseline activity (6.9 d *vs* 9.7 d, $P < 0.001$) when compared to parietex mesh. Also less postoperative pain at 1 mo, but no difference at 6 mo
Progrip by Covidien[43]	Self gripping PP mesh with small, absorbable hooks	Promotes abdominal wall adhesion, prevents migration, and decreases the number of tack or sutures fixation points	Has been used in laparoscopic inguinal, ventral, and incisional hernia repairs One study asserts less postoperative pain after laparoscopic inguinal hernia repair, but another shows no difference with open repair[43,44] Operative times may be less

PP: Polyethylene.

in the fixation of that mesh. Most surgeons cover the hernia defect with a 3 to 5 cm overlap circumferentially, and then secure the mesh in place with transfascial sutures and/or intra-abdominal peritoneal tacking[8,11]. Little is known about the physiologic movement of mesh *in vivo* during physiologic stress, however, the ideal technique would prevent migration and folding of the mesh[45].

Over the years, surgeons have varied greatly in the number of tacks, the number of sutures, as well as the materials of tacks and sutures used for fixation[46]. The goal has been to balance adequate fixation to prevent recurrence against excessive fixation that can lead to unnecessary pain. It is also important to minimize the amount of permanent component of mesh without sacrificing overlap, because large meshes require multiple, potentially painful fixation points, and have an increased risk of chronic pain from foreign body reaction[47]. The use of transfascial sutures may allow the surgeon to limit overlap to only 3 cm, whereas the use of tacks requires at least 5 cm of overlap[48]. An intuitive understanding of biomechanical forces suggests that transfascial sutures provide better fixation, as they are secured to the strong anterior fascia. Unfortunately, transfascial sutures risk abdominal wall nerve entrapment and muscle strangulation, which is thought to contribute to the significant postoperative pain[46]. Tacks provide a 3.8 to 6.8 mm posterior to anterior purchase of the abdominal wall and do not capture the anterior fascia[49]. The tensile strength of sutures was 2.5 times greater than that of tacks in a pig cadaver model; however, a laparoscopic pig model showed no signs of migration or recurrence, and no additional fixation strength at 4 wk when only tacks were used[46]. More tacks are used than suture, and increasing the number of tacks theoretically cause more pain. Schoenmaeckers *et al*[50] demonstrated that decreasing the average number of tacks to 20 from 40 significantly decreases their visual pain analog scale at 3 mo from 5.8 to 1.8 out of 100 ($P = 0.002$), which is not likely to be clinically significant. Of note, this study did not control for the type of mesh.

Recently absorbable tacks have been developed, with the objective of reducing pain, foreign body reactions, and adhesion formation. One porcine model proved similar tensile fixation strength between a 4.1 mm poly (glycolide-co-L-lactide) tacks and a control titanium tacks at 6 mo and less tensile strength with 6.8 mm poly (D,L)-lactide tacks[49].

Many studies compare sutures *vs* spiral tackers; however, many of these studies do not adequately control for patient demographics, hernia size, technical variations, suture type, and mesh size and type, to name a few. Multiple reviews largely showed no optimal technique to prevent recurrence and reduce pain. A recent systematic review by Reynvoet *et al*[46] grouped 25 prospective and retrospective studies from 1999 to 2011 into suture only repair, tack only repair, and

both sutures and tacks. Other reviews included many of the same studies, however, this study used the DerSimonian-Laird random effects model to assign relative weights in relation to study sample size. The hernia recurrence rate for the suture only group (0.9%CI: 0%-1.7%) was less than the tacks only group (3.4%CI: 2.4%-4.5%) and the combination of suture and tack group (2.5%CI: 1.3%-3.7%). As the CIs were overlapping, there was no significant difference in recurrence rate between the three fixation techniques. This is consistent with other past reviews[46,48,51].

The review by Reynvoet *et al*[46] was unable to statistically analyze the outcome of pain following hernia repair, as there was not a standardized way between studies to report pain outcomes. Chronic pain was defined as pain anywhere from 4 wk to 6 mo. Narcotic use, pain analog scales, and quality of life surveys measured pain threshold. Despite these methodological variations between individual studies, Reynvoet *et al*[46] concluded that literature currently shows no significant difference in postoperative pain between suture and tack repairs.

In contrast, the WoW trial (with or without sutures), a randomized controlled trial from Belgium, showed significantly more pain with "sutures and tackers" *vs* a "double crown" tack arrangement[52]. Patients were asked to draw a line representing postoperative pain; significant pain was defined as a visual analog scale score greater than 1 cm. There was a significant difference at 4 h when coughing, and 3 mo at rest (31.4% *vs* 8.3%, $P = 0.036$). Secondary outcomes were reported, showing less operative time in the tacks only group and similar hernia recurrence at 24 mo. However, the main limitation was the somewhat arbitrary 1 cm visual analog scale for pain (VAS) cutoff for significant. A similar study by Wassenaar *et al*[53] used VAS mean scores instead of the 1 cm cutoff. It showed no difference between double crown tackers, absorbable suture and tackers, and non-absorbable suture and tackers.

New less invasive, less painful alternatives for mesh fixation have been developed for hernia repair. Fibrin sealant initially was used for inguinal hernia repair; however, it has also been studied for laparoscopic incisional repair[54]. In 2011, a randomized prospective study was performed comparing the use of fibrin sealant only to the use of titanium tacks only after laparoscopic umbilical hernia repair[55]. At 4 wk follow-up, there was significantly less acute postoperative pain both at rest and during activity, as well as shorter convalescence (median 7 d *vs* 18 d, $P = 0.027$) with use of fibrin sealant. At 1-year follow-up, these differences were not significant, and the hernia recurrence rate was predictably higher in the fibrin only group, though statistically insignificant (26% *vs* 6%, $P = 0.18$). Another study used fibrin sealant in the hernia sac after laparoscopic hernia reduction[56]. This showed a significant reduction in the incidence of seromas at 1 mo (72% control *vs* 28% with sealant, $P = 0.002$). Although promising for some limited applications, the current data does not show an advantage to routine use of fibrin sealant, and shows a trend toward increased recurrence rates if it is used alone for mesh fixation.

EVOLVING TECHNIQUES

Primary defect closure

Once the hernia contents are reduced, the defect is measured and prepared for mesh placement[11]. Traditionally, a tension free repair is created by placing mesh over the defect and securing it in place. Some surgeons prefer to close the hernia defect primarily prior to this step. Three main laparoscopic approaches have been described: (1) interrupted percutaneous closure with suture passer; (2) intra-corporeal suturing; or (3) Endo Stitch™ suturing with a knot pusher[13]. Barbed suture can be used for defect closure or mesh fixation in order to decrease the tension needed when placing each suture. Lyons *et al*[57] used a porcine model to show that barbed suture requires the application of 75% less force than conventional suture, while maintaining adequate mesh fixation strength.

There are many proposed advantages of performing primary defect closure before applying the mesh[13,58]. Re-approximating the abdominal fascia is thought to be a more physiologic repair, and thus stronger. Additionally, it provides a greater surface area of abdominal wall for the mesh to be in contact with. Furthermore, it prevents postoperative bulging of the mesh into the defect. Bulging is not ideal for cosmesis, and may allow mesh to come closer to the skin surface, which can increase the risk of mesh infection and erosion. Conversely, closing the defect increases tension, which may be counterproductive. Also, placement of extra suture in the abdominal wall increases the risk of postoperative pain. Many surgeons have yet to adopt this technique, most likely due to the technical difficulty, and the current lack of evidence suggesting its superiority when compared to mesh placement alone.

Current literature lacks randomized control trials examining the effectiveness of concomitant primary defect closure during laparoscopic ventral and incisional hernia repair. Nguyen *et al*[58] performed a systematic review of 11 studies, including case series and retrospective reviews. Recurrence rate ranged from 0% to 7.7%, and seroma rates were 0% to 11.4%. Three of the retrospective reviews included compared laparoscopic hernia repairs with and without primary defect closure. Clapp *et al*[59] was the only risk adjusted study and followed 72 cases for an average of 24 mo. Hernia recurrence was 16.7% in the group without primary defect closure, whereas no recurrences were seen in the group with primary defect closure. Bulging in this study was decreased from 69.4% in the non-closure group to 8.3% in the closure group. In addition, superficial wound infections were decreased from 13.9% to 8.3%, and the incidence of seroma was decreased from 27.8% to 5.6%. Another retrospective comparative review of 128 patients also reported low recurrence rates after concomitant primary defect closure (6.25%), but

this was not significantly different when compared to the group without primary defect closure[13]. Interestingly, the incidence of seroma formation was higher in the group with primary defect closure than the group without primary defect closure (11.4% *vs* 4.3%).

Component separation

The separation of components technique includes various methods of dissecting the abdominal wall layers in order to advance facial edges and decrease physiologic tension. In 1990, Ramirez *et al*[60] first described releasing the external oblique aponeurosis alone, which allows approximately 5 cm of unilateral fascia advancement at the umbilicus, and 3 cm inferiorly and superiorly. The drawback is that it weakens the abdominal wall, especially laterally at the semilunar line[61]. In 2000, Lowe *et al*[62] combined an open technique with balloon dissection endoscopy. A few years later, Rosen *et al*[63] began separating the external and internal oblique muscles laparoscopically, followed by release of the external oblique aponeurosis. In the morbidly obese population, the presence of thick subcutaneous tissue can make this last technique challenging. After laparoscopic myofascial release, the overlying attached subcutaneous tissue limits movement of that fascia toward the midline[64]. This restricts the advancement to 86% of that of the open release[63].

Although minimally invasive separation of components provides less myofascial release, it avoids creating large skin flaps and spares vital perforating vessels[61,64]. On the other hand, open technique allows excision of dystrophic and tissue expanded skin in conjunction with the hernia sac. One could assume that subsequent advancement of normal skin into the wound may lead to better wound healing and cosmetic result. However, recent studies note a decrease in wound complications with the minimally invasive approach, without significantly affecting recurrence rates[64]. A systematic review comparing minimally invasive component separation with open component separation included 7 non-randomized controlled studies and 56 case series with a total of 3055 patients[61]. Minimally invasive component separation as compared to open component separation resulted in lower rates of total complications (20.6% *vs* 34.6%), superficial wound infection (3.5% *vs* 8.9%), necrosis (2.1% *vs* 6.8%), and hematoma/seroma (4.6 % *vs* 7.4%). Open component separation had a lower rate of recurrence (11.1% *vs* 15.1%), possibly due to a higher rate of simultaneous midline mesh repair in this group. They went on to perform a meta-analysis of the 7 non-randomized controlled studies, which included 387 patients. This showed a significant decrease in skin dehiscence (OR = 3.18) favoring minimally invasive component separation.

Most studies use variations of the Rosen anterior release technique. Posterior component release techniques have also been described, most notably the transversus abdominis muscle release[65]. This involves dissection in the retrorectus space to the semilunar line. The transversus abdominis muscle is then divided vertically that allows entry to the preperitoneal space below, dissection is carried laterally, and a mesh is placed as a sublay. This dissection is tedious and theoretically carries higher risk with a wider learning curve due to the presence of neurovascular structures. It is therefore rarely performed laparoscopically. However, the added dexterity of robotics make the minimally invasive technique feasible.

Multiple concomitant procedures

Ventral and incisional hernias are relatively common in patients requiring other procedures, such as cholecystectomy and bariatric procedures. Previous studies have shown a high recurrence rate and complications rate with ventral and umbilical hernia repair during bariatric procedures[66]. However, a recent retrospective review of 54 patients reported a favorable experience with laparoscopic mesh repair after gastric banding, sleeve gastrectomy, and Roux-en-y gastric bypass[67]. There were no mesh infections and only one hernia recurrence after 12 mo of follow-up. Eleven percent of patients had complications including leak, abdominal wall hematoma, and pulmonary embolism. This was consistent with expected outcomes for bariatric surgery.

Similar results were not obtained when ventral hernia repair was performed with cholecystectomy. Orr *et al*[68] queried the NSQIP database and found 357 cases of simultaneous cholecystectomy and ventral hernia repair. Stepwise multi-variable logistic regression analysis was performed for over 50 risk factors in the NSQIP database, comparing these to 74019 cases of cholecystectomy alone. This model determined that patients undergoing the combination procedure were 2.4 times more likely to have a wound complication, 3.1 times more likely to have sepsis or septic shock, and 2.8 times more likely to have pulmonary complications. The study was limited as it was only able to analyze 30-d outcomes. Also, it was not able to separate out which patients had mesh repair or suture repair. Nevertheless, this study gives great pause to surgeons promoting laparoscopic hernia repair during cholecystectomy.

Avoiding port site hernia

The rate of incisional hernias due to previous laparoscopic port placement is 1% to 22%, which has stimulated interest in more advanced minimally invasive options[69]. Bucher *et al*[69] also reported a case series of 52 patients undergoing single port ventral and incisional hernia repair through one 10-mm endoscope with a working channel. There were no conversions to open and no morbidity, with exception of two seromas. No recurrences were noted at 16 mo. Other surgeons seek to avoid 10-mm ports altogether. Agarwal *et al*[70] described a technique of introducing the mesh through a port placed in the hernia defect. This obviated the

need for a 10-mm port in the flank.

Natural orifice transluminal endoscopic surgery

Natural orifice transluminal endoscopic surgery (NOTES) continues to be explored as a future option for general surgery. One case report describes repairing an umbilical port site hernia through a 2 cm incision in the posterior vaginal fornix[71]. Panait *et al*[72] reported a series of 107 patients undergoing transvaginal appendectomy, cholecystectomy, and ventral hernia repair. Proponents of this approach claim a potential benefit in cosmesis, decreased pain, early return to work, decreased port site complications, and specific advantages in the obese population. Most agree that NOTES operations for hernia repair increase the risk of a major complication, and these techniques should strongly be considered as experimental for now and performed under institutional research protocols.

Robotic surgery

The use of the da Vinci robot has expanded since its approval by the Food and Drug Administration in 2000[73]. Initially applied for hysterectomy and prostatectomy, it has recently been used for an increasing number of general surgery procedures, including Nissen fundoplication, single site cholecystectomy, colectomy, and ventral or incisional hernia repair. The magnified, three-dimensional high-definition view, computer-aided elimination of tremor, and seven degrees of freedom at the distal ends of the instruments with superior maneuverability, have led to its increasing adoption by several prominent surgeons[74]. In fact, LeBlanc *et al*[75] presented his early experiences with robotic approach at a recent American college of surgeons meeting, asserting its role in replicating open technique with minimally invasive methods.

Many surgeons are currently utilizing the robot simply to facilitate their ability to suture the hernia defect closed, and thus place the mesh as an intraperitoneal onlay. Gonzalez *et al*[76] compared a standard laparoscopic intraperitoneal mesh placement technique without defect closure, to a similar technique, which utilized the robot to close the hernia defect. They found an increased operative time for the robot with no difference in wound complications or recurrence. In our practice (AC-Greenville), we have developed a robotic approach to replicate the open Rives-Stoppa retromuscular incisional hernia repair technique. We are able to perform a retrorectus dissection, with or without the addition of a transversus abdominis release, or posterior component separation. We then suture the posterior rectus sheaths closed in the midline, followed by uncoated polypropylene mesh placement in the retrorectus space, and closure of the abdominal wall defect. A case controlled retrospective cohort study comparing our robotic Rives-Stoppa to the open technique favored the robotic approach with less blood loss and a shorter length of stay with no difference in operative time or direct hospital cost. Surgical site infection was 9.5% in the open group and 0% in the robotic group (P = 0.48)[77]. The sample size was small, which increased the likelihood of type Ⅱ statistical error. Like any new operation, there is a steep learning curve. On the other hand, the ergonomic nature of the robotic system may allow a novice user to rapidly progress. Initially, the robotic retrorectus mesh repair with simultaneous posterior component release was taking upwards of 6 h to perform. With some technique modifications and experience, we have been able to decrease operative times into the 2.5-4 h range depending upon the degree of intraperitoneal adhesions. Interestingly, the initial cost analysis suggests that this repair is equal to open repair. Decreased cost with robotic use is not unprecedented. In fact, one study in the United States showed decreased costs with robotic single site cholecystectomy *vs* laparoscopic cholecystectomy ($1319 *vs* $1710, P = 0.001), mostly due to decreased use of supplies[78].

POSTOPERATIVE CONSIDERATIONS: COMPLICATIONS, RECURRENCE, AND QUALITY OF LIFE

The patient centered outcome reporting initiative is a nonprofit organization in the United States authorized by congress in the patient protection and affordable care act. It is charged to "improve the quality and relevance of evidence available" on healthcare topics such as this[79]. They noted that a lack of convincing trials makes it difficult to develop and validate an ideal, standardized approach to laparoscopic ventral and incisional hernia repair. However, it is generally accepted that decreased risk of postoperative infection is the primary advantage, especially in the obese population[80-82].

Recently, there has been a movement to separate primary ventral and secondary incisional hernias into two different categories. Stirler *et al*[15] showed that laparoscopic repair of incisional hernias on average results in more adhesiolysis, a higher conversion to open, a longer procedure, and a higher recurrence rate when compared to primary ventral hernias. In 2014, Awaiz *et al*[83] performed a meta-analysis with strict exclusion criteria in order to evaluate elective repair of incisional hernias. There was a statistical reduction in bowel related complications favoring open repair *vs* laparoscopic repair. However, "bowel injury" included an aggregate of enterotomies, serosal tears, and small bowel obstructions. There was no difference in other postoperative morbidities. Arita *et al*[84] reviewed ventral and incisional hernias separately, and found that superficial surgical site infection rates were higher in open repairs for both hernia types, but there was no difference in recurrence rates between open and laparoscopic approaches.

There has also been an attempt to correlate the acuity of hernia presentation with outcomes. Our group used NSQIP database to determine propensity score adjusted OR in 26766 subjects undergoing open *vs*

laparoscopic ventral and incisional hernia repair for reducible and incarcerated/strangulated hernias[85]. Laparoscopic repair was found to have a small but significant decrease of length of stay in both reducible (open = 2.79, 2.59-3.00; laparoscopic 2.39, 2.20-2.60; $P < 0.01$) and strangulated/incarcerated hernias (open = 2.64, 2.55-2.73; laparoscopic 2.17, 2.02-2.33; $P < 0.01$). Open repair of incarcerated/strangulated hernias increased the risk of superficial surgical site infection (OR = 3.1, $P < 0.01$), deep surgical site infection (OR = 8.0, $P < 0.01$), and wound disruption (OR = 9.3, $P < 0.01$) when compared to laparoscopic repair. Open repair had a lower risk of organ/space surgical site infection after repairing reducible hernias when compared to laparoscopic repair, but there was no increased risk of other infections.

Quality of life

As the incidence of recurrence decreases, there is an increasing focus on secondary patient reported outcomes that affect postoperative quality of life. Surrogates have been created because there is no consensus on how to measure pain, mobility, cosmesis, and length of convalescence. A 2011 Cochrane review found no significant differences in acute postoperative pain (mean difference 0.09, 95%CI: -0.45 to 0.62), and return to full activity (mean difference -0.70, 95%CI: -2.10 to 0.70)[81]. One study showed no difference in acute postoperative pain, but another study showed less chronic neuralgia in the laparoscopic group. Regarding return to full activities, Pring *et al*[86] revealed no difference between open and laparoscopic repairs. However, Itani *et al*[87] found a near significant advantage for laparoscopic repair (23 d *vs* 28.5 d, adjusted hazard ratio 0.54, 95%CI: 0.28-1.04; $P = 0.06$). The Cochrane review showed a significant difference in hospital stay (mean difference -4.63, 95%CI: -5.95 to -3.32); however, this was only if the open repair control group stayed longer than 5 d[81]. There was no significant difference in quality of life (mean difference 0.44, 95%CI: -0.24 to 1.11).

In 2014, Jensen *et al*[88] reviewed 26 articles for quality of life assessment methods. Fifty-four percent of these used the short-form 36 (SF-36), which is a non-surgery or hernia specific scoring of general physical and mental health. The physical component focuses on pain, energy/fatigue, and functional limitations. The mental health component focuses on social functioning, emotional wellbeing, and general perception of health. Two of the studies discussed found no difference when comparing open to laparoscopic repair[87-89]. On the contrary, some other authors showed better quality of life, and better short-term physical functioning with laparoscopic repair[90]. In addition, when tack and transfascial suture techniques were compared using the SF-36, no significant difference was noted between the two approaches[52,53,88].

Only two of the quality of life assessment methods are hernia specific. These include the Carolinas comfort scale and the hernia-related quality of life survey (HerQLes). The Carolinas comfort scale assesses pain, limitations in movement, and mesh sensation for eight daily activities. Colavita *et al*[91] assessed 710 patients and showed worse quality of life one month after laparoscopic repair when compared to open repair, but there was no long-term difference. Two other studies showed large hernia defects and the presence of preoperative pain to be strong predictors of a short-term decrease in quality of life, most likely due to pain[92,93]. The HerQLes is a newly developed assessment first reported by Krpata *et al*[94]. It associates hernia specific physical limitations with overall physical and mental effects on quality of life. It shows an advantage in laparoscopic repair at 4 wk, but no difference at 6 mo. Based on the available literature, it appears that there might be some improvement in short-term quality of life with the laparoscopic approach, but this benefit balances out in the long run.

FUTURE DIRECTIONS

Preoperative patient selection and risk modification

Most surgeons attempt to decrease modifiable risk factors through patient encouragement; however, there are very few multidisciplinary programs that actively and successfully accomplish this. Further research is required to validate methods to decrease known modifiable risk factors, such as obesity and smoking. Furthermore, only 20% to 27% of hernias are repaired laparoscopically, despite the benefits noted above[12,18].

Considering the plethora of procedural and equipment options, surgeons need criteria to develop a tailored surgical technique for each patient, including surgical approach, mesh material, fixation material, and fixation method. Several algorithms have been developed for operative planning, but no one method has become ubiquitous. Eid *et al*[95] developed an algorithm to stratify obese patients, taking into account body mass index, abdominal wall thickness, and presence of symptoms. Parker *et al*[96] proposed another algorithm to determine open *vs* laparoscopic component separation, and concomitant open *vs* laparoscopic ventral hernia repair. Further research is needed to create a reliable and validated algorithm for surgical selection.

Mesh selection

No one mesh has become dominant in intraperitoneal onlay repair. There is an ongoing study at Washington University determining the adhesion profile of these meshes[29]. Several other studies have attempted to stratify mesh characteristics, but the numbers are too small to draw definitive conclusions[24]. Mesh technology continues to develop ahead of validating research. Long-term absorbable meshes, self-gripping meshes, and titanium reinforced meshes are now available for

use. The robotic platform increases the ability to place mesh in the retrorectus space, which may obviate the need for different mesh materials. Surgeons and patients would benefit from more level 1 clinical studies scientifically comparing the risks and benefits of evolving mesh technologies.

New techniques

Non-standard laparoscopic techniques are being increasingly utilized, such as simultaneous primary hernia closure, retrorectus mesh placement, concomitant component release, and mesh fixation, in order to decrease wound complications, postoperative pain, and hernia recurrence. Surgeons are more likely to attempt laparoscopic repair of more complex hernias, such as incarcerated/strangulated ventral hernias, as their collective experience grows. In the same way, newer fixation methods might decrease postoperative pain, such as barbed suture or fibrin sealant, but may risk re-herniation if they do not provide adequate fixation. Simultaneous component release has gained popularity as it allows reconstruction of the midline. Considering the relatively low incidence of complications, mesh registries may be useful to increase the power of future studies.

The robotic platform

The ease of robotics may decrease the learning curve for surgeons, making a good laparoscopic surgeon better able to replicate the tenets of open repair. It permits relatively easy access to the anterior abdominal wall, allowing the surgeon to perform the ideal repair for that patient - including possible primary defect closure, retrorectus mesh placement, intracorporeal suturing, and concomitant posterior component release. It also might allow for standardization of surgical technique in order to develop a reliable approach to hernia repair that can be offered to an increasing number of patients. Further research is needed to determine the ability to decrease patient morbidity *vs* the increased cost of technology.

Patient reported outcome measures

Patient reported outcome measures (PROM) are standardized measures used to assess symptom status, physical function, mental health, social function, and wellbeing, with the goal of patient centered improvement of care. This system has been implemented in the United Kingdom and the National Health Service for many years with variable success[97]. Previously discussed studies have attempted to assess quality of life using similar standardized measures for ventral hernia repair, such as the SF-36, Carolinas comfort scale, and the HerQLes. Thus far, these studies have been experimental and have not been used to guide treatment. Further research might develop specific PROM that may be used to enable cost analysis, standardization of treatment, and quality improvement.

CONCLUSION

Laparoscopic ventral and incisional hernia repair has evolved significantly since its roots in the crude endoscopy of Hippocrates. The experience of the last 25 years has allowed us to significantly decrease the morbidity of post-laparotomy incisional hernia and *de novo* ventral hernias. Preoperative risk factor modification and a useful diagnostic algorithm have a significant role in preparing a patient for the right operation. New hernia repair techniques have the potential to continue to reduce the associated morbidity, and perhaps robotic surgery will be the tool to accomplish the ideal hernia repair in the appropriate setting. Despite the advances noted above, open surgical technique is many times necessary and should not be overlooked. Improved postoperative evaluation is necessary to effectively weigh the results of our innovations, and continue to evolve solutions to ventral and incisional hernias.

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Watch and wait approach to rectal cancer: A review

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Abstract

In 2014, there were an estimated 136800 new cases of colorectal cancer, making it the most common gastrointestinal malignancy. It is the second leading cause of cancer death in both men and women in the United States and over one-third of newly diagnosed patients have stage Ⅲ (node-positive) disease. For stage Ⅱ and Ⅲ colorectal cancer patients, the mainstay of curative therapy is neoadjuvant therapy, followed by radical surgical resection of the rectum. However, the consequences of a proctectomy, either by low anterior resection or abdominoperineal resection, can lead to very extensive comorbidities, such as the need for a permanent colostomy, fecal incontinence, sexual and urinary dysfunction, and even mortality. Recently, trends of complete regression of the rectal cancer after neoadjuvant chemoradiation therapy have been confirmed by clinical and radiographic evaluation-this is known as complete clinical response (cCR). The "watch and wait" approach was first proposed by Dr. Angelita Habr-Gama in Brazil in 2009. Those patients with cCR are followed with close surveillance physical examinations, endoscopy, and imaging. Here, we review management of rectal cancer, the development of the "watch and wait" approach and its outcomes.

Key words: Rectal cancer; Watch and wait approach; Neoadjuvant chemotherapy rectal cancer; Nonoperative management rectal cancer

Core tip: Standard treatment for stage Ⅱ and Ⅲ rectal cancer includes neoadjuvant chemoradiation followed by radical surgical resection. Recent studies have demonstrated that a select population of patients will achieve a pathological complete response with the absence of residual cancer present after surgical resection. Preliminary attempts to identify those rectal cancer patients with a clinical complete response to neoadjuvant therapy, through various diagnostic modalities, may prevent future patients from having to undergo a very morbid operation.

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INTRODUCTION

Colorectal cancer is the most common gastrointestinal malignancy with an estimated 136800 new cases diagnosed in 2014 in the United States[1]. Over one third of colorectal cancers consist of Stage Ⅲ node-positive disease and rectal cancer accounts for approximately a third of these cases. Proctectomy has been the cornerstone of therapy to achieve long-term oncological results either *via* low anterior resection or abdominoperineal resection. Standard surgical technique involves total mesorectal excision as proposed by Heald *et al*[2] to achieve the lowest rates of regional recurrences with reported morbidity and mortality rates of 35% and 4%-5%, respectively and over a third of patients report some degree of urologic and sexual dysfunction, and fecal incontinence[3].

Additionally, landmark studies, like the Dutch trial and German trial CAO/ARO/AIO-94, have proven the beneficial effects of preoperative chemoradiation therapy (CRT)[4,5]. Locoregional failure rates are reported as < 10% and thus, neoadjuvant CRT plus radical surgical resection have become the standard of care for rectal cancer. Long-term results with this approach show stage-specific 5-year survival rates between 63% and 77.4%[6-8].

Despite excellent oncologic outcomes with neoadjuvant CRT followed by radical surgery, contemporary data is shifting the current paradigm of rectal cancer management towards nonoperative therapy. Multiple studies have shown an absence of viable malignant cells in surgical resection specimens after CRT, termed pathological complete response (pCR) in 18.1%-26% of cases[9]. Thus questions arise in colorectal surgery: Do patients benefit from radical surgery after an "adequate" response to CRT? How does one define an "adequate" response to neoadjuvant therapy? Do these patients achieve equivalent oncological long-term outcomes with reduced morbidity and mortality?

This paper reviews the non-operative treatment algorithm known as the "Watch and Wait" protocol, first proposed by Habr-Gama *et al*[10] in Brazil. Indications, treatment algorithms, outcomes, and areas of uncertainty are assessed from a worldwide perspective.

The utilization of an inaccurate staging system: Treating with uncertainty

According to the American joint committee on cancer, tumor depth is denoted by T; N is nodal metastasis, and M is distant metastasis - for evaluation of TNM cancer staging. Nodal positivity or a ≥ T3 tumor (stages Ⅱ and Ⅲ disease) qualifies a patient for neoadjuvant CRT prior to surgical resection[11,12]. Digital rectal examination (DRE) combined with imaging modalities including endorectal ultrasound (ERUS), magnetic resonance imaging (MRI) and/or positron emission tomography - computed tomography are utilized to determine TNM status. Staging determines prognosis and guides therapy.

The depth of tumor invasion can be determined with acceptable accuracy rates of > 90% with either ERUS or MRI, whereas lymph node (N) status is much less reliable with these imaging modalities. Accuracy rates have been determined to be between 60%-80%[13,14]. The evaluation of lymph node status is limited by the shortcomings of current diagnostic methods available in rectal cancer staging. Failure to identify up to 25% of malignant lymph nodes because of their size being less than 3 mm counters conventional beliefs that lymph node size must exceed 1 cm in order to be deemed positive for metastasis[15,16]. In other words, our current diagnostic imaging modalities understage N status. Furthermore, tumor response may not correlate with lymph node status in patients after CRT. Previous studies have shown that between 16.3%-28% of patients with complete clinical response (cCR) harbor nodal disease and its incidence is associated with initial T stage[17,18].

Defining response after CRT: Clinical complete response vs pathological complete response

pCR has been defined as the absence of neoplastic cells in the surgical resection specimen after neoadjuvant CRT and resection. Fifteen to forty percent of patients who receive neoadjuvant chemotherapy will have a pCR[19-21]. Tumor response is considered a marker of tumor biology. Patients with complete tumor response after neoadjuvant CRT have improved disease-free survival (DFS) and distant metastatic rates of 89.5% and 7%-10.5%, respectively, when compared to poor responders of neoadjuvant therapy (65% and 26%-31%, respectively)[9,22]. Variables such as sex, age and tumor location are not predictors of tumor response, whereas lymph node status is significantly associated with the risk of locoregional recurrence and subsequent distant metastases.

At present, no predictive factors exist to determine which patients will respond to CRT based on preoperative data. However, pCR is not an appropriate primary endpoint to guide clinical decision-making because it depends on the pathological results after radical surgery. Habr-Gama *et al*[10,23] developed the "watch and wait" protocol by creating a new endpoint: cCR. Based on a strict surveillance protocol, patients are determined to be responders once they have no evidence of tumor on: (1) DRE; (2) endoscopic assessment; and (3) imaging. When irregularities of the rectal wall (including mass, ulceration, or stenosis) are palpated on digital

Table 1 Watch and wait protocol surveillance schedule (adapted from Habr-Gama *et al*[10])

Assessment of complete response	Initial assessment	First year	Second year	Third year and after
DRE	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
CEA	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
Endoscopic assessment	10 wk	Every 1-2 mo	Every 3 mo	Every 6 mo
MRI	10 wk	If 1st assessment normal with cCR, then every 6 mo	Every 6 mo	Every 6 mo

DRE: Digital rectal examination; CEA: Carcinoembryonic antigen; MRI: Magnetic resonance imaging; cCR: Clinical complete response.

rectal examination, it is concerning for residual cancer. Endoscopic assessment not only confirms DRE but identifies ulceration or mucosal irregularity that may have been missed during DRE. During flexible or rigid proctoscopy, the procurement of biopsies is helpful in verifying a cCR. MRI evaluates for mixed signal intensity of the rectal wall, in addition to malignant mesorectal lymph node involvement (Figures 1 and 2). Finally, carcinoembryonic antigen (CEA) levels are obtained pre- and post-neoadjuvant CRT. If abnormal CEA levels persist after CRT, this suggests an incomplete response to neoadjuvant therapy and/or distant metastatic disease.

As previously discussed, lymph node status is the most important prognostic factor in rectal cancer. The challenge of a nonoperative approach is determining whether contemporary imaging modalities adequately evaluates lymph node status in these patients; thus yielding an inferior oncological outcome compared to that of conventional operative management.

This is the basis of uncertainty and the main criticism to the "watch and wait" protocol. Deciding not to offer radical surgery based on inaccurate diagnostic tools that could potentially understage neoplastic process has been a deterrent to the acceptance of the "watch and wait" protocol in the United States. Studies are ongoing to determine whether this protocol is acceptable as standard of care.

Outcomes with watch and wait protocol: Brazil, Netherlands, United Kingdom, and United States

The "watch and wait" approach was first proposed by Habr-Gama[1] in Brazil in 2009. The current protocol by Habr-Gama[1], includes radiation therapy of 54 Gy with combination 5-fluorouracil and leucovorin chemotherapy, which extends for an additional 3 cycles beyond the neoadjuvant radiation period for a duration of 9 wk. At 10 wk, patients undergo an initial assessment with DRE, flexible sigmoidoscopy, and imaging for cCR. The patients then enroll in a vigorous surveillance program: DRE, CEA, and endoscopic assessment every 1-2 mo in the first year, every 3 mo in the second year, and every 6 mo in the third year and beyond. If the initial radiologic assessment shows cCR, then serial imaging may be performed every 6 mo (Table 1)[10]. Habr-Gama[1] prospectively studied 70 patients, of which one died due to cardiac complications from chemotherapy. On initial assessment, 68% of patients had cCR. After follow-up of 12 mo, 56% of patients had sustained cCR. For those who initially had cCR, the 3-year overall survival was 90% and DFS was 72%[24].

Another study from the Netherlands prospectively followed 192 patients with locally advanced rectal cancer who were treated with CRT[4,25]. Twenty-one patients had cCR and were followed for 25 ± 19 mo. The control cohort consisted of 20 patients who had a pCR after chemoradiation followed by surgical resection. Out of the twenty-one patients in the watch and wait protocol group, one patient developed a small endoluminal local recurrence without nodal recurrence at 22 mo follow-up. The remaining 20 patients neither had local nor distant recurrence of disease. DFS and overall survival did not statistically differ between both the watch and wait and control groups.

There are two retrospective studies from the United States and the United Kingdom which are concordant with the aforementioned prospective studies. Disease-free and overall survival rates are similar in patients with cCR, who undergo the watch and wait protocol *vs* conventional neoadjuvant chemoradiation therapy, followed by surgery (Table 2)[24-28].

In conclusion, advances in chemoradiation therapy for rectal cancer have delineated a select population of patients who have a pCR after surgical resection. Observation of this pCR led to the conception of the watch and wait protocol by Habr-Gama *et al*[24], in Brazil. Patients are identified as having a cCR and followed with close surveillance by physical examination, endoscopic assessment, and imaging studies. Thus far, they have followed prospectively, a highly selected patient population. This study has been confirmed by a study in the Netherlands[26,27].

However, the watch and wait protocol has not been widely accepted as standard of care. There are limitations for current data in the literature. First, only two prospective cohort studies exist with small sample sizes. No randomized controlled trials exist, comparing the watch and wait protocol with standard neoadjuvant chemoradiation therapy followed by surgery. Enrollment into these studies is biased by patient selection due to the lack of randomization. Despite close surveillance, no studies have delineated patient characteristics

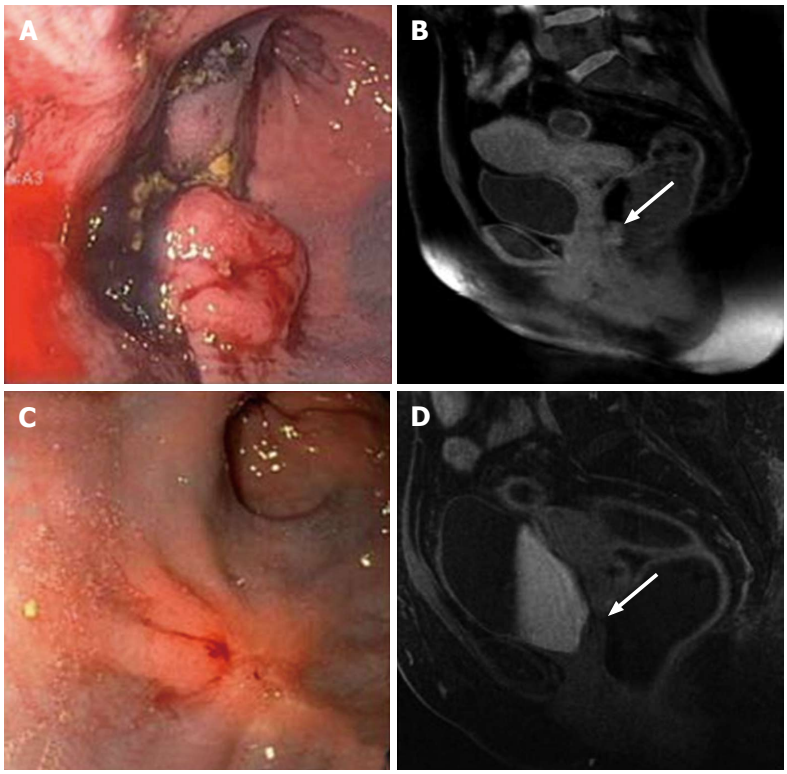

Figure 1 Clinical incomplete response. Evaluation of the rectal cancer prior to the initiation of neoadjuvant chemoradiation therapy by flexible sigmoidoscopy (A) and MRI (B, white arrow: Tumor). Evaluation of 7 wk after completion of neoadjuvant chemoradiation therapy. The tumor has decreased in size; however, it continues to be present as evidenced by flexible sigmoidoscopy (C) and MRI (D, white arrow: Tumor). MRI: Magnetic resonance imaging.

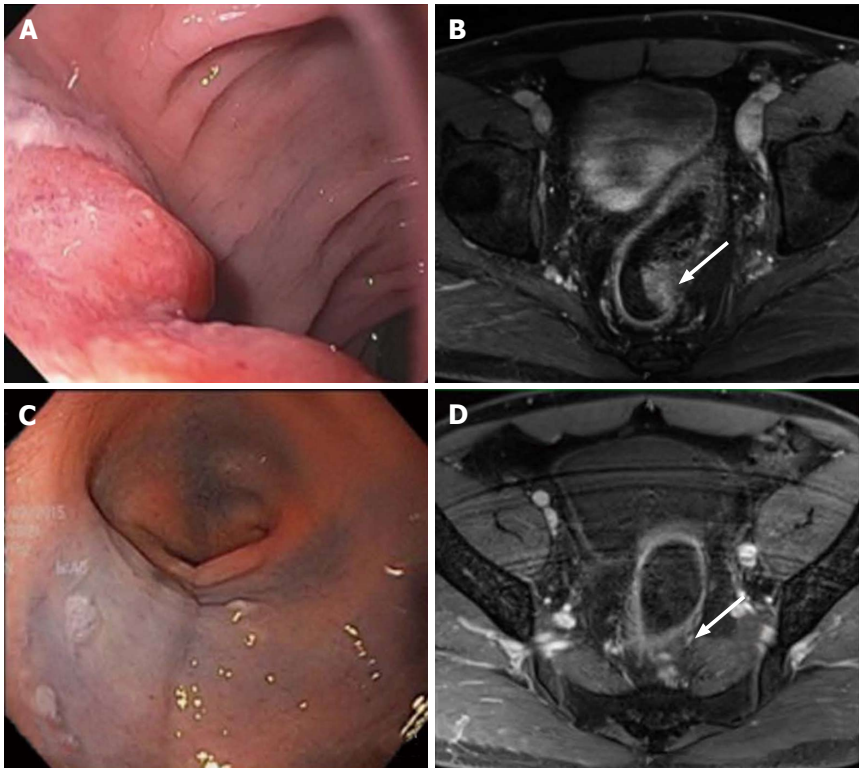

Figure 2 Complete clinical response. Evaluation of the rectal cancer prior to the initiation of neoadjuvant chemoradiation therapy by flexible sigmoidoscopy (A) and MRI (B, white arrow: Tumor). Evaluation of 7 wk after completion of neoadjuvant chemoradiation therapy showed no evidence of tumor by flexible sigmoidoscopy (C) and MRI (D, white arrow: Tumor). MRI: Magnetic resonance imaging.

or predictive factors that predict tumor response to chemoradiation therapy. Though patients undergo a

Table 2 Studies evaluating the watch and wait protocol

Study	Patients (*n*)	Neoadjuvant therapy		Details	Outcomes/endpoints
		Radiation	Chemotherapy		
Prospective					
Habr-Gama *et al*[24] (Brazil)	69	54 Gy radiation (45-Gy delivered as 3-field approach with daily doses of 1.8 Gy on weekdays to pelvis, followed by 9-Gy boost to the primary tumor and perirectal tissue)	3 cycles of 5-FU (450 mg/m^2) bolus and a fixed dose of 50 mg leucovorin for 3 consecutive days every 3 wk. After completion of radiation, patients received 3 additional identical cycles of chemotherapy every 3 mo	Assessment after CRT: 10 wk; assessment for sustained cCR: From 10 wk to 12 mo after CRT; patients with local recurrences after sustained cCR classified as LR	3-yr OS for patients with initial cCR = 3-yr DFS for patients with initial cCR = 72%
Lambregts *et al*[25] and Maas *et al*[26] (Netherlands)	21	28 fractions of 1.8 Gy = 50.4 Gy	IV oxaliplatin and capecitabine	Assessment after CRT: 6-8 wk; evaluation for cCR: MRI and endoscopy; operative management with CRT and resection (control group): 20 patients with pCR after surgery	Nonoperative management group; 1 patient developed LR and had surgery as salvage treatment; 20 patients are alive without disease; no difference in 2-yr DFS and OS between the watch and wait and the CRT and resection groups
Smith *et al*[27] (United States)	32	External beam radiation over 5-6 wk, median dose 50.4 Gy (range 45-56 Gy)	5-FU or capecitabine	Assessment after CRT: 4-10 wk; evaluation for cCR: DRE, endoscopy ± biopsy; evaluation for cCR at 1-yr: DRE, flexible sigmoidoscopy every 3 mo; evaluation for cCR subsequent years: DRE, flexible sigmoidoscopy every 4-6 mo; operative management (control group): 256 patients, 57 (22%) with pCR; median follow up: 28 mo	Nonoperative management group had a higher rate of LR (21% *vs* 0%, $P = 0.001$): 6 recurred locally (median 11 mo), 3 had concurrent DR; 2-yr DR (8% *vs* 2%, $P = 0.30$), DFS (88% *vs* 98%, $P = 0.27$), and OS (97% *vs* 100%, $P = 0.56$) were similar for nonoperative management and rectal resection/pCR groups
Dalton *et al*[28] (United Kingdom)	12	45 Gy in 25 fractions over 5 wk	Concurrent capecitabine	Assessment after CRT: 8 wk; evaluation for cCR: MRI complemented with EUA/biopsy and PET/CT if tumor regression is suspected; cCR patients are followed with repeat EUA at 3 mo and 12 mo, and 6-monthly PET/CT and MRI; median follow up 25.5 mo	cCR in 12/49 (24.4%); 6/12 patients with cCR without evidence of disease

LR: Local recurrence; DR: Distant recurrence; DFS: Disease-free survival; OS: Overall survival; Gy: Gray; CRT: Chemoradiation therapy; DRE: Digital rectal examination; EUA: Examination under anesthesia; 5-FU: 5-fluorouracil; cCR: Clinical complete response; pCR: Pathological complete response; PET/CT: Positron emission test/computerized tomography; MRI: Magnetic resonance imaging.

very strict surveillance protocol, the ultimate question arises as to whether cancer remains in the rectum and whether they exist in the lymph nodes. The inaccuracies of current imaging modalities limit the accurate staging of rectal cancer. Further precision in rectal cancer staging would require innovative advances in diagnostic technologies in order to avoid radical surgery.

The uncertainty of outcomes of a cCR after chemoradiation therapy for rectal cancer continues to exist. Further randomized controlled trials are required to validate the watch and wait protocol. As nonoperative management for rectal cancer advances, we predict that the evolution of rectal cancer treatment will mimic that of anal cancer. Prior to the 1970's anal cancer management was purely surgical. However, with the ground-breaking work of Nigro *et al*[29], the anal cancer treatment paradigm has shifted to a nonsurgical approach with primary treatment consisting of multimodality therapy with chemotherapy and radiation. Further changes in the standard of care to nonoperative management will be dependent on the identification of patient factors that can predict a pCR. The introduction of molecular techniques that allow the identification of high-risk patients could play a substantial role in the creation of a genetic profile that would funnel a highly selected group of rectal cancer patients into the watch and wait protocol.

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Natural history of uncomplicated sigmoid diverticulitis

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Abstract

While diverticular disease is extremely common, the natural history (NH) of its most frequent presentation (*i.e.*, sigmoid diverticulitis) is poorly investigated. Relevant information is mostly restricted to population-based or retrospective studies. This comprehensive review aimed to evaluate the NH of simple sigmoid diverticulitis. While there is a clear lack of uniformity in terminology, which results in difficulties interpreting and comparing findings between studies, this review demonstrates the benign nature of simple sigmoid diverticulitis. The overall recurrence rate is relatively low, ranging from 13% to 47%, depending on the definition used by the authors. Among different risk factors for recurrence, patients with C-reactive protein > 240 mg/L are three times more likely to recur. Other risk factors include: Young age, a history of several episodes of acute diverticulitis, medical *vs* surgical management, male patients, radiological signs of complicated first episode, higher comorbidity index, family history of diverticulitis, and length of involved colon > 5 cm. The risk of developing a complicated second episode (and its corollary to require an emergency operation) is less than 2%-5%. In fact, the old rationale for elective surgery as a preventive treatment, based mainly on concerns that recurrence would result in a progressively increased risk of sepsis or the need for a colostomy, is not upheld by the current evidence.

Key words: Diverticulitis; Colon; Cohort; Recurrence; Natural history

Core tip: The natural history of sigmoid diverticulitis is poorly understood. While there is a clear lack of uniformity in terminology, which results in difficulties interpreting and comparing findings between studies,

this comprehensive review demonstrates the benign nature of simple sigmoid diverticulitis. The overall recurrence rate is relatively low. Several risk factors are found to be associated with recurrence.

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INTRODUCTION

Colonic diverticulosis is an increasingly common condition in the Western world. Half of the population is affected by the 6th decade and two-thirds by the 9th decade[1,2]. Fortunately, the majority of patients with diverticulosis remains asymptomatic; diverticulitis, the most common presentation of diverticular disease, has a life time prevalence of 25%[3,4]. The diagnosis of sigmoid diverticulitis is usually suspected clinically in a patient presenting with acute lower abdominal pain, associated with an inflammatory syndrome. The preferred imaging modality is computed tomography (CT)[5] scan, which may also demonstrate complicated diverticulitis (abscess, fistula or peritonitis)[6]. A full colonoscopy once the acute inflammatory process has resolved[5] is recommended in order to exclude cancer or inflammatory bowel disease[7]. Most patients presenting with simple diverticulitis will be successfully managed symptomatically or with antibiotics alone[8-11].

Whilst diverticular disease is extremely common, there are few prospective series documenting the natural history (NH) of sigmoid diverticulitis[12,13]. Studies from the 1960s had suggested that a recurrent episode of diverticulitis occurs in > 40% of patients, and that these are complicated in up to 60%[14]. However, recent series suggest that the NH of sigmoid diverticulitis, in the era of modern antibiotics, is more benign[15,16], as shown in our prospective cohort study[17]. A few have looked at the incidence and severity of recurrent diverticulitis but with the diagnosis based upon clinical parameters only[18]. Without a CT scan it is difficult to differentiate between simple and Hinchey Ⅰ-Ⅱ diverticulitis[10,19,20]. So, the existing studies probably do not provide reliable information regarding the NH of simple diverticulitis.

The object of this review is to evaluate the NH of simple sigmoid diverticulitis.

DEFINITIONS

There is a clear lack of uniformity in terminology resulting in difficulties interpreting and comparing findings between studies[10,18].

NH can be defined as the longitudinal outcomes for patients whose disease was managed non-operatively[21]. In our own cohort (NCT01015378), we chose a definition of simple diverticulitis, which comprised 4 criteria[22]: (1) Clinical: Acute lower abdominal pain or discomfort; (2) Biological: Inflammatory syndrome [C-reactive protein (CRP) > 50 mg/L or white blood cell count > 11000 G/mm^3]; (3) Radiological: Signs of inflammation of the sigmoid and/or descending colon on a CT scan ideally performed with triple contrast injection (oral, rectal, and intra-venous); and (4) Endoscopic: To document the presence of diverticula (*i.e.*, confirming the diagnosis) and rule out another associated condition.

All patients are usually encouraged to undergo routine colonoscopy six to twelve weeks after the first attack, in order to rule out malignancy, although the evidence supporting this practice is weak[10,18].

Regarding outcomes, a diagnosis of recurrent diverticulitis implied that the patient has completely recovered from their first episode. An interval of 12 wk without symptoms in between two attacks was required. All the aforementioned criteria were required to confirm a recurrent diverticulitis (including an abdominal CT). The Hinchey classification[23], or its modified versions[24], was used to stage complicated diverticulitis. In addition, we considered a fistula and a stenosis as a complicated attack[18].

NH OF SIMPLE DIVERTICULITIS

Recent advances in the understanding of diverticular pathophysiology and NH have led to substantial changes in diverticulitis treatment guidelines[21].

We have recently published a large prospective single center cohort study focusing on the NH of sigmoid diverticulitis[17]. We demonstrated that, after a first episode of simple diverticulitis, the overall recurrence rate was 16%, and that 87% of recurrences were of similar severity (Figure 1). Of note, four patients only (1.4%) underwent emergency surgery for complicated (Hinchey stages Ⅲ/Ⅳ) diverticulitis. The main predictor of recurrence after a first attack was a serum CRP > 240 mg/L. Subsequently, 23 (8.2%) patients proceeded to an elective laparoscopic sigmoid colectomy because of chronic symptoms. In addition, as reported by others, the highest risk of recurrence was within the first year (10%) and dropped to approximately 3% in the years thereafter[25,26].

In series without adequate imaging with CT scan as a prerequisite for inclusion, recurrence rates ranged from 13% to 47% (Table 1), depending on the definition used by the authors. Two United States series using large administrative databases have reported recurrence rates between 13% and 19%, which is in accordance with the results from our institution[17] and from other centers[27,28]. Indeed, in a study population of 3165 patients with acute diverticulitis, Broderick-Villa *et al*[28] reported a recurrence rate of 13.3% after a follow-up of 8.9 years. Less than 4% presented with a second recurrence, as others have shown[26].

The emerging picture is then that recurrence is relatively rare, and that recurrent diverticulitis is rarely

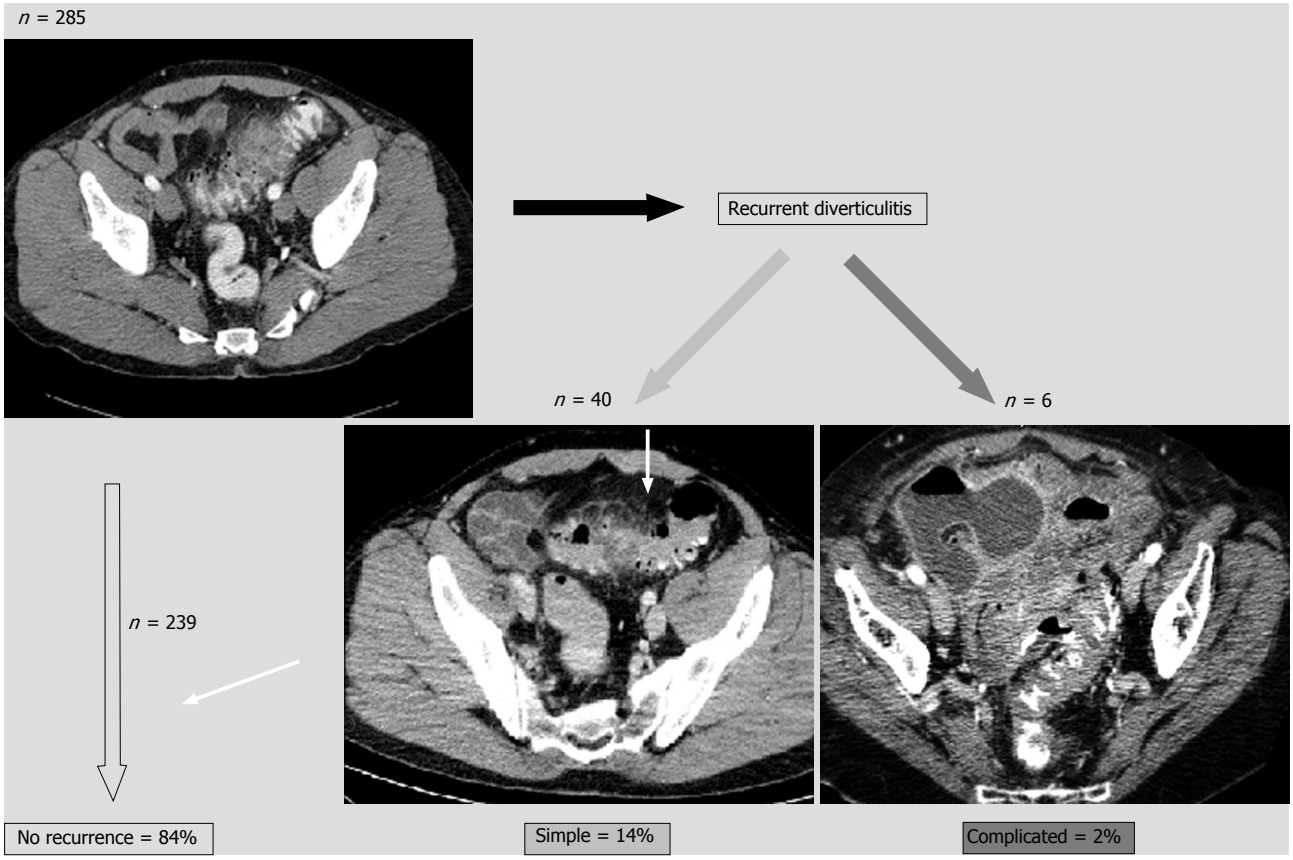

Figure 1 Flow chart of patients' outcome. Simple: Uncomplicated acute attack (Hinchey Ⅰa) (no abscess, no perforation); Complicated: Presence of abscess (Hinchey Ⅰb and Ⅱ) or peritonitis (Hinchey Ⅲ and Ⅳ).

severe[16,26]. The results of our study[17] confirm that a non-surgical strategy for the treatment of uncomplicated diverticulitis is safe in the long term[29]. They also contradict the once popular view that diverticulitis is a progressive disease[30]. Out of the 6 patients (2.1%) who developed complicated diverticulitis during follow-up, four (1.4%) patients developed peritonitis (Hinchey Ⅲ/Ⅳ) and underwent emergency Hartmann operation. A conservative policy after a first episode of simple diverticulitis is thus associated with a colostomy rate, which is similar to the risk of anastomotic dehiscence after an elective sigmoid colectomy[31]. Eglinton *et al*[26] found a risk of 5% for developing complicated disease after a first episode of uncomplicated diverticulitis. The risk of stoma formation was only 0.9%, all of which were temporary and subsequently reversed. Most perforations do not occur after recurrences, but after the first attack of acute diverticulitis[19,30,32-34]. Humes and West[35] however showed that, although most patients in their study (72.3%) had suffered no prior episodes of acute diverticulitis, further episodes of acute diverticulitis were associated with an increased risk of developing a fistula (OR = 1.54, 95%CI: 1.08-2.19), but there was no clear relationship with perforation or abscess.

Among the different risk factors for recurrence, age has often been mentioned (Table 1)[15,36]. In the past, sigmoidectomy was advocated in young patients (< 50 years at the first episode)[37]. But, younger patients have a similar absolute risk of recurrence, and a higher lifetime risk[10]. Buchs *et al*[17] do not agree with the general thought that younger patients has more aggressive diverticulitis, as suggested by others[26,36,38-40]. We agree the recent shift towards a more conservative management of diverticulitis is effective for all the different age groups. There is no evidence that younger patients should be treated differently from older patients[5,18].

The gravity of inflammation (measured by the CRP level) is associated with a higher probability of recurrence, as shown in our series[17]. The risk of recurrence at 6 mo was 22% for patients with CRP > 240 mg/L during their initial episode. Recently, CRP was seen as an interesting marker in simple cases of sigmoid diverticulitis. A level higher than 200 mg/L can be associated with local complication[41,42]. We recently proposed that the diagnostic criteria for diverticulitis should include CRP[22]. In our series, free pelvic fluid seen on CT was not associated with further recurrence. However, the discovery of a pneumoperitoneum was of borderline significance. Others groups have reported risk factors for recurrence, including: Age younger than 40 (or 50), a history of a least 3 episodes of acute diverticulitis, medical *vs* surgical management, male patients, radiological signs of complicated first episode

Table 1 Studies evaluating the natural history of acute diverticulitis

Ref.	No. of patients	Type of study	FU	Recurrence rate	Comments
Lahat *et al*[38], 2013	261	Prospective	88 mo	21.5%	21% operated, 46.6% asymptomatic
Buchs *et al*[17], 2013	280	Prospective	24 mo	16.4%	RF: CRP > 240
Humes and West[35], 2012	2950	Population-based cohort study	7.99 yr	-	Risk of fistula correlates to the number of prior episodes of diverticulitis
Binda *et al*[36], 2012	743	Multicenter, retro-prospective	10.7 yr	17.2%[1]	RF: < 40 yr, 3 episodes
Hall *et al*[16], 2011	672	Retrospective	42.8 mo	36%	RF: Family history, length of involved colon > 5 cm, retroperitoneal abscess
Mäkelä *et al*[20], 2010	555	Retrospective	-	42%	38% of recurrence diagnosed on clinical findings
Eglinton *et al*[26], 2010	320	Retrospective	101 mo	18.8%	4.7% more than one recurrent episode
Pittet *et al*[19], 2009	271	Retrospective	-	25%	Similar severity
Mueller *et al*[48], 2005	252	Retrospective	89 mo	47% (with 10% readmitted)	Based on symptoms
Anaya and Flum[27], 2005	25058	Cohort study, retrospective	-	19%	RF: < 50 yr, number of recurrent episodes
Broderick-Villa *et al*[28], 2005	3165 (2366 managed conservatively)	Cohort study, retrospective	8.9 yr	13.3%	RF: < 50 yr, charlson comorbidity index ≥ 1
Biondo *et al*[40], 2002	327	Retrospective	24-90 mo	15.9%	Age not a RF
Chautems *et al*[15], 2002	118	Prospective	9.5 yr	31%	Considering only patients undergoing an operation
Somasekar *et al*[34], 2002	108	Two-center, retrospective	-	2.7%[1]	Only patients with complicated disease
Mäkelä *et al*[43], 1998	366	Retrospective	-	22%	RF: < 50 yr, male
Ambrosetti *et al*[44], 1997	300	Prospective	46 mo	2%	RF: Radiological signs of complicated first episode
Parks[14], 1969	317	Retrospective	-	24.6%	Only readmitted patients

[1]If medically treated (*vs* 5.8% if surgically treated; $P < 0.001$); 22.7% of the studied population (complicated diverticulitis) was known for a previous acute diverticulitis. FU: Follow-up; RF: Risk factor; CRP: C-reactive protein.

(abscess formation and extra-colonic contrast or gas), higher comorbidity index, family history of diverticulitis, and length of involved colon > 5 cm[16,27,28,36,43,44].

In addition, risk factors for the development of complicated diverticulitis include smoking, non-steroidal anti-inflammatory drugs use, renal failure, organ transplants and steroid use[10].

After the resolution of an episode of diverticulitis, a variety of medical therapies have been used to prevent future attacks. Supplemental fiber, antispasmodics, rifaximin, Mesalamine 5-aminosalicyclic acid (5-ASA), and probiotics have all been studied. These studies included heterogeneous patients however the history of diverticulitis was poorly characterized[5]. 5-ASA has been reported to reduce the risk of recurrent symptomatic diverticular disease[10], but there is no evidence that it may prevent recurrent diverticulitis. A recent randomized controlled trial showed that 5-ASA did not reduce the risk of recurrence or time to recurrence. The proportion of patients requiring surgery was comparable among 5-ASA and placebo groups[45]. Whilst a protective benefit for these agents has been suggested, their role in prevention of diverticulitis remains to be properly defined[5,46].

This review has some limitations. First, most of the studies consider only individuals who received in-hospital treatment, and it is known that 50% of diverticulitis patients are safely managed in an outpatient setting[18,47]. There is a risk of bias in considering for inclusion the most severe cases of diverticulitis. Second, longer follow-up is needed to draw definitive conclusions. Finally, the clear lack of uniformity in terminology results in difficulties interpreting and comparing findings between studies.

In conclusion, we have demonstrated the benign nature of simple sigmoid diverticulitis in the vast majority of cases, with a low rate of recurrence, and most importantly a very low rate of subsequent peritonitis requiring emergency surgery. The risk of complication after sigmoidectomy for simple diverticulitis is probably superior than the risk to develop a complication related to the disease itself. And surgery does not completely protect against recurrence[36]. The old rationale for elective surgery as a preventive treatment, based mainly on concerns that recurrence would result in progressively increased risk of sepsis or the need of colostomy[21], is thus not supported by current series.

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Role of laryngeal mask airway in laparoscopic cholecystectomy

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Abstract

Laparoscopic cholecystectomy is one of the most commonly performed surgical procedures and the laryngeal mask airway (LMA) is the most common supraglottic airway device used by the anesthesiologists to manage airway during general anesthesia. Use of LMA has some advantages when compared to endotracheal intubation, such as quick and ease of placement, a lesser requirement for neuromuscular blockade and a lower incidence of postoperative morbididy. However, the use of the LMA in laparoscopy is controversial, based on a concern about increased risk of regurgitation and pulmonary aspiration. The ability of these devices to provide optimal ventilation during laparoscopic procedures has been also questioned. The most important parameter to secure an adequate ventilation and oxygenation for the LMA under pneumoperitoneum condition is its seal pressure of airway. A good sealing pressure, not only state correct patient ventilation, but it reduces the potential risk of aspiration due to the better seal of airway. In addition, the LMAs incorporating a gastric access, permitting a safe anesthesia based on these commented points. We did a literature search to clarify if the use of LMA in preference to intubation provides inadequate ventilation or increase the risk of aspiration in patients undergoing laparoscopic cholecystectomy. We found evidence stating that LMA with drain channel achieves adequate ventilation for these procedures. Limited evidence was found to consider these devices completely safe against aspiration. However, we observed that the incidence of regurgitation and aspiration associated with the use of the LMA in laparoscopic surgery is very low.

Key words: Laryngeal mask airway; Laryngeal mask airway Proseal; Laryngeal mask airway Supreme; I-gel; Laparoscopic cholecystectomy; Oropharyngeal leak pressure; Ventilation

Core tip: Use of the laryngeal mask airway (LMA) in laparoscopy is controversial, largely because of a concern about increased risk of regurgitation and aspiration, also due to an inadequate or suboptimal ventilation of the patient during these procedures. We performed the first review of this topic and we found evidence to recommend the LMA with gastric access in laparoscopy for selected patients based on its ability for optimal ventilation. A potential risk of aspiration cannot be totally rejected, however, clinical performance using these devices has reported a very low incidence of aspiration-related morbidity, so future research may provide some evidence about this topic.

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INTRODUCTION

Laparoscopic cholecystectomy is one of the most commonly performed surgical procedures in the world, in fact, it is the most frequent laparoscopic procedure performed. Over one million cholecystectomies are performed in the United States annually, with over 96% of those being performed laparoscopically[1].

It is common practice in most of the countries for anesthesia to be carried out with the use of the laryngeal mask airway (LMA), the most important and popular supraglottic airway device (SAD).

This device has several advantages when compared to tracheal intubation (TI), in particular avoidance of complications associated with TI, quick and ease of placement of the airway device itself, a lesser requirement for neuromuscular blockade, as well as a lower incidence of postoperative adverse events such as sore throat, dysphagia and dysphonia (based on its design to be a minimally stimulating to the airway)[2-4].

However, the use of the LMA in this context is controversial, the main concern being that it does not offer definitive airway protection from pulmonary aspiration of potential regurgitated gastric contents. The other controversial point is the ability of the LMA to provide correct ventilation in patients undergoing laparoscopic procedures. Laparoscopy is thought to increase the risk of aspiration due to the pneumoperitoneum-induced, which increase intra-abdominal pressure and it is accompanied by high peak airway pressure[5-7].

Therefore, many anesthesiologists advocate TI and mechanical ventilation for this kind of procedures.

When LMA is fully inserted using the recommended insertion technique, the distal tip of the cuff is at the upper esophageal sphincter, its sides face into the pyriform fossae and the upper border rests against the base of the tongue[8]. In this position, the LMA create an airway sealing, which permit a correct ventilation of the patient as well as a protection of airway against aspiration. We usually measure this sealing pressure or oropharyngeal leak pressure (OLP) in order to know how capable the LMA is to protect airway against potential aspiration of gastric contents. Different types of airway seal pressure tests can be performed using different test, it is commonly done by the anesthetist after general anesthesia induction for assessing OLP with the LMA prior to the beginning of the surgery[9].

The classical laryngeal mask airway (LMA-C) is the most widely studied SAD and in the last 15 years, several devices have been incorporated in order to improve the SAD's indications, these devices have bigger and better cuff, some of them with gastric access incorporation.

These designs offers a cuff that allows a higher seal pressure than the LMA-C and a drain tube that allows venting of the stomach contents and blind insertion of standard gastric tubes. Therefore, these new generation LMAs provides certain protection against regurgitation and prevents gastric insufflation when correctly placed.

These devices are a reasonable choice when performing anesthesia for procedures accompanied by high peak airway pressure, such as laparoscopy.

There are six SADs with a drain tube available in the market at this moment: Laryngeal Tube Suction™ (LTS or LTS-D if disposable), LMA Proseal™ (LMA-P), LMA Supreme™ (LMA-S), i-gel™ and recently the Guardian CPV™, the Baska Mask™ and the Ambu AuraGain™. LMA-P, LMA-S and i-gel are the most commonly used devices with gastric access in clinical anesthesia.

LMA was evaluated in laparoscopic cholecystectomy for the first time in 1996[10]. Between 2000 and 2002, a few studies reported the use of LMA-C and LMA-P for this kind of procedures[11-14]. Since 2010, several clinical studies have investigated the use of LMA with drain channel for laparoscopic cholecystectomy[2,15-19].

We will try to clarify if evidence-based medicine guides us to choose a LMA instead of an endotracheal tube (ETT) when performing a general anesthesia for laparoscopic cholecystectomy. And also what is the most appropriate airway device for this laparoscopic procedure. This review is an approach based on defining a specific and clinically relevant question, followed by a systematic search for evidence about the appraised topic.

Table 1 Summary of the studies investigating ventilation and aspiration with the laryngeal mask airway

Ref.	Group	*n*	Ventila-tory efficiency (%)	No. of insertion attempt ($1^{st}/2^{nd}/3^{rd}$)	Airway insertion time (*s*)	OLP (cm H_2O)	Peak airway pressure before pneumoperi-toneum (cm H_2O)	Peak airway pressure after pneumoperi-toneum (cm H_2O)	Blood on mask (%)
Lu *et al*[12], 2002	LMA-P	40	100	33/7/0	-	29 ± 6	18.3 ± 3	24.1 ± 2	15
	LMA-C	40	80	40/0/0	-	19 ± 4	17.6 ± 2	22.7 ± 3	
Maltby *et al*[13], 2002	LMA-P	50	92	-	-	34 ± 4	18 ± 5	25 ± 5	-
Sharma *et al*[15], 2010	LMA-P	30	100	24/5/1	14.2 ± 5.5	38.9 ± 3.2	15.9 ± 3.2	21.5 ± 3.2	26.6
	i-gel	30	100	28/2/0	13.6 ± 4.2	35.6 ± 4.8	14.9 ± 2.9	20 ± 3.7	10
Beleña *et al*[16], 2011	LMA-S	100	100	91/0/0	12 ± 4.6	28.8 ± 5.2	17.5 ± 3.3	22.9 ± 1	0
Hoşten *et al*[17], 2012	LMA-P	29	100	27/2/0	15.6 ± 6	27 ± 4.7	-	-	6.8
	LMA-S	30	100	28/2/0	12.5 ± 6	27 ± 2.9			3.3
Beleña *et al*[18], 2013	LMA-P	60	100	51/9/0	11.2 ± 4	30.7 ± 6	19 ± 3	26 ± 5	3.3
	LMA-S	60	100	55/5/0	11.8 ± 2	26.8 ± 4	18 ± 4	24 ± 4	0

Values are presented as numbers, mean ± SD, numbers or percentage. LMA-C: Laryngeal mask airway classic; LMA-P: Laryngeal mask airway Proseal; LMA-S: Laryngeal mask airway Supreme; OLP: Oropharyngeal leak pressure.

LITERATURE SEARCH QUESTION

The search question was clarified to "In healthy patients with no risk factors for regurgitation, undergoing elective laparoscopic cholecystectomy, does the use of the LMA in preference to tracheal intubation provide inadequate ventilation or increase the risk of pulmonary aspiration?"

Search methods

The ideal study design to answer this question is a randomized, controlled trial that compares ventilatory efficacy and the incidence of aspiration between LMA and tracheal intubation in patients undergoing laparoscopic cholecystectomy. We did not limit this search to those articles dealing with ventilatory efficacy and the incidence of aspiration, but we included all studies about LMA for laparoscopic cholecystectomy. A search was performed in MEDLINE, EMBASE, CENTRAL and Google Scholar in November 2014, and updated in February 2015. Search terms used in various combinations were: "laryngeal mask airway", "LMA", "laparoscopic cholecystectomy" and "laparoscopy".

All studies that met these criteria were included regardless of publication language. Review articles, case reports, case-series, letters to the editor, commentaries, proceedings, laboratory science studies, comparative studies using manikins, and any other non-relevant studies were excluded.

Summary of findings

The search identified ten randomized controlled trials, case series and large prospective observational studies (Table 1).

There was no meta-analysis on the specific subject of our appraised topic but a meta-analysis of trials, other studies and cases reporting the use of the LMA, involving 706 patients, reported optimal ventilation in 99.5% of the patients and no aspiration was identified[2,11-19]. The vast majority of the patients were successfully ventilated through the assigned laryngeal mask [LMA-C (n = 120), LMA-P (n = 306), LMA-S (n = 250), i-gel (n = 30)]. We excluded 62 patients ventilated with the streamlined liner of the pharynx airway (SLIPA™), because this SAD is not really considered a LMA[19].

Four of 16 obese LMA-P patients (BMI > 30 kg/m^2) crossed over to ETT because of respiratory obstruction or airway leak (0.5%)[13]. In 3 patients treated with LMA-C, ventilation failed but was subsequently optimal with the LMA-P[12].

Sharma *et al*[15] reported only 3 cases of regurgitation in patients ventilated with LMA-P, although no cases of aspiration were recorded. No more cases or regurgitation nor aspiration were found among the 706 patients studied.

Most of the studies analyzing and comparing the use of LMA in laparoscopy have focused on gynecological patients. Therefore, most part of LMA data were derived from gynecological laparoscopic procedures[5,20-39]. These data are not comparable with ours because gynecological laparoscopic has some differences when compared to cholecystectomy, such as higher intra-abdominal pneumoperitoneum pressure, trendelenburg position and all patients are women.

Other studies included different types of laparoscopic procedures apart from cholecystectomy (gynecological, appendicectomy or nephrectomy) and they were also excluded from our analysis[10,40,41]. We only found two studies involving the use of LMA for pediatric laparoscopic procedures and they were as well excluded[42,43].

Maltby *et al*[11] studied 101 adult American society of anesthesiologists (ASA) 1-2 patients scheduled for elective laparoscopic cholecystectomy using LMA-Classic or ETT, focused on gastric distension and ventilation parameters. They concluded that positive pressure ventilation with LMA-C of permitted adequate pulmonary ventilation and gastric distension occurred with equal frequency with either airway device. These authors, conducted another similar study in 2002[13] comparing LMA-P with ETT. They included 109 patients stratifying

them as non-obese or obese (BMI > 30 kg/m^2) and stated that LMA-P provided a correct ventilation without clinically significant gastric distension in all non-obese patients. Four of 16 obese LMA-P patients crossed over to TI because of failed ventilation, so the recommended that further studies were required to determine the use of the LMA-P for laparoscopic cholecystectomy in obese patients.

The third study, conducted by Lu *et al*[12], tested the hypothesis that the LMA-P was a more effective ventilatory device than LMA-C for laparoscopic cholecystectomy in 80 ASA 1-2 patients. Ease of insertion, efficacy of seal, peak airway pressures and oxygenation were recorded. These authors determined that LMA-P was a more effective ventilatory device for laparoscopic cholecystectomy than the LMA-C. Although first-time insertion success rates were higher for the LMA-C, OLP was higher for the LMA-P and ventilation was suboptimal less frequently with the LMA-P under pneumoperitoneum condition. In 3 patients receiving LMA-C, ventilation failed but was subsequently optimal using the LMA-P.

This is an important work, because it was the first one considering that LMA-P is a better device than LMA-C for laparoscopy and they did not recommend the use of the LMA-C for laparoscopic cholecystectomy.

Natalini *et al*[14], compared the frequency of airway seal and sore throat with the LMA-P and the LMA-C in a study involving 60 ASA 1-3 patients for laparoscopic cholecystectomy. Patients were ventilated adding positive end-expiratory pressure 10 cm H_2O through the proseal or the standard LMA, in order to improve ventilation. Both devices showed similar ventilatory efficiency during laparoscopy. The sore throat evaluation performed in recovery room was scored as mild and there were no differences between the groups.

The fifth research, involved 60 patients and compared respiratory mechanics in laparoscopic cholecystectomy using LMA-P and i-gel[15]. They observed that OLP was higher in LMA-P group, however, dynamic compliance was higher with the i-gel. They performed a fibreoptic evaluation of positioning of the devices, showing a higher malrotation for i-gel. Although regurgitation occurred in 3 cases (LMA-P), aspiration was not reported. Both devices provided optimal ventilation and oxygenation.

Another prospective observational study was performed in 100 patients undergoing laparoscopic cholecystectomy with LMA-S[16]. This device was successful inserted in all patients (first attempt *n* = 91 and second attempt *n* = 9) and mechanical ventilation was adequate in all cases. Gastric tube insertion was successful in all patients and graded as easy in 97% of the cases. Mean OLP was 28.8 cm H_2O (± 5.2; range 18-40 cm H_2O) and median (range) of stomach size on entry of the laparoscope, and change in stomach size during surgery (scored by the surgeon on an ordinal scale of 0-10) did not interfere with the procedure in any patient. The study concluded that supreme is an easy to insert and effective ventilatory device for laparoscopic cholecystectomy that provided an optimum airway seal with minimum adverse events.

A prospective randomized study conducted in 2012[17], compared the safety and efficacy of supreme and proseal during laparoscopic cholecystectomy. LMA-S was easier device to insert, as well as its drainage tube which was more quickly inserted. Seal pressure was similar in both groups and they did not find differences regarding the degree of gastric distension. Therefore, the study stated that both devices provided optimal ventilation and LMA-S is a good alternative to LMA-P for laparoscopy in suitable patients and experienced users.

The next publicated study was conducted at Sureste University Hospital in Madrid (Spain)[18] and it is the largest comparison performed between two LMA for laparoscopic cholecystectomy. This prospective randomized single-blind study, tested the efficacy and safety of the LMA supreme *vs* the LMA proseal in 120, ASA 1-3 patients undergoing elective laparoscopic cholecystectomy. These authors found that the LMA-S has a lower OLP and achieves a lower maximum tidal volume compared to the LMA-P. The success rate of the first attempt insertion was higher for the LMA-S group and this could have important implications when using the LMAS as an airway rescue device. The easy of insertion of the drain tube, adequacy of ventilation and complication rates are comparable for the two airway devices.

Aydogmus *et al*[2], studied a small sample of 60 patients wondering if LMA-S can be an alternative to endotracheal intubation in laparoscopic surgery. They focused on ventilation efficacy, ease of insertion, hemodynamic response (heart rate and mean arterial blood pressure) during insertion and removal of the mask and postoperative adverse events. In the end, they concluded that this device can be a suitable alternative to intubation for laparoscopy in selected patients.

Our last selected article, compared the quantitative clinical performances of the SLIPA and the LMA proseal regarding intensity of gastric distension in 124 anesthetized and paralyzed patients undergoing laparoscopic cholecystectomy. Secondary outcomes were the fiberoptic bronchoscopic view of the glottis, the severity of blood stain, and postoperative sore throat. There were no statistically significant differences between groups for each of these parameters[19].

DISCUSSION

In summary, in our review involving 706 patients undergoing laparoscopic cholecystectomy, ventilation was optimal in almost all the cases (99.5%) and it only failed in 4 obese patients (in the other 3 patients it was not considered as a failure because it was solved using another kind of LMA), which underlines the importance of a good selection of the patients. As showed in this review, the use of LMAs (particularly those LMA with gastric access) for these laparoscopic procedures

provided an adequate tidal volume and it was consistent with an optimal ventilation and oxygenation. Moreover, most of the studies performed with LMA involving gynecological laparoscopy or other kind of surgical procedures, permitted adequate ventilation in nearly 100% of the patients.

The studies reviewed also included capnography measurement during surgery as an important parameter to control hypercapnia in laparoscopic procedures. Mean $EtCO_2$ was maintained between 30-36 mmHg and it always remained < 45 mmHg[12-18].

These studies suggested a safe pneumoperitoneum pressure even using a relatively high peritoneal insufflation pressure of 15 mmHg used in the early studies[12,13]. Recent articles also found safe pressure when using lower values of 12-13 mmHg[16-18].

Regarding the risk of aspiration when using a LMA for general anesthesia during laparoscopic cholecystectomy, we observed a very low incidence of regurgitation and aspiration. This review found only 3 cases of regurgitation out of 706 patients studied (0.4%) and no cases of pulmonary aspiration were reported. Our results coincide with other authors; the largest study ever performed using LMA conducted by Chandi Verghese and Joseph Brimacombe[10] in 11910 patients for conventional and nonconventional usage, including 1534 laparoscopies (1469 gynecological and 65 cholecystectomies), only found four cases of regurgitation and one aspiration case. This patient was a female undergoing spontaneous ventilation anesthesia for an elective non-laparoscopic surgery who aspirated gastric contents during the procedure. She experienced an initial adverse outcome but with full recovery. These authors used LMA-C, because at that time, LMA with gastric access had not been introduced yet.

Brimacombe[44], stated that the LMA-C was used in 3000 selected women undergoing gynecological laparoscopy without serious morbidity. This suggests that the true risk of aspiration is likely to be less than 1 in 1000 (using 3/n to estimate the upper limit of a 95%CI).

Finally, a meta-analysis by Brimacombe and Berry[45] in 1995 about the incidence of aspiration associated with the LMA, involving 12901 patients, gave a final incidence of 2 aspiration in 10000 and case reports showed that most cases has one or more predisposing factors.

These three articles stated a very low incidence of aspiration over large series of patients when using the classic LMA (this device has not gastric access). We must have into account that, our review was performed over a sample mostly constituted by LMA with drain channel and this device is more appropriate for nonconventional usage such as laparoscopy than LMA-C. Based on the characteristics of these devices, its better airway seal pressure and the incorporation of a gastric access that allows the insertion of a gastric tube and the aspiration of gastric contents if necessary, makes this masks the optimal device to use for laparoscopic cholecystectomy.

The presence of gastric drainage channel should be mandatory for these procedures, because a common situation is the need for aspiration of gastric contents (including air) in order to properly expose the surgical field (gastric distention may impair the exposure of the triangle of Calot).

CONCLUSION

The published evidence does not allow us to totally answer the question we posed for this appraised topic. On the one hand, mechanical ventilation has been proved to be adequate when using LMA for laparoscopic cholecystectomy in selected patients. Although we do not recommend the use of the classic LMA for these procedures, only LMA with gastric access are advised. We do not either recommend the use of any type of LMA in laparoscopy for spontaneously breathing patients.

On the other hand, there is limited evidence to support the use of the LMA for laparoscopy. In particular, it is not completely clarified that the use of the LMA is not associated with an increased risk of pulmonary aspiration. We found, however, that the reported incidence of aspiration associated with the use of the LMA in laparoscopic surgery is very low. Moreover, we have found a non-existent incidence of aspiration when using LMA with drain channel for laparoscopic cholecystectomy in selected patients.

Based on our findings, we suggest the following inclusion criteria for using LMA in laparoscopic cholecystectomy: ASA 1-3 patients scheduled for elective laparoscopic cholecystectomy, non-obese patients (BMI < 30 kg/m^2), pneumoperitoneum pressure value lower than 13 mmHg, always using a LMA with drain channel and maybe performing a prophylactic routine gastric aspiration in order to minimize the risk of regurgitation and properly expose the surgical field.

Future research should focus on actual adverse outcomes and morbidity of these devices. A randomized comparison of tracheal intubation and LMA, investigating the risk of aspiration laparoscopy (assuming an incidence of 1 in 1000), would require a sample size of more than 30000 to find a twofold increase in risk. Such a trial is not feasible, but every year, hundreds of patients are successfully anesthetized using these devices with no morbidity. Clinical practice and the performance of more studies could provide satisfactory evidence in the future for anesthesiologists and patients.

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Endoscopic surgery - exploring the modalities

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Abstract

The adoption of endoscopic surgery continues to expand in clinical situations with the recent natural orifice transluminal endoscopic surgery technique enabling abdominal organ resection to be performed without necessitating any skin incision. In recent years, the development of numerous devices and platforms have allowed for such procedures to be carried out in a safer and more efficient manner, and in some ways to better simulate triangulation and surgical tasks (*e.g.*, suturing and dissection). Furthermore, new novel techniques such as submucosal tunneling, endoscopic full-thickness resection and hybrid endo-laparoscopic approaches have further widened its use in more advanced diseases. Nevertheless, many of these new innovations are still at their pre-clinical stage. This review focuses on the various innovations in endoscopic surgery, with emphasis on devices and techniques that are currently in human use.

Key words: Transanal total mesorectal excision; Natural orifice transluminal endoscopic surgery; Endoscopic surgery; Submucosal tunneling technique; Endoscopic submucosal dissection; Endoscopic full-thickness resection; Endo-laparoscopic

Core tip: This article is a comprehensive review of endoscopic surgery. It analyses the different types of endosurgery from endoscopic submucosal dissection, endoscopic full-thickness resection and natural orifice transluminal endoscopic surgery. This article highlights the relevant topics and recent advances in this area. In addition all the latest procedural devises such as the master and slave transluminal endoscopic robot endoscopic robot, multitasking endoscopes and other examples are described. Finally a clear and comprehensive review of the latest human clinical trials and their outcomes are outlined. Hence overall, readers will have a full understanding of endosurgery, the currently available as well as upcoming technology and their safety profiles.

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INTRODUCTION

Endoscopic resection has emerged as an alternative to many cases that were traditionally managed by surgery alone. Natural orifice transluminal endoscopic surgery (NOTES) has now offer truly scarless minimally invasive procedures for resection of abdominal organs. Since its introduction in 2000, more than 1000 reports have been published describing various applications NOTES in both animal and human[1]. The concept is continuously expanding in parallel to the advancement in technology and innovation of mechanics.

Endoscopic surgery is becoming increasingly popular among surgeons especially in Asian countries because many surgeons here were capable of performing flexible endoscopy. The Asia Pacific NOTES working group was formed in 2006 by a group of endoscopists and laparoscopic surgeons from Hong Kong, China, South Korea, Japan, Singapore, India and Malaysia. Since its establishment, many collaborative efforts between these countries have produced innovative developmental breakthroughs that address the barriers faced and clinical application in NOTES[2]. One example is the robotic endoscopic prototype named master and slave transluminal endoscopic robot (MASTER) that was developed in Singapore to perform complicated NOTES procedure.

Many novels endoscopic interventions have been described over the past decade, but none has have been formally approved as standard of care. There are many preliminary data that suggest its feasibility and safety, but there are still at preclinical stage. This article aims to provide a comprehensive review on endoscopic surgery, focuses on various innovations in endoscopic surgery, with emphasis on devices and techniques that are currently in human use.

Endoscopic submucosal dissection

Endoscopic resection was first reported by Hirao *et al*[3], a surgeon, for the treatment of early gastric cancer using local injection of hypertonic saline-epinephrine. The ideal result of endoscopic submucosal dissection (ESD) is that the specimen is resected *en bloc* and has sufficient depth to ensure accurate histopathological assessment and achieve R0 resection, while avoiding hazardous complications, mainly perforation and bleeding. Colonic ESD is technically more difficult because of the colon has thin wall, narrow lumen, and acute bends. At times, this is further complicated with the lesions being situated at proximal colon or behind a mucosal fold[4,5]. Various advances in the knives and other accessories have been developed to overcome these challenges (Table 1).

The devices used are generally divided into two broad categories: The needle-knife type and the grasping (scissors) type[6,7]. The most commonly used are the Dual knife and the insulated-tipped knife. The grasping scissors may be used when there is inadequate elevation of the submucosa plane to allow safe dissection. EndoLifter is a novel innovation in which an additional external grasping forceps is used to provide countertraction and make the submucosal plane wider. This is widely used in gastric ESD.

One of the disadvantages of ESD is that it can be time consuming. To reduce procedure time by eliminating the need for frequent switching of instrument, a new hybrid knife that combines both submucosal injection and dissection facilities into a single instrument has been developed (HybridKnife by ERBE, Tübingen, Germany). HybridKnife allow fluid injection into submucosal plane under safe and preselected pressure *via* the tip of the knife. The operators can perform marking, circumferential cutting and submucosal dissection with just one instrument. This device have shown to decrease procedure time, perforation rate and increase the rate of en bloc resection[8]. Another new water-jet system that also combines both submucosal injection and dissection known as the ENKI-2 has also recently been developed in France (by NESTIS, Lyon). The water jet is produced by a high pressure chamber. It is delivered *via* a flexible catheter hence enable ESD in retroflexion position. This system has proven its safety and efficiency in an animal study when compared to Dual knife[9]. A prospective human trial is currently underway.

Endoscopic full-thickness resection

Endoscopic full-thickness resection is a new technique that involves en bloc resection of the tumor which resulting in perforation, and closure of the defect. Initial experience with endoscopic full-thickness resection (EFTR) involves secondary defect closure using either over-the-scope-clip (OTSC), conventional clipping, T-tags or endoloops[10-12]. This may potentially cause peritoneal contamination or seedling of early cancer. Sarker *et al*[13], Fähndrich and Sandmann[14] have separately reported the successful use of grasp-and-snare techniques with preresection closure using OTSC system in human studies. The key aspect of this technique is to apply the clip at the base of the target lesion, and followed by resection above the ensnared lesion (Figure 1). There was no complication reported in their case series and all specimens had achieved complete resection margin. A significant disadvantage of using the OTSC system is that the size of the cap limits the size of the lesion that can be resected. Schmidt *et al*[15] described another preresection closure method using suturing devices (Plicator and GERDIX) in which it was found feasible for tumor of approximately 4 cm.

EFTR procedure still need to be investigated as current available evidence is mainly of animal models or from small series of human studies. EFTR could have a great impact in management of gastrointestinal stromal tumour and neuroendocrine tumor that would currently

Table 1 Characteristic of various endoscopic submucosal dissection knives

Type	Manufacturer	Description	Comments
Needle-knife type			
Insulated tip knife	Olympus	Ceramic ball attached to the tip of the knife	Insulator helps to prevent perforation. Small ceramic ball is suitable to operate on thinner submucosal plane; *e.g.*, in the esophagus and colon
Hook knife	Olympus	Tip of the knife is right-angled	Submucosal tissue is hooked and pulled before incision, lessen the risk of perforation
Flex knife	Olympus	Knife formed by soft, flexible loop cutting wire with adjustable length	Less risk of perforation. Distal end of the sheath is thick to serve as stopper to allow precise control of incision depth
Dual knife	Olympus	Small ball-like process on the tip, knife can be fixed in two positions - retracted or extended	Ball tip prevents slipping
Flush knife	Fujinon	Short needle knife that comes in 5 different projection lengths Water emission through the lumen of the needle	Water jet is activated by a foot pedal, helps to washout blood at operative field and debris at the tip of knife. Provide better visualization and less time consuming without having to switch instruments
Splashneedle	Pentax	Similar to Flush knife	
Mucosectomy	Pentax	Circumferentially insulated knife with single cutting wire on the side of the tip	Insulated plastic sheath can lie on the muscular layer, allowing safe dissection by cutting wire on the submucosal plane
Grasping type scissor forceps			
SB knife	Sumitomo Bakelite	Rotatable monopolar scissors, surrounded with no-conductive coating. Clawed and curved tip	Large insulated claw prevents injury to the muscular layer
Clutch Cutter	Fujinon	Thin serrated cutting scissor, insulated on the outer forcep, rotatable	Serrated edges help to grasp tissue better

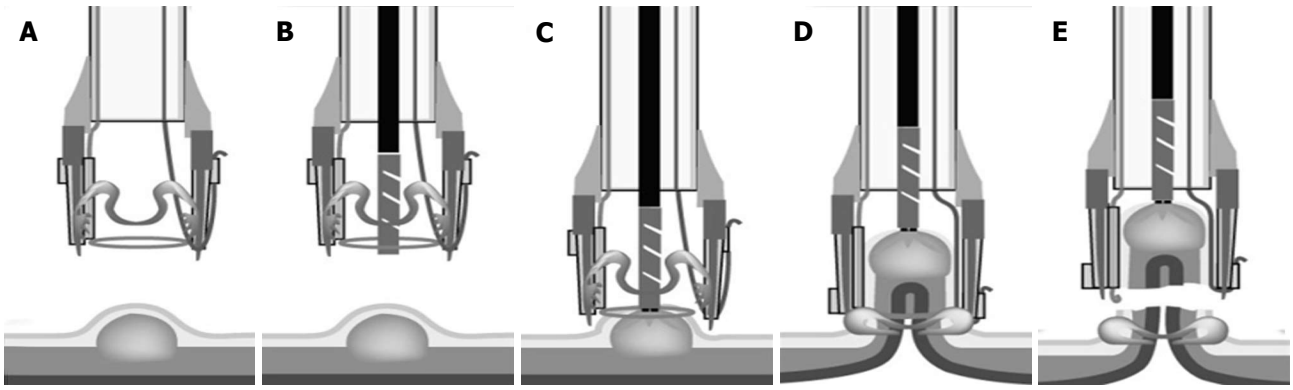

Figure 1 Endoscopic full-thickness resection of a submucosal lesion by application of an over-the-scope-clip followed by snare polypectomy. A: Endoscope is equipped with a cap mounted with clip; B: Identified lesion grasped; C: Pulled into the cap; D: Clip applied at the base; E: Full-thickness of the targeted lesion resected with closure of snare.

be treated by surgical resection.

NATURAL ORIFICE TRANSLUMINAL ENDOSCOPIC SURGERY

Endoscopic surgery has in recent years achieved yet another breakthrough, going beyond the boundaries of the gastrointestinal lumen, and entering into the peritoneum to perform intra-abdominal intervention. This concept, widely known as NOTES, was first introduced by Kalloo *et al*[16]. In 2004 whereby he reported the success of transgastric peritoneoscopy using a flexible endoscope in an animal model 3 years later, Rao *et al*[17] performed the first ever human NOTES procedure, which was a transgastric appendicectomy. Since then NOTES has been increasingly adopted to perform intra-abdominal exploration and extraction of various organs.

One of the most common NOTES access route is transvaginal access. Its accessibility and safety has long been proven through the use of culdoscopy in gynaecology and of the vaginal route to extract surgical specimen. However, in clinical practice, transvaginal NOTES is mostly facilitated with the help of abdominal wall entry, hence these surgeries are sometime known as hybrid procedures. One of the most studied procedures is transvaginal cholecystectomy (TVC). To date, TVC has been put up against laparoscopic cholecystectomy on a few prospective studies, and the results have favor TVC being associated with decreased risk of port site hernia, less postoperative pain and shorter recovery time (Table 2)[18-20]. Many intra-abdominal operations have now been undertaken *via*

Table 2 Randomised controlled trials that reported on no significant difference in major outcomes between transvaginal cholecystectomy and conventional laparoscopic cholecystectomy

Ref.	Study type	Type of TVC	Outcome					
			Median/min Duration of surgery (min)		Median/min Length of stay (d)		Median/min Pain score	
			TVC	CLC	TVC	CLC	TVC	CLC
Kilian *et al*[18]	RCT	Hybrid	68	55	3	4	1	3
Noguera *et al*[19]	RCT	Hybrid	64.85	47.04	1	1	3.94	4.65
Borchert *et al*[20]	RCT	Hybrid	65.1	64.2	2.81	2.81	1.81	2.03

These studies proved that TVC is not inferior to CLC. RCT: Randomised controlled trials; TVC: Transvaginal cholecystectomy; CLC: Conventional laparoscopic cholecystectomy.

this route. The drawbacks to transvaginal access are its associated risk of bladder and urethra injury, potential risk of infertility, and it is only applicable to female. It may be less acceptable in Asian countries due to cultural differences[21].

NOTES *via* gastrointestinal lumen have been proven to be virtually possible for every type of surgery in animal models. Despite this breakthrough, there are reservations of utilizing this route among patients mainly due to fear of introducing infection from gut wall penetration. A transcolonic approach carries the highest risk, followed by transgastric, transesophageal, transvaginal and transvesical approaches. Over the past years, evidence from experimental and clinical studies have shown that infectious complication from NOTES is low (< 3%)[22-24]. At present, the transvaginal and transgastric approaches are the most relevant for intraperitoneal NOTES procedures in human.

Pure NOTES is technically challenging. Conventional flexible endoscopes are inadequate to perform complex transluminal surgical procedures. They lack a multitasking platform that allows more variety of surgical manipulation. Like in any laparoscopic procedures, the key element to successful pure NOTES is triangulation. The evolution of NOTES devices has seen many efforts put into developing devices and platforms that simulate triangulation and surgical tasks (*e.g.,* suturing and dissection) in a laparoscopic procedure. Presently, all multitasking system developed for NOTES procedures can be broadly classified into two different types: (1) Mechanical platforms, which includes the dual channel endoscope (DCE) (Olympus, Japan), R-Scope (Olympus, Japan), the ANUBISCOPE (Karl-Storz, Germany), the EndoSAMURAI (Olympus, Japan), incisionless operating platform (IOP) (USGI Medical, United States), and DDES system (Boston Scientific, United States). DCE, R-Scope (a modified DCE), EndoSAMURAI and the ANUBISCOPE are integrated system comprising of the visual and the instrument manipulation function. The IOP and DDES systems serve as multitasking platforms that have multiple operating channels and they rely on conventional endoscopes for visualization. Generally, these systems have an average diameter of not more than 22 mm in order to be able to intubate pass the pharynx. Triangulation is achieved by having two or more working arms and therefore increases the degree of freedom of the end effectors. To date, DCE, R-scope and the IOP have data published on human studies. The EndoSAMURAI, the more advanced platform, has two independently movable arms with an additional non-articulating arm. The moveable arms are mechanically cable actuated. They serve to provide traction and counter-traction on dissecting tissue, and perform more advanced maneuvers such as suturing. The non-articulating arm allows insertion of generic endoscopic instruments meant dissection, cautery and clipping. This system has console very similar to conventional laparoscopic instruments. During the early stage, Spaun *et al*[25] compared between DCE and EndoSAMURAI, and found that EndoSAMURAI has significant advantage over the conventional endoscopes in regards to accuracy and efficiency in performing complex surgical task. This device has been used successfully to perform transgastric small bowel full thickness resection in animal studies[26,27]. Another promising multitasking endoscope prototype is the ANUBIScope, which has a special tulip shaped tip that allow two deflectable instrument channels to be positioned for instrument triangulation, and a third central channel for suction. These instruments are controlled through a trigger handle that is similar to that seen in laparoscopic instruments. In 2012, Perretta *et al*[28] successfully completed a cholecystectomy on a human in 60 min using the ANUBISCOPE. Of the available integrated endoscope platforms, the ANUBIScope is likely to be the most successful.

IOP is another promising device which was first designed specifically to perform intraperitoneal NOTES procedures. One of the unique features of this multi-lumen access device is that its flexible over-sheath is equipped with ShapeLock function. ShapeLock function is formed by a series of titanium rings that are connected by wire, and the rings lock into position when the connecting wires are tightened. The stiffened over-sheath ensures a stable platform while articulating the instruments. As such, many extralumenal intraperitoneal procedures including those that require significant retroflexion such as transgastric cholecystectomy, fundoplication, gastric restriction and diaphragmatic repair have been performed in animal and human cadaveric study[29]. The IOP has since been used by surgeons in the Europe and Middle East for the novel primary obesity surgery

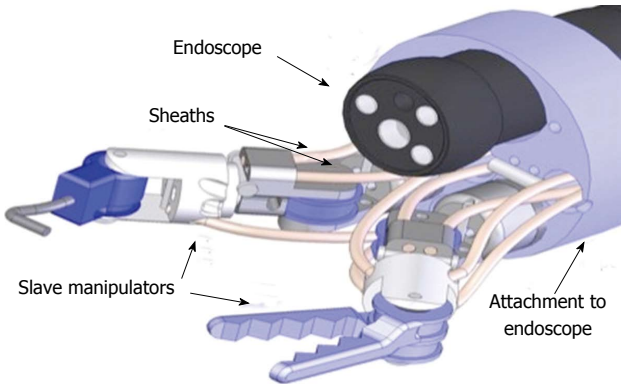

Figure 2 Design of prototype slave manipulator.

Figure 3 Master console controlled by surgeon.

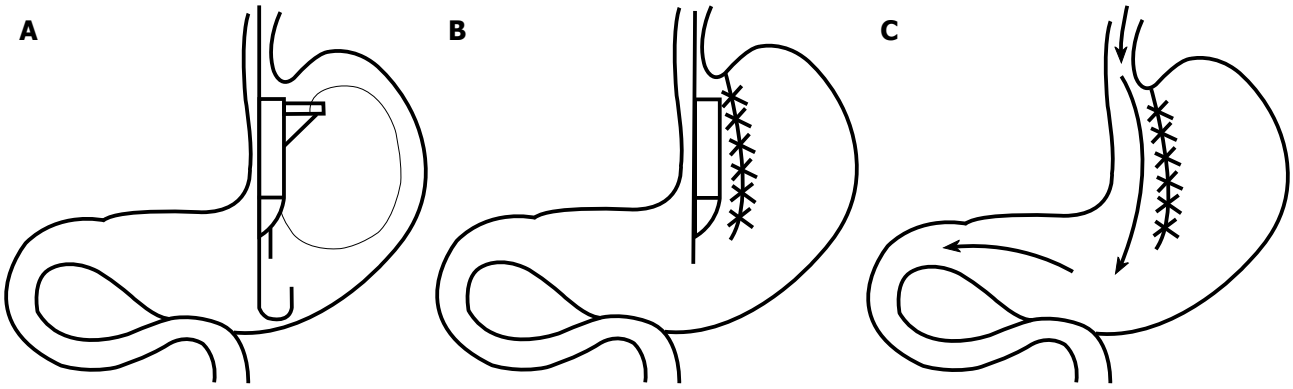

Figure 4 Endoscopic creation of restrictive pouch with transoral gastroplasty device. A: TOGA system deployed within the stomach, and having the endoscope at retroflex view; B: Anterior and posterior gastric mucosa brought into the suction chamber and stapled on; C: A restrictive luminal tube created within the stomach. TOGA: Transoral gastroplasty.

endoluminal (POSE) procedures. With this technique, multiple transmural plications are placed in the fundus and the distal body using specialized suture anchors that is facilitated by the IOP device. Espinós *et al*[30] has demonstrated clinical safety and effectiveness of POSE with IOP in 45 obese patients; (2) Robotic platforms: At present, two state-of-the-art robotic systems have been developed, namely the MASTER (Nanyang University, Singapore) and the ViaCath (Hansen Medical, United States). Master and slave translumenal endoscopic robot is an endoscopic robotic platform that is composed of a human-master robotic interface, a telesurgical workstation, and slave manipulator. This system works with a front-viewing endoscope equipped with two cable-actuated robotic arms (Figures 2 and 3). The robotic arm prototypes are designed with four "joints" which allows them to supinate, pronate, hyperextension, and flexion. One arm has a grasper and the other arm a cauterizing hook. The MASTER robotic system requires an endoscopist and a surgeon to operate. Once the endoscopist had positioned the endoscope, the surgeon then controls the finer motion of the robotic arms to perform surgery (Figure 4).

The MASTER system has been used to perform ESD in *ex vivo* and *in vivo* porcine models and was found to be comparable to standard endoscopic therapy in terms of operation time[31]. In 2014, Chiu *et al*[32] demonstrated that full thickness resection with MASTER for the treatment of gastric submucosal tumors in animal models with and closure of the defect with Overstitch is safe and feasible. First reported use of MASTER in clinical setting was a multicenter prospective study of 5 patients with early-stage gastric neoplasia[33]. All submucosal dissections were performed using the MASTER system, and no perioperative complications encountered. The resection margins were clear of tumors in all 5 patients. From these studies, the MASTER system has shown to have met its objectives on successfully performing true NOTES procedures. We are still awaiting further studies to assess its capability and safety to perform other surgical procedures.

ViaCath system is another robot driven actuator that consists of a flexible overtube that runs alongside a standard endoscopes with two distal articulated robotic instruments. It functions similar to the IOP except it is robotic assisted hence allow more precise manipulation of the operating arms. ViaCath is yet to be fully utilized for NOTES procedures in human.

Although the most common access route for NOTES procedures is the vagina, selective indications have emerged for each different access techniques, including submucosal tunneling techniques *via* the transesophageal

approach, staging, gastric restriction and small tumor resection *via* the transgastric approach, and colorectal resections *via* the transanal/transcolonic approach.

Transeophageal approach: Submucosal tunneling techniques

Submucosal tunneling technique was first developed at the Mayo clinic with the intention to create a mucosal flap prior to penetration through the deeper layer and subsequent entry into the peritoneal cavity[34]. In this technique, the submucosal layer is endoscopically tunneled into with the resulting space that can be used either for dissection onto the deeper layer, or an offset exit into the peritoneal cavity. The mucosal flap serves as a sealant valve that minimizes the risk of intraperitoneal soiling with the luminal contents. Experimental studies on animal models have shown safe entry *via* the submucosal tunnel into the mediastinum and peritoneum, resulting in successful transesophageal approach for epicardial coagulation and transgastric cholecystectomy, respectively[35,36].

This submucosal tunneling technique has been adapted into the esophageal myotomy procedure to treat achalasia. The procedure, first introduced in 2008 by Inoue *et al*[37] as per oral endoscopic myotomy (POEM), involves dissection and division of the inner circular muscle layer of the esophagus through a submucosal tunnel created endoscopically by a small proximal opening in the esophageal mucosa. The submucosal entry point is usually created at 10-15 cm from the gastroesophageal junction (GEJ). Once the subumucosal layer is exposed, the dissection is carried out using electrosurgical ESD technique. The mucosal layer is separated from the underlying circular muscle fibers, and this dissection is extended until the endoscope is 2-3 cm beyond the GEJ. Myotomy then begins from 2 cm distal to the entry point up to the GEJ. Once completed, the mucosal closure can easily be performed with clips or endoscopic suturing device. Five years later, Inoue *et al*[38] published the largest series of POEM with overwhelming success. Out of 300 patients, dysphagia was relief following one session of POEM in 98.2% of the subjects. There were only 2 patients with perforation that resulted in pneumomediastinum and pneumoperitoneum, one each respectively. In another prospective, multicentre study, 6 and 12 mo symptom remission rates was reported as 89% and 82%, respectively[39]. All current studies have indicated that POEM is a safe and effective treatment for esophageal achalasia.

The success in POEM has led to the further use submucosal tunneling technique for resection of subepithelial tumor. Usually, the submucosal tunnel begins at 5 cm proximal to the lesion. A short tunnel approaching the lesion is created by additional submucosal dissection with CO_2 or air insufflations. Subepithelial tumour is excised using needle-knife and removed completely through the tunnel. Mucosal entry flap is then approximated using endoclips. To date, successful attempts were reported for submucosal tumors in the esophagus and cardia that is ≤ 4 cm in size[40-42]. Resection of gastric lesion distal to cardia appears to be technically difficult, and endoscopic full thickness resection, as described above is the more preferred treatment of choice.

Transgastric access: Peritoneoscopy, gastric restriction surgery, full-thickness gastric tumor resection

Transgastric NOTES access is typically *via* gastrostomies performed in the anterior stomach with needle knife puncture and balloon dilation. Currently, its role in clinical practice is mainly for staging peritoneal exploration, small bowel tumor resection and gastric tumor resection. A study involving a series of 130 patients who underwent transgastric NOTES by Nau *et al*[43] found that endoscopic peritoneoscopy is not inferior to laparoscopic exploration for assessment of peritoneal metastasis. Interestingly, the former was also found to be equally effective and safe in a subgroup of patients with previous abdominal surgery. Transgastric peritoneoscopy can be performed with conventional flexible endoscopes, but the gastrotomies would require a specialized closure device. Since the development of abovementioned multitasking platforms, full thickness resections of gastric and small bowel tumors are currently performed *via* transgastric route.

Novel endoscopic gastric restriction surgery is the new frontier in bariatric surgery, to offer a less invasive approach which can be performed without general anesthesia. In theory, this may potentially reduce the risks commonly associated with laparoscopic bariatric surgery such as cardiopulmonary event, anastomotic leak, marginal ulcer formation and wound related complications. Endoscopic approach can serve either as a bridge to surgery or as "stand-alone" procedure for patients who are poor surgical candidates especially in super-obese (BMI > 50). Currently, there are two established techniques and, known as the transoral gastroplasty (TOGA™) and endoluminal vertical gastroplasty. Table 3 provides a summary of reported outcome for these endoscopic restrictive gastroplasty procedures. TOGA uses an endoscopic full-thickness stapling device to create a pouch along the lesser curve. The device uses vacuum suction to oppose the anterior and the posterior gastric wall prior to deploying the staplers. A restrictor is used to clamp the gastric folds, and the process can be repeated to achieve the desired luminal narrowing (Figure 4). A multicentre trial of 67 patients showed that this procedure resulted in substantial weight loss after 1 year without severe complications and no mortality[44]. Endoluminal vertical gastroplasty uses a endoscopic suturing device (Bard EndoCinch) to create a sleeve intraluminally. The suturing device is contained within a capsule that is attached at the end of the gastroscope. Tissue is sucked into the capsule and a needle is advanced through the captured tissue. Several sutures are deployed in a

Table 3 Summary of reported outcome data for endoscopic restrictive gastroplasty

Technique	Study design	Excess BMI/weight loss (%)	Effects of comorbidities	Postoperative complications
Transoral gastroplasty[44]	Prospective multicentre study with 67 patients enrolled Average BMI: 41.5 (range 35.0-52.7) Follow up period: 12 mo	52.2% for patients with baseline BMI < 40; 41.3% for patients baseline BMI > 40	Successful reduction of HbA1c to 5.7% (baseline of 7%), improvement in triglyceride level	2 patients had respiratory insufficiency and asymptomatic pneumoperitoneum, respectively. Both were successfully managed conservatively
Endoluminal vertical gastroplasty using Bard EndoCinch suturing system[45]	Prospective, single centre observational study Average BMI: 39.9 (range 28.0-60.2) Follow up period: 12 mo	Overall EWL of 58.1% Patients with BMI < 35 have highest EWL of 85.1%	NE	No serious adverse events reported
Endoscopic transmural gastric plication using Incisionless Operating Platform[30]	Prospective single centre Average BMI: 36.7 (range 28.1-46.6) Follow up period: 6 mo	49.4% EWL at 6 mo	NE	Minor postoperative side effects, *i.e.*, fever, sore throat, stomach pain, nausea, vomiting and chest pain

NE: Not evaluated; BMI: Body mass index; EWL: Excess weight loss.

continuous and cross-linked fashion from the proximal fundus to the distal stomach. Once the suture is fixed, a vertical sleeve is created. Fogel *et al*[45], the first to describe the use of EndoCinch for this procedure, reported a 12 mo excess weight loss of 58.1 ± 19.9 in 64 patients. The main concern with this technique is its durability, for which additional studies are needed to evaluate its long-term efficacy. Recent modifications to this technique is the use of the restoring suturing system that enabled suture reloading without device withdrawal and provide greater depth of suturing. The incisionless operating platform has also being used for this procedure.

Transanal/transcolonic natural orifice transluminal endoscopic surgery: Transanal endoscopic microsurgery

From experience derived from transanal endoscopic microsurgery (TEM), surgeons have expanded the utilization of the transanal route for complete rectal and colonic resection. In 2007, Whiteford *et al*[46] described the first transanal NOTES radical sigmoidectomy in human cadavers. Various attempts by others were successful in swine and cadaveric models, but all has found significant technical difficulty for dissection of the mesentery and more proximal colon using solely the TEM platform. This has led to the use hybrid technology that uses transabdominal laparoscopy to provide camera visualization, triangulation by assisting grasper, dissection with energy source device. Ever since, this approach has made it to clinical application for treating rectal cancer and inflammatory bowel disease[47-49]. Transanal approach has two distinct techniques: (1) Using origin TEM technique to dissect the lower rectum and perform colorectal resection and rectal anastomosis; and (2) abdominal cavity is entered *via* transanal route or *via* transcolonic approach at the desired anastomotic site. Currently, pure transanal NOTES colorectal resection is still at preclinical stage.

CONCLUSION

The innovation in endoluminal techniques and development of endoscopic instruments encouragingly implies that it is now possible to perform fully incisionless surgery. The progress of endoscopic surgery is still at an experimental stage. Further development of multitasking platforms and surgical instruments is necessary to allow safe and widespread application of endoscopic surgery for more complex procedures, especially for malignant tumors. Despite its current limitations, endoscopic surgery has met with considerable success and has proven to be not inferior to conventional laparoscopic surgery in numerous areas. The future of NOTES seems promising and may one day provide the ultimate version of minimally invasive surgery.

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ORIGINAL ARTICLE

Retrospective Study

Application of single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy

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Abstract

AIM: To investigate the simplicity, reliability, and safety of the application of single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy.

METHODS: A retrospective analysis was performed on the data of patients who received pancreaticoduodenectomy completed by the same surgical group between January 2011 and April 2014 in the General Hospital of the People's Liberation Army. In total, 51 cases received single-layer mucosa-to-mucosa pancreaticojejunal anastomosis and 51 cases received double-layer pancreaticojejunal anastomosis. The diagnoses of pancreatic fistula and clinically relevant pancreatic fistula after pancreaticoduodenectomy were judged strictly by the International Study Group on pancreatic fistula definition. The preoperative and intraoperative data of these two groups were compared. χ^2 test and Fisher's exact test were used to analyze the incidences of pancreatic fistula, peritoneal catheterization, abdominal infection and overall complications between the single-layer anastomosis group and double-layer anastomosis group. Rank sum test were used to analyze the difference in operation time, pancreaticojejunal anastomosis time, postoperative hospitalization time, total hospitalization time and hospitalization expenses between the single-layer anastomosis group and double-layer anastomosis group.

RESULTS: Patients with grade A pancreatic fistula accounted for 15.69% (8/51) *vs* 15.69% (8/51) (P = 1.0000), and patients with grades B and C pancreatic fistula accounted for 9.80% (5/51) *vs* 52.94% (27/51) (P = 0.0000) in the single-layer and double-layer anastomosis groups. Although there was no significant difference in the percentage of patients with grade A pancreatic fistula, there was a significant difference in the percentage of patients with grades B and C pancreatic fistula between the two groups. The

operation time (220.059 ± 60.602 min *vs* 379.412 ± 90.761 min, *P* = 0.000), pancreaticojejunal anastomosis time (17.922 ± 5.145 min *vs* 31.333 ± 7.776 min, *P* = 0.000), postoperative hospitalization time (18.588 ± 5.285 d *vs* 26.373 ± 15.815 d, *P* = 0.003), total hospitalization time (25.627 ± 6.551 d *vs* 33.706 ± 15.899 d, *P* = 0.002), hospitalization expenses (116787.667 ± 31900.927 yuan *vs* 162788.608 ± 129732.500 yuan, *P* = 0.001), as well as the incidences of pancreatic fistula [13/51 (25.49%) *vs* 35/51 (68.63%), *P* = 0.0000], peritoneal catheterization [0/51 (0%) *vs* 6/51 (11.76%), *P* = 0.0354], abdominal infection [1/51 (1.96%) *vs* 11/51 (21.57%), *P* = 0.0021], and overall complications [21/51 (41.18%) *vs* 37/51 (72.55%), *P* = 0.0014] in the single-layer anastomosis group were all lower than those in the double-layer anastomosis group.

CONCLUSION: Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis appears to be a simple, reliable, and safe method. Use of this method could reduce the postoperative incidence of complications.

Key words: Pancreaticojejunal anastomosis; Pancreatic fistula; Pancreaticoduodenectomy

Core tip: Pancreaticoduodenectomy is a complex surgical procedure with a high perioperative complication rate and a high mortality rate, therefore, pancreaticoduodenectomy is considered a dangerous surgery. Pancreaticojejunal anastomosis plays an important role in pancreaticoduodenectomy; its success determines the success of the surgery. In our study, there was a significant difference in the percentage of patients with grades B and C pancreatic fistula between the two groups. Single-layer anastomosis was better than double-layer anastomosis when the pancreatic texture was soft. The use of this method could reduce the rates of postoperative pancreatic fistula, abdominal infection and peritoneal catheterization.

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INTRODUCTION

Pancreaticoduodenectomy is the primary surgical method for the treatment of pancreatic head tumors, distal bile duct tumors, ampullary tumors, duodenal tumors, and duodenal papilla tumors. However, because it is a complex surgical procedure with a high perioperative complication rate and a high mortality rate, pancreaticoduodenectomy is considered a dangerous surgery. In the literature, the reported incidence of postoperative pancreatic fistula associated with this procedure differs due to the use of different definitions of pancreatic fistula; overall, the incidence ranges from 10% to greater than 30%[1-4]. Pancreatic fistula was associated with delayed gastric emptying, intra-abdominal abscess, local infection at the incision site, sepsis, and blood loss after pancreaticoduodenectomy[5-8]. Although the complication and mortality rates associated with pancreatic fistula have decreased due to improvements in perioperative management, surgical techniques and timely and proper management of postoperative complications[5,9,10], the incidence of postoperative complications during the perioperative period is still 30%-60%[11-15].

Pancreaticojejunal anastomosis plays an important role in pancreaticoduodenectomy; its success determines the success of the surgery. Currently, pancreaticojejunal anastomosis is considered a weak link in pancreaticoduodenectomy[16,17]. Although several advocated methods of pancreaticojejunal anastomosis are considered to be able to reduce the occurrence of pancreatic fistula, the question of which pancreaticojejunal anastomosis method is best is still debatable[18-25]. This study describes a new, safe, simple, easy-to-suture, and reliable method for pancreaticojejunal anastomosis.

MATERIALS AND METHODS

General information

This study retrospectively analyzed data on pancreaticoduodenectomies completed by the same surgical group between January 2011 and April 2014 at our hospital. In these surgeries, a variety of pancreaticojejunal anastomosis methods were used, including single-layer mucosa-to-mucosa pancreaticojejunal anastomosis (referred to hereafter as single-layer anastomosis) and double-layer mucosa-to-mucosa pancreaticojejunal anastomosis (referred to hereafter as double-layer anastomosis). Patients whose surgery involved either of these two pancreaticojejunal anastomosis methods in pancreaticoduodenectomy were enrolled, and patients who did not meet the inclusion criteria for the study were excluded. There were 102 patients in the two groups, with 51 cases in each group. Of these patients, 19 had hypertension, 14 had a history of diabetes mellitus, 30 had a past history of drinking, 27 had a history of smoking, and 14 cases had a history of abdominal surgery. There were 62 males and 40 females. Other general information on these patients is presented in Tables 1 and 2. All 102 cases were confirmed by postoperative pathology (Table 3).

Double-layer anastomosis group

General information: There were 51 patients in

Table 1 General information on patients in the single-layer anastomosis group

Item	Mean value	Standard deviation	Minimum value	Maximum value
Age (yr)	58.804	9.466	38.000	79.000
BMI (kg/m^2)	22.866	2.755	17.900	29.400
Albumin (g/L)	38.039	3.891	26.100	45.000
Blood glucose (mol/L)	6.472	2.540	3.960	16.610
Total bilirubin (μmol/L)	122.618	122.204	6.400	412.600
Alkaline phosphatase (u/L)	359.631	258.629	39.900	1396.900
r-GT	620.853	522.464	7.000	2503.200
Operation time (min)	220.059	60.602	135.000	480.000
Pancreaticojejunal anastomosis time (min)	17.922	5.145	11.000	40.000
Amount of blood loss (mL)	292.549	146.940	100.000	800.000
Pancreatic duct diameter (mm)	4.863	2.322	1.000	12.000
Hospitalization time (d)	25.627	6.551	15.000	49.000
Postoperative hospitalization time (d)	18.588	5.285	7.000	33.000
Hospitalization expense (yuan)	116787.667	31900.927	64874.000	237762.000

BMI: Body mass index.

Table 2 General information on patients in the double-layer anastomosis group

Item	Mean value	Standard deviation	Minimum value	Maximum value
Age (yr)	58.020	12.820	18.000	78.000
BMI (kg/m^2)	23.858	3.272	13.360	32.690
Albumin (g/L)	39.480	4.182	29.600	50.000
Blood glucose (mol/L)	6.482	2.228	4.120	13.550
Total bilirubin (μmol/L)	73.510	78.244	3.500	313.000
Alkaline phosphatase (u/L)	303.245	268.287	42.000	1105.600
r-GT	533.655	631.956	5.800	2744.000
Operation time (min)	379.412	90.761	210.000	570.000
Pancreaticojejunal anastomosis time (min)	31.333	7.776	16.000	47.000
Amount of blood loss (mL)	482.353	293.909	50.000	1500.000
Pancreatic duct diameter (mm)	3.961	2.362	1.500	12.000
Hospitalization time (d)	33.706	15.899	16.000	105.000
Postoperative hospitalization time (d)	26.373	15.815	11.000	101.000
Hospitalization expense (yuan)	162788.608	129732.500	84497.000	968534.000

BMI: Body mass index.

the double-layer anastomosis group. Sixteen of these received pancreaticoduodenectomy (PD); of these, 3 also received combined portal vein resection and reconstruction. Thirty-five patients received pylorus-preserving pancreaticoduodenectomy (PPPD); of these, 2 also received combined portal vein resection and reconstruction.

Surgical method: The pancreas was transected at the left side of the portal vein using a surgical knife. The bleeding points on the pancreatic resection surface were sutured and ligated using 6-0 PDS Ⅱ for complete hemostasis. An appropriate pancreatic duct supporting tube was placed in the pancreatic duct. The pancreatic head was resected, and the duodenum and lymph nodes were completely cleaned. Approximately 2-3 cm of the pancreatic stump was freed, and an incision approximately 0.5 cm in length was made on the jejunal wall 4-5 cm from the jejunal stump. The distal end of the pancreatic duct supporting drainage tube was placed into the jejunum loop. The pancreatic parenchyma and the jejunal seromuscular layer were intermittently sutured using 4-0 Vicryl sutures; surgical knots were not made at this point. Next, 6-0 PDS Ⅱ absorbable thread was used to intermittently penetrate the pancreatic duct and the jejunal opening to form the mucosa-to-mucosa pancreaticojejunal anastomosis using intermittent sutures for 6 stitches. One suture on the middle of the posterior wall was reserved to fix the pancreatic duct supporting tube. The intermittent suture between the pancreatic parenchyma and the jejunal seromuscular layer was ligated to complete the anastomosis. After the cholangioenteric anastomosis and gastrointestinal anastomosis were completed, two abdominal drainage tubes were inserted, one before and one after the pancreaticojejunal anastomotic site to facilitate postoperative observation and conventional monitoring of the quantity and properties of the drainage fluid and to provide samples for the measurement of indicators such as bilirubin and amylase.

Single-layer anastomosis group

General information: There were 51 patients in the single-layer anastomosis group. Twenty of these received

Table 3 Pathology data

Pathological type	Number of cases
Distal bile duct adenocarcinoma	29
Chronic inflammation at the end of the distal bile duct mucosa combined with moderate atypical dysplasia	3
Villous adenoma at the end of distal bile duct mucosa and moderate-severe atypical dysplasia of some glands	1
Ampullary adenocarcinoma	14
Duodenal stromal tumors	1
Adenocarcinoma of the descending duodenum	3
Duodenal papilla adenocarcinoma	20
Duodenal neuroendocrine tumors	2
Tubulovillous adenoma of duodenal papilla with severe atypical dysplasia of some epithelia	1
Duodenal papilla adenocarcinoma	1
Chronic pancreatitis	1
Pancreatic head adenocarcinoma	22
Solid-pseudopapillary tumor of pancreatic head	1
Neuroendocrine tumor of pancreatic head	2
Neuroendocrine carcinoma of pancreatic head	1

PD; of these, 1 also received combined portal vein resection and reconstruction. Thirty-one of the patients in this group received PPPD; 1 of these also received combined portal vein resection and reconstruction.

Surgical method: The pancreas was transected at the left side of the portal vein using a small knife. The bleeding points on the pancreatic resection surface were sutured and ligated using 5-0 prolene sutures for complete hemostasis. Appropriate pancreatic duct supporting tubes were placed in the pancreatic duct. The pancreatic head was resected, and the duodenum and lymph nodes were completely cleaned.

Step 1: The pancreatic stump was freed for approximately 3-4 cm of its length. At 1-2 cm from the pancreatic stump, the anterior wall of the pancreatic duct and the anterior wall of the pancreas were intermittently penetrated and sutured using 4-0 absorbable Vicryl sutures for 3-4 stitches; surgical knots were not made at this point, and the suture was reserved for suturing the anterior wall of the jejunal incision and for suspension of the anterior wall of the pancreatic duct. The needling direction was from the whole layer of the anterior wall of the pancreas to the inside of the anterior wall of the pancreatic duct (Figure 1A).

Step 2: The proximal jejunum was lifted, and a 0.5-0.8 cm incision was made at the jejunal wall 4-5 cm from the jejunal stump. A 4-0 absorbable Vicryl suture was used to intermittently penetrate and suture the whole layer of the posterior-lateral wall of the jejunum, the posterior-lateral wall of the pancreatic duct, and the whole layer of the posterior-lateral wall of the pancreas for a total of 5-7 stitches (3-5 stitches in the posterior wall and 1 stitch in each lateral wall). Surgical knots were not made at this point. The needling was conducted from outside the jejunum to the inside of the jejunal section for suturing; then, the posterior-lateral wall of the pancreatic duct and the whole layer of the posterior-lateral wall of the pancreas were penetrated and sutured. The knot was tied at one side. It is important to ensure that this knot is tied properly; if it is too tight, the pancreas and the pancreatic duct may be cut; if it is too loose, the attachment will be insufficient (Figure 1B).

Step 3: A supporting tube was placed in the jejunum with its distal end projecting over the mouth of the cholangioenteric anastomosis by approximately 5-8 cm. The anterior wall suspension suture was used to intermittently suture the whole layer of the anterior wall of the jejunum section; knots were then tied one by one to create an anastomosis between the pancreatic duct mucosa and the jejunal mucosa. After the pancreaticojejunal anastomosis was finished, the suture was ligated; at this point, an excellent attachment of the jejunum to the whole pancreatic stump could be observed (Figure 1C). After the cholangioenteric anastomosis and gastrointestinal anastomosis were completed, abdominal drainage tubes were placed at the inferior-posterior and superior-anterior sides of the pancreaticojejunal anastomotic site to facilitate postoperative observation and conventional monitoring of the quantity and properties of the drainage fluid and to provide samples for the measurement of indicators such as bilirubin and amylase.

Postoperative treatment

After surgery, conventional infection prevention, nutrition, rehydration, and maintenance of water-electrolyte and acid-base balance were provided. All patients in both groups received total parenteral nutrition support. Conventional drugs for inhibition of pancreatic secretion were not administered after surgery. The amylase level in the drainage fluid at the pancreaticojejunal anastomotic site was measured 1, 3, 4, 5, 6, 7, and 10 d after surgery. On postoperative day 7, abdominal computed tomography (CT) was conventionally performed. If no pancreatic fistula was present 10 d after surgery, the peritoneal drainage tube at the pancreaticojejunal anastomotic site was removed. In patients with pancreatic fistula, the peritoneal drainage tube was removed after the pancreatic fistula had healed.

Observation indicators

Intraoperative blood loss, pancreaticojejunal anastomosis time, operation time, pancreatic fistula rate, abdominal infection rate, peritoneal catheterization rate, total complication rate, total hospitalization time, postoperative hospitalization time, and hospitalization expenses were recorded.

Diagnosis of pancreatic fistula

Pancreatic fistula was defined according to the ISGPF as output *via* operatively or postoperatively placed drains of any measurable volume of drainage fluid with amylase content greater than three times the upper

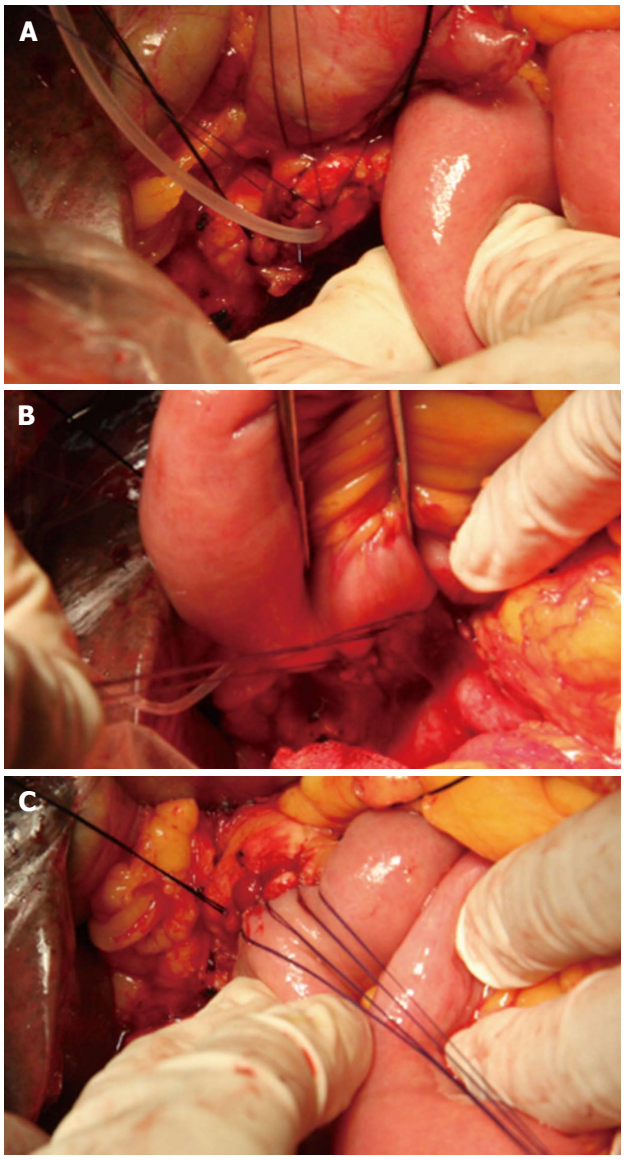

Figure 1 Surgical method using in single-layer anastomosis group. A: The pancreatic stump was freed for approximately 3-4 cm of its length; B: The proximal jejunum was lifted, and a 0.5-0.8 cm incision was made at the jejunal wall 4-5 cm from the jejunal stump; C: A supporting tube was placed in the jejunum with its distal end projecting over the mouth of the cholangioenteric anastomosis by approximately 5-8 cm.

normal serum value on or after postoperative day 3. Three grades of pancreatic fistula were determined according to the clinical severity of the individual cases. The grades were determined only after complete healing of the fistula had occurred[26].

Statistical analysis

Statistical analyses of the data on the patients in the two groups were performed using SPSS 17.0 software. Quantitative data that did not conform to a normal distribution or that had heterogeneous variances were examined using the non-parametric rank sum test. Qualitative data were examined using the χ^2 test or the Fisher exact probability test. The examination level was $\alpha = 0.05$. $P < 0.05$ indicated that the difference was statistically significant.

RESULTS

Comparison of preoperative and intraoperative patient data in the two groups

Gender, age, hypertension history, diabetes mellitus history, drinking history, smoking history, abdominal surgery history, preoperative biliary drainage, body mass index, total bilirubin, albumin, blood glucose, disease composition, surgical methods, jejunum-jejunum anastomosis (Braun anastomosis), pancreatic texture, and pancreatic duct diameter did not show significant differences in the two groups (Table 4).

Comparison of complications

Abdominal CT examination of 51 patients in the single-layer anastomosis group after surgery showed that the mouth of the pancreaticojejunal anastomosis and the surroundings did not have effusion. Abdominal CT examination of 51 patients in the double-layer anastomosis group after surgery showed that 6 cases had effusion surrounding the mouth of the pancreaticojejunal anastomosis. Table 5 shows the incidences of postoperative complications such as pancreatic fistula, peritoneal catheterization, abdominal infection, and total complications in the single-layer and double-layer anastomosis groups.

In the single-layer anastomosis group, patients with pancreatic fistula accounted for 25.49% (13/51), patients with grade A pancreatic fistula accounted for 15.69% (8/51), and patients with grade B pancreatic fistula accounted for 9.80% (5/51); there were no patients with grade C pancreatic fistula. In the double-layer anastomosis group, patients with pancreatic fistula accounted for 68.63% (35/51), patients with grade A pancreatic fistula accounted for 15.69% (8/51), patients with grade B accounted for 45.10% (23/51), and patients with grade C accounted for 7.84% (4/51). In the single-layer anastomosis group, 10 of the 27 patients with soft pancreas had pancreatic fistula, 2 of the 14 patients with normal pancreatic texture or mild fibrosis of the pancreas had pancreatic fistula, and 1 of the 10 patients with hard pancreas had pancreatic fistula. In the double-layer anastomosis group, 21 of the 24 patients with soft pancreas had pancreatic fistula, 10 of the 17 patients with normal pancreatic texture or mild fibrosis of the pancreas had pancreatic fistula, and 4 of the 10 patients with hard pancreas had pancreatic fistula. A comparison of the incidence of pancreatic fistula in patients with different pancreatic textures is presented in Table 6.

Comparison of intraoperative operation time, pancreaticojejunal anastomosis time, postoperative hospitalization time, total hospitalization time, and hospitalization expenses in the two groups

Because the intraoperative operation time, pancreatico-

Table 4 Comparison of patient data in the two groups, *n*

Item	Single-layer anastomosis group	Double-layer anastomosis group	*P*-value
Gender	Female: 21	Female: 19	0.6850
	Male: 30	Male: 32	
Age	> 60 yr: 24	> 60 yr: 25	0.8429
	≤ 60 yr: 27	≤ 60 yr: 26	
Hypertension	Yes: 6	Yes: 13	0.0750
	No: 45	No: 38	
Diabetes mellitus	Yes: 10	Yes: 4	0.0843
	No: 41	No: 47	
Drinking history	Yes: 14	Yes: 16	0.6638
	No: 37	No: 35	
Smoking history	Yes: 13	Yes: 14	0.8224
	No: 38	No: 37	
Abdominal surgery history	Yes: 5	Yes: 8	0.3731
	No: 46	No: 43	
Preoperative biliary drainage	Yes: 13	Yes: 10	0.4772
	No: 38	No: 41	
BMI	> 25: 13	> 25: 17	0.3847
	≤ 25: 38	≤ 25: 34	
Total bilirubin	> 171 μmol/L: 16	> 171 μmol/L: 10	0.1728
	≤ 171 μmol/L: 35	≤ 171 μmol/L: 41	
Serum albumin	≥ 35 g/L: 40	≥ 35 g/L: 47	0.0503
	< 35 g/L: 11	< 35 g/L: 4 cases	
Blood glucose	> 6.1 mmol/L: 19	> 6.1 mmol/L: 24	0.3161
	≤ 6.1 mmol/L: 32	≤ 6.1 mmol/L: 27	
Disease composition	Pancreatic head: 11	Pancreatic head: 16	0.5418
	Duodenum and papilla: 16	Duodenum and papilla: 14	
	Ampulla: 5	Ampulla: 5	
	Distal bile duct: 19	Distal bile duct: 14	
Surgical method	PD: 20	PD: 16	0.4072
	PPPD: 31	PPPD: 35	
Braun anastomosis	Yes: 5	Yes: 2	0.2400
	No: 46	No: 49	
Pancreatic texture	Soft: 27	Soft: 24	0.7918
	Normal or mild fibrosis: 14	Normal or mild fibrosis: 17	
	Hard: 10	Hard: 10	
Pancreatic duct diameter	> 3 mm: 30	> 3 mm: 26	0.4261
	≤ 3 mm: 21	≤ 3 mm: 25	
Intraoperative blood transfusion	Yes: 4	Yes: 1	0.3590
	No: 47	No: 50	

BMI: Body mass index; PD: Pancreaticoduodenectomy; PPPD: Pylorus-preserving pancreaticoduodenectomy.

Table 5 Comparison of postoperative complications, *n*

Complication	Single-layer anastomosis group	Double-layer anastomosis group	χ^2	*P*-value
Pancreatic fistula	Yes: 13	Yes: 35	19.0463	0.0000
	No: 38	No: 16		
Peritoneal catheterization	Yes: 0	Yes: 6	4.4271	0.0354
	No: 51	No: 45		
Abdominal infection	Yes: 1	Yes: 11	9.4444	0.0021
	No: 50	No: 40		
Total complications	Yes: 21	Yes: 37	10.2320	0.0014
	No: 30	No: 14		

jejunal anastomosis time, postoperative hospitalization time, total hospitalization time, and hospitalization expenses in the quantitative data of these two groups did not show normal distributions and/or exhibited heterogeneous variances, the data regarding these parameters were examined using the rank sum test to determine whether there were differences in these parameters between the two groups (Table 7).

DISCUSSION

The most important factor resulting in complications and deaths after pancreaticoduodenectomy was pancreatic fistula[13,26-28]. The tightness of the pancreaticojejunal anastomosis to a large extent determines the success of pancreaticoduodenectomy. The modification of the pancreaticojejunal anastomosis method and the

Table 6 Comparison of the incidence of pancreatic fistula in patients with different pancreatic textures in the two groups

Pancreatic texture	Single-layer anastomosis group	Double-layer anastomosis group	χ^2	*P*-value
Soft	10/27	21/24	13.5737	0.0002
Normal or mild fibrosis	2/14	10/17		0.0245
Hard	1/10	4/10		0.3034

Table 7 Comparison of intraoperative and postoperative conditions in the single-layer anastomosis group and the double-layer anastomosis group

Item	Single-layer anastomosis group	Double-layer anastomosis group	Mann-Whitney	*P*-value
Operation time (min)	220.059 (± 60.602)	379.412 (± 90.761)	179.000	0.000
Pancreaticojejunal anastomosis time (min)	17.922 (± 5.145)	31.333 (± 7.776)	185.000	0.000
Postoperative hospitalization time (d)	18.588 (± 5.285)	26.373 (± 15.815)	854.500	0.003
Total hospitalization time (d)	25.627 (± 6.551)	33.706 (± 15.899)	841.000	0.002
Hospitalization expense (yuan)	116787.667 (± 31900.927)	162788.608 (± 129732.500)	800.000	0.001

improvement in surgical techniques described here can be used for pancreaticojejunal anastomotic leakage to reduce the incidence of pancreatic fistula. The single-layer pancreaticojejunal anastomosis method is a simple, reliable, and safe method for pancreaticojejunal anastomosis[29,30].

The single-layer mucosa-to-mucosa pancreaticojejunal anastomosis elucidated in this study is associated with pancreatic duct diameters ranging from 1-12 mm and a mean pancreatic duct diameter of 4.863 mm. We considered that when the pancreatic duct diameter was greater than 2 mm, single-layer pancreaticojejunal anastomosis was a better choice.

Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis is a simple and time-saving anastomosis method. It should be emphasized that during the process of pancreaticojejunal anastomosis, the suturing between the anterior wall of the pancreatic duct and the whole layer of the anterior wall of the pancreas, involving 3-4 stitches, should be conducted first, together with the suspension and opening of the pancreatic duct; this sequence is conducive to posterior wall suturing. During the suturing process, the distribution of needling should be even to prevent the formation of large spaces and the occurrence of non-strict pairing in some regions, which may cause pancreatic leakage. During the suturing of the anterior, lateral, and posterior walls of the duct, the needling site was approximately 1-2 cm from the pancreatic stump. To prevent damage to the pancreas and to small branches of the pancreatic ducts by multiple needling, which may cause pancreatic leakage, the needling for suturing the pancreas and the pancreatic duct should be conducted only once. The suturing method described here is simple and does not require sophisticated suturing techniques. The pancreaticojejunal anastomosis time in the single-layer mucosa-to-mucosa pancreaticojejunal anastomosis was 17.922 ± 5.145 min, and the pancreaticojejunal anastomosis time in the double-layer mucosa-to-mucosa pancreaticojejunal anastomosis was 31.333 ± 7.776 min. The Mann-Whitney value for comparison of this parameter between the two groups was 185.000 (P = 0.000); thus, the difference in anastomosis time between the two groups was statistically significant, indicating that the single-layer anastomosis time was significantly lower than the double-layer anastomosis time.

Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis is a reliable pancreaticojejunal anastomosis method. The 51 patients in the single-layer anastomosis group received conventional upper abdominal CT examination 1 wk after surgery to determine the condition of the mouth of the pancreaticojejunal anastomosis and its surroundings; the results showed that neither the mouth of the pancreaticojejunal anastomosis nor the surrounding area had effusion in any of the 51 patients. The 51 patients in the double-layer anastomosis group received conventional upper abdominal CT examination after 1 wk of surgery to display the condition of the mouth of the pancreaticojejunal anastomosis and its surroundings; the results showed that 6 patients had effusion at the mouth of pancreaticojejunal anastomosis and/or in the surrounding area. A χ^2 test of the data for the two groups yielded a χ^2 value of 4.4271 (P = 0.0354); thus, the difference in the incidence of effusion in the two groups was statistically significant. In the single-layer anastomosis patients, the suture used for the anastomosis was tight, and the mouth of the pancreaticojejunal anastomosis and its surroundings did not show effusion after surgery. In the single-layer mucosa-to-mucosa pancreaticojejunal anastomosis, the jejunum completely covered the pancreatic section, and the resulting pressure on the pancreatic section and on the small pancreatic ducts within the pancreatic section contributed to hemostasis and thus reduced the risk of postoperative pancreatic section bleeding and pancreatic fistula. These results indicate that the application of

single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy is reliable.

The application of single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy was shown to be safe. The pancreatic fistula rate in the single-layer anastomosis group was 25.45% (13/51), whereas the pancreatic fistula rate in the double-layer anastomosis group was 68.63% (35/51). A χ^2 test of the data regarding the incidence of pancreatic fistula in the two groups yielded a χ^2 value of 19.0464 (P = 0.0000). Thus, the difference between the two had statistical significance; the pancreatic fistula rate in the single-layer anastomosis group was lower than that in the double-layer anastomosis group.

Lin *et al*[31] summarized data from 1891 pancreaticoduodenectomy patients and concluded that soft pancreatic texture was the most important reason for the occurrence of pancreatic fistula. In our study, when the pancreatic texture was soft, the postoperative pancreatic fistula rate in the single-layer anastomosis group was 37.03% (10/27), whereas the rate of postoperative pancreatic fistula in the patients in the double-layer anastomosis group who displayed soft pancreatic texture was 87.50% (21/24). Comparison between the values obtained for the two groups yielded a χ^2 value of 13.5737 (P = 0.0002). The difference was statistically significant, indicating that single-layer anastomosis was better than double-layer anastomosis when the pancreatic texture was soft. The use of single-layer anastomosis reduced the time needed for suturing the pancreas, reduced the damage to the pancreas, and decreased the incidence of pancreatic fistula. When the pancreatic texture was normal or the pancreas displayed mild fibrosis, the incidence of postoperative pancreatic fistula was 14.28% (2/14) in the single-layer anastomosis group and 58.82% (10/17) in the double-layer anastomosis group. Comparison of the difference between the two groups using the χ^2 test and the Fisher exact probability test showed that the P-value was 0.0245, indicating that the difference between the two groups was statistically significant. For normal or mild fibrosis pancreatic texture, the pancreatic fistula rate in the single-layer anastomosis group was lower than that in the double-layer anastomosis group. In the single-layer anastomosis group, there were 5 cases of grade B pancreatic fistula, and the pancreatic fistula rate was 9.80%; there was no grade C pancreatic fistula in this group. In the double-layer anastomosis group, there were 23 cases of grade B pancreatic fistula, with a rate of 45.10%; in this group, there were 4 cases of grade C pancreatic fistula, with an incidence rate of grade C pancreatic fistula of 7.84%. Comparison of the incidences of grade B and grade C pancreatic fistula in the two groups yielded a χ^2 value of 22.0393 (P = 0.0000), indicating that the difference between the two groups was statistically significant. The incidence of grade B and grade C pancreatic fistula in the single-layer anastomosis group was significantly lower than that in the double-layer anastomosis group.

In the single-layer anastomosis group, the rate of postoperative peritoneal catheterization was 0/51, and that of abdominal infection was 1/51. In the double-layer anastomosis group, the rate of postoperative peritoneal catheterization was 6/51, and the rate of abdominal infection was 11/51; the differences in these two parameters in the two groups were statistically significant (P < 0.05). The rates of postoperative peritoneal catheterization and abdominal infection in the single-layer anastomosis group were significantly lower than those in the double-layer anastomosis group. The total postoperative complication rate in the single-layer anastomosis group was 41.17% (21/51) and the total postoperative complication rate in the double-layer anastomosis group was 72.55% (37/51). A χ^2 test comparing the data for the two groups yielded a χ^2 value of 10.232 (P = 0.0014); thus, the difference between the two groups was statistically significant. The postoperative complication rate in the single-layer anastomosis group was lower than that in the double-layer anastomosis group. In summary, the foregoing data show that the application of the single-layer mucosa-to-mucosa pancreaticojejunal anastomosis in pancreaticoduodenectomy is safe.

Patients who experienced pancreatic fistula after pancreaticoduodenectomy had prolonged hospitalization time and increased hospitalization expenses[32]. The pancreatic fistula rate in the single-layer mucosa-to-mucosa pancreaticojejunal anastomosis group was lower than that in the double-layer mucosa-to-mucosa pancreaticojejunal anastomosis group. In addition, postoperative hospitalization time, total hospitalization time, and hospitalization expenses were all lower in the single-layer anastomosis group than in the double-layer anastomosis group. The rank sum test results showed that the P-values for all of these comparisons were < 0.05; thus, the differences were statistically significant. These results indicate that postoperative hospitalization time, total hospitalization time, and hospitalization expenses were all lower in the single-layer anastomosis group than in the double-layer anastomosis group.

In summary, the results of this study show that single-layer mucosa-to-mucosa pancreaticojejunal anastomosis is a simple, reliable, and safe anastomosis method. The use of this method could reduce the rates of postoperative pancreatic fistula, abdominal infection and peritoneal catheterization, overall complication rate, postoperative hospitalization time, total hospitalization time, and hospitalization expenses.

COMMENTS

Background

Pancreaticoduodenectomy is a standard treatment for various tumors of peri-ampullary region and pancreatic head. Pancreaticoduodenectomy is a difficult surgery with a high perioperative complication rate and a high mortality rate. Pancreatic fistula is associated with delayed gastric emptying, intra-abdominal abscess, local infection at the incision site, sepsis, and blood loss postoperation. Pancreaticojejunal anastomosis plays an important role in pancreaticoduodenectomy; its success determines the success of the surgery.

Research frontiers

Although the complication and mortality rates associated with pancreatic fistula have decreased due to improvements in surgical techniques, the incidence of postoperative complications during the perioperative period is still high. There are various pancreaticojejunal anastomosis procedures in pancreaticoduodenectomy, but so far none of the pancreaticojejunal anastomosis procedures is regarded as best. No matter what kind of way of pancreaticojejunal anastomosis use in pancreaticoduodenectomy, pancreatic fistula is still high.

Innovations and breakthroughs

In this study, single-layer anastomosis group applied single layer mucosa-to-mucosa pancreaticojejunal anastomosis to pancreaticoduodenectomy. It should be emphasized that during the process of pancreaticojejunal anastomosis, the suturing between the anterior wall of the pancreatic duct and the whole layer of the anterior wall of the pancreas, involving 3-4 stitches, should be conducted first, together with the suspension and opening of the pancreatic duct; this sequence is conducive to posterior wall suturing. There was no knots inside of pancreaticojejunal anastomosis. During the suturing process, the distribution of needling should be even to prevent the formation of large spaces and the occurrence of non-strict pairing in some regions, which may cause pancreatic leakage.

Applications

Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis is a simple pancreaticojejunal anastomosis. Surgeons can apply it to pancreaticoduodenectomy, especially when the pancreatic texture is soft. It can reduce the incidence rate of grade B and C pancreatic fistula and may reduce the mortality.

Terminology

Pancreaticojejunal anastomosis is essential and crucial anastomosis in pancreaticoduodenectomy. It plays an important role in pancreaticoduodenectomy; its success determines the success of the surgery. Single-layer mucosa-to-mucosa pancreaticojejunal anastomosis could help the surgeon to enhance the reliability of pancreaticojejunal anastomosis.

Peer-review

The article is an helpful and original research paper. It provides a new way of pancreaticojejunal anastomosis to surgeon in pancreaticoduodenectomy. The study is well designed, and the retrospective study was carried out at a very high accuracy and quality.

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CASE REPORT

Gastric remnant twist in the immediate post-operative period following laparoscopic sleeve gastrectomy

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Informed consent statement: The patient involved in this study has given her written informed consent authorizing use and disclosure of her protected health information.

Conflict-of-interest statement: All the authors have no conflict of interest to declare.

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Abstract

Twist of stomach remnant post sleeve gastrectomy is a rare entity and difficult to diagnose pre-operatively. We are reporting a case of gastric volvulus post laparoscopic sleeve gastrectomy, which was managed conservatively. A 38-year-old lady with a body mass index of 54 underwent laparoscopic sleeve gastrectomy. Sleeve gastrectomy was performed over a 32 French bougie using Endo-GIA tri-stapler. On post-operative day 1, patient had nausea and non-bilious vomiting. An upper gastrointestinal gastrografin study on post-operative days 1 and 2 revealed collection of contrast in the fundic area of stomach with poor flow distally, and she vomited gastrograffin immediately post procedure. With the suspicion of a stricture in the mid stomach as the cause, the patient was taken back for a exploratory laparoscopy and intra-operative endoscopy. We found a twist in the gastric tube which was too tight for the endoscope to pass through. This was managed conservatively with a long stent to keep the gastric tube straight and patent. The stent was discontinued in 7 d and the patient did well. In laparoscopic sleeve gastrectomy the stomach is converted into a tube and is devoid of its supports. If the staples fired are not aligned appropriately, it can predispose this stomach tube to undergo torsion along its long axis. Such a twist can be avoided by properly aligning the staples and by placing tacking sutures to the omentum and new stomach tube. This twist is a functional obstruction rather than a stricture; thus, it can be managed by endoscopy and stent placement.

Key words: Gastric remnant; Stent; Sleeve gastrectomy; Volvulus; Obesity

Core tip: Twist of the stomach remnant post sleeve gastrectomy is a rare entity. We are reporting a case of gastric twist post laparoscopic sleeve gastrectomy.

This was managed conservatively with a long stent for 7 d. In laparoscopic sleeve gastrectomy the stomach is converted into a tube and is devoid of its supports, making it prone for twisting. Such a twist can be avoided by properly aligning the staples and by placing tacking sutures to the omentum. This twist is a functional obstruction rather than a stricture; thus, it can be managed by endoscopy and stent placement.

Subhas G, Gupta A, Sabir M, Mittal VK. Gastric remnant twist in the immediate post-operative period following laparoscopic sleeve gastrectomy. *World J Gastrointest Surg* 2015; 7(11): 345-348 Available from: URL: http://www.wjgnet.com/1948-9366/full/v7/i11/345.htm DOI: http://dx.doi.org/10.4240/wjgs.v7.i11.345

INTRODUCTION

Laparoscopic sleeve gastrectomy is a restrictive bariatric surgical strategy. Compared to other bariatric surgeries, this procedure has relatively lower surgical risk in patients with extreme obesity. However sleeve gastrectomy does have complications which includes leaks, bleeding, splenic trauma, sleeve stenosis, and gastroesophageal reflux[1].

Gastric volvulus is a rare condition which involves the rotation of all or part of the stomach around the anatomic axes[1]. We would like to report a case of twist of the gastric remnant in the immediate post laparoscopic sleeve gastrectomy period, done for morbid obesity. This was managed non operatively with stent placement.

CASE REPORT

A 38-year-old morbidly obese lady with a body mass index of 54 underwent laparoscopic sleeve gastrectomy. Sleeve gastrectomy which was performed over a thirty two french bougie using Endo-GIA stapler with the tri staple purple load (Covidien Tri-Staple™, Mansfield, MA). Intraoperatively, post application of stapler, there was a bleeding from the stapled line at the mid stomach which was managed by a single imbricating stitch. On post-operative day 1, patient had persisting nausea and non bilious vomiting. An upper gastrointestinal (GI) gastrografin study revealed collection of contrast in the fundic area of stomach with poor flow distally; she vomited gastrografin immediately post procedure (Figure 1). She was kept nil per os (NPO) and the upper GI gastrografin study was repeated on post-operative day 2. Similar findings of collection of contrast in the fundic region of stomach with very little filling distally were noted. This raised a suspicion of stricture in the mid stomach. With a suspicion of the imbricating stitch in the mid stomach as the cause, the patient was taken back for a exploratory laparoscopy and intra operative endoscopy.

During exploratory laparoscopy, the stitch did not seem to be causing any constriction. The stitch was cut and no bleeding was noted. An intraoperative endoscopy showed complete obstruction in the mid stomach with inability pass the scope beyond the obstruction. Manipulation of stomach laparoscopically with simultaneous scope manipulation was needed to negotiate the narrowed mid stomach. A diagnosis of twist of the stomach along the long axis of the tubular remnant was made. She was kept NPO and started on total parenteral nutrition.

A long esophageal 18 mm × 15 cm long, fully silicone covered stent (WallFlex™, Boston Scientific, Natick, MA) was placed endoscopically on post-operative day 6 (Figure 2). She was able to tolerate liquid diet and was discharged home. The stent was removed endoscopically a week after its placement. She was put on a liquid diet for 2 wk and advanced to soft diet subsequently, which she tolerated well. Patient was seen to be doing well on a 6-mo follow-up visit.

DISCUSSION

Sleeve gastrectomy is a safe, reproducible technique with a relatively low rate of complications. Benefits of sleeve gastrectomy include the lower complications, the maintenance of normal gastro-intestinal continuity, the absence of mal-absorption and the ability to convert to multiple other operations. Excising the ghrelin producing stomach mass plays a significant role compared to other gastric restrictive procedures[2]. Laparoscopic sleeve gastrectomy is still associated with complications, these include, but are not limited to: Staple line leak (1.17%), post-operative hemorrhage (3.57%), and the irreversibility of gastrectomy[3].

Gastric volvulus is a rare condition which involves the rotation of the stomach around the anatomic axes. There are two forms of gastric volvulus, organo-axial (axis is longitudinal and passes through the pylorus and gastroesophageal junction) and mesenteric-axial (axis is transverse and passes through the middle of stomach). Gastrosplenic, gastrophrenic, gastrocolic, and gastrohepatic ligaments hold the stomach in anatomotical position. Stomach can be prone for volvulus whenever there is laxity in the gastric fixation or incorrect positioning of the stomach post surgical manipulation[1]. Twist of the gastric remnant is a condition similar to the organo-axial gastric volvulus.

Sleeve stenosis, which is currently seen in 0.2% to 4% of laparoscopic sleeve gastrectomies, can occur due to the intentionally creating a narrow tube of the stomach[4]. A twisted or spiral sleeve caused by the progressive rotation of the staple line in an anterior to posterior plane can lead to a functional narrowing despite a fairly normal luminal diameter, and is another cause of symptomatic stenosis. This functional stenosis makes it difficult for gastric contents to pass through, in spite of easy passage of the endoscope or balloon dilator through the narrowed area. This can be equated

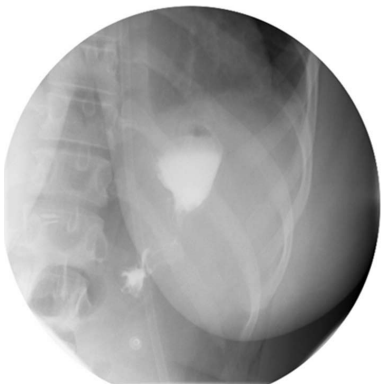

Figure 1 Oral gastrograffin swallow showing poor flow distally.

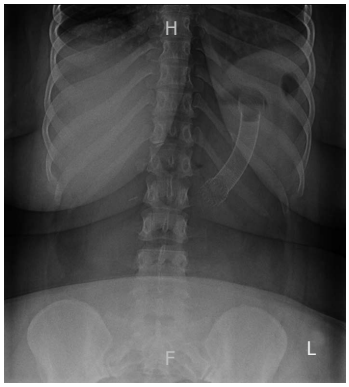

Figure 2 Abdominal X-ray showing stent placement.

to twisting a straight balloon wherein there is a twist at the incisura (Figure 3). An endoscope can be made to pass through by twisting in the same direction, which will undo the twist. Unless supported by a stent, the twist recurs on withdrawal of the endoscope. Scarring caused by hematomas can also lead to sleeve stenosis. Mechanical short-segment stenosis may be treated successfully with single or multiple endoscopic balloon dilation. But mechanical long-segment stenosis may ultimately require conversion to Roux-en-Y gastric bypass[4].

The dissection performed during sleeve gastrectomy including separation of greater omentum from the greater curvature of the stomach, makes the remnant stomach prone for volvulus as there are no fixations along the entire greater curvature[1]. Cases of organoaxial gastric volvulus have been reported after laparoscopic gastric banding, due to excessive dissection of the posterior wall of the stomach, which makes it mobile[5,6]. It is recommended to do a proper posterior dissection of the stomach in sleeve gastrectomy in order to achieve a symmetric stapling of the posterior and anterior wall to avoid twisting of the remnant stomach tube[7]. Pexy of omentum to the gastric remnant may also help to avoid such a twist in the remnant stomach after sleeve gastrectomy.

Flexible covered stents use has been described for patients with suture line leaks and strictures following

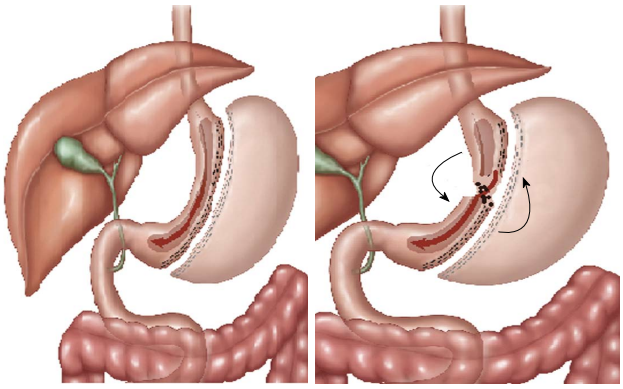

Figure 3 Animated diagram of the volvulus.

sleeve gastrectomy[4,8]. Following stent placement, patients may experience nausea, hypersialysis, early satiety and mild retro-sternal discomfort, which usually disappear in the first few days. Stent removal is not always easy, due to scarring around the stent, and mucosal injury and bleeding are frequently seen after removal. Another complication is stent migration, which can be seen in up to one third of cases[8].

Our patient developed obstruction due to torsion along the long axis of the remnant stomach on post operative day 1. There is a possibility of asymmetrical staples leading to initiation of the twist but completion of twist to an extent of obstruction as in a volvulus is attributed to a long tubular remnant with no supports. We feel that in this patient, creation of a longer stomach tube post removal of ligaments namely gastrosplenic and gastrophrenic made the tubular stomach devoid of its support, which then became susceptible to torsion. Some degree of a twist is seen in every stomach post laparoscopic sleeve gastrectomy but none of these cause functional stricture. These twists can be managed non-operatively with placement of covered stent. Also, mobilized omentum can tacked to the gastric tube on the stapled side and this could help in prevention of rotation by virtue of its weight.

The tubular gastric remnant is devoid of its supports and is predisposed to volvulus. In this present case we feel that a twist could have been initiated by asymmetrical staples which then progressed to a complete torsion in the organo-axial axis with functional stricture due to a long tubular remnant without anatomical support. We currently tack the mobilized omentum to the stapled side of gastric tube to help prevent post-operative twist. This condition can be managed non-operatively with placement of covered stent. There is always an option of converting it to a Roux-en-Y gastric bypass if the non-operative management fails.

COMMENTS

Case characteristics

A 38-year-old morbidly obese lady with a body mass index of 54 underwent laparoscopic sleeve gastrectomy and presented with post-operative gastric remnant twist.

Clinical diagnosis
Post-operative gastric remnant twist.

Differential diagnosis
Stricture, post-operative edema, hematoma.

Laboratory diagnosis
All labs were within normal limits.

Imaging diagnosis
Upper gastrointestinal gastrograffin study showed collection of contrast in the fundic area of stomach with poor flow distally.

Treatment
Placement of a long stent endoscopically.

Related reports
Most of the reports are of gastric volvulus which was managed by operative intervention.

Experiences and lessons
During laparoscopic gastric sleeve resection the authors currently tack the mobilized omentum to the stapled side of gastric tube to help prevent post-operative twist and post-operative gastric twist can be managed non-operatively with placement of covered stent.

Peer-review
This is a nice and well documented case report.

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