Individualized Laparoscopic and Related Technique in Rectal Cancer Surgery

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Declaration on ethics

The research presented and reported in this thesis was conducted within the guideline for research ethics outlined in the National Statement on Ethics Conduct in Research Involving Humans (1999), the joint NHMRC/AVCC Statement and Guideline on Research Practice (1997), the James Cook University Policy on Experimentation Ethics, Standard Practices and Guidelines (2001), and the James Cook University Statement and Guidelines on Research Practice (2001). Specific ethic approval details are provided in each publication.

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Chapter overview

Chapter 1 Introduction

This chapter described the context of this research; why rectal cancer treatment is challenging; impact of multidisciplinary treatment on the outcomes.

Chapter 2 Overview in colorectal cancer treatment

To review of role of various treatment modalities and variations to optimise both short-term and long-term outcomes;

- Hiranyakas A, Yik Hong H. Surgical Treatment of Colorectal Cancer – a Review. *Int Surg. 2011*; *96(2):120-6.*

Chapter 3 Laparoscopic surgery for rectal cancer

To discuss and propose appropriate laparoscopic techniques / approaches in the challenging surgical conditions to achieve the best possible outcomes;

- Hiranyakas A, Yik Hong H. Laparoscopic Ultralow Anterior Resection Versus Laparoscopic Pull-through with Coloanal Anastomosis for Rectal Cancers – a Comparative Study. *Am J Surg. 2011*; *202(3):291-7.*

Chapter 4 Factors influencing rectal cancer treatment outcomes

To discuss and propose the factors influencing the optimal outcomes for rectal cancer treatment;

- Hiranyakas A, Yik-Hong H, da Silva, GM, Wexner SD, Allende D, Berho M. Factors Influencing Circumferential Resection Margin in Rectal Cancer. *Colorectal Dis. 2013 ;15(3):298-303*.

Chapter 5 Technique to avoid postsurgical complication

To discuss and propose surgical techniques essential in avoiding serious postsurgical consequences;

- Hiranyakas A, da Silva GM, Denoya P, Shawki S, Wexner SD. Colorectal Anastomotic Stricture: Is it associated with inadequate Colonic Mobilization? *Tech Coloproctol. 2013 ;17(4):371-5*.

Chapter 6 Protocols for rapid recovery

To discuss in depth for the appropriate immediate postsurgical-care protocals to achieve the smooth and rapid recovery (among the most common diseased population);

- Hiranyakas A, Bashankaev B, Seo CJ, Khaikin M, Wexner SD. Epidemiology, Pathophysiology and Medical Management of Postoperative Ileus in the Elderly. *Drugs Aging. 2011*; 28(2):107-18.

Chapter 7 Closure of the ileostomy

To discuss and propose the necessity of certain surgical procedures to enhance optimal immediate postsurgical outcomes in low rectal cancer patients;

- Hiranyakas A, Rather A, da Sliva GM, Wexner SD, Weiss EG. Loop ileostomy Closure after Laparoscopic vs. Open Surgery: Is There a Difference? *Surg Endosc. 2013 ;27(1):90-4*.

Chapter 8 Treatment of common stomal complication

To discuss and propose minimally invasive surgical approaches in the treatment of the common stomal consequence;

- Hiranyakas A, Yik Hong H. Laparoscopic Parastoma Hernia Repair, Multi-media Article. *Dis Colon Rectum 2010*; 53(9):1334-6.

Chapter 9 Conclusion, outcomes and future research directions

This chapter gives the conclusions from the studies and proposes future research directions.

Preface and acknowledgements

The research studies included in this thesis involved a number of co-investigators. It was my great honor to conduct and published each of the studies involved in the thesis under the guidance and support of the two world-renowned colorectal surgeons from two continents. It was such an exceptional privilege and a wonderful experience to work and learn from the two highly experienced and highly respected colorectal surgeons. My experience as clinical and research fellow in both colorectal surgery landmarks had sharpened and enlighten my clinical and research skills to complete all the related publications demonstrated in the thesis.

The main studies listed in each chapter were carefully selected as to reflect the critical knowledge essential in each of the important steps to overcome the main challenges toward the success in achieving the best possible outcomes in rectal cancer patient care. However, the main original contribution of the thesis was demonstrated clearly in "**Chapter 3** Laparoscopic surgery for rectal cancer" where the proposed laparoscopic pull-through with coloanal anastomosis was highlighted. The chapter showed a prospective comparative study comparing all aspects of the two techniques; laparoscopic ultralow anterior resection *versus* laparoscopic pull-through with coloanal anastomosis for rectal cancers. All the published studies involved in each chapter of the thesis were carefully illustrated in their original format with my great respect to the international peer-review. Nevertheless, each chapter contained the overview aiming to state the connectivity of the ideas for each specific detail contained in each chapter. Despite the fact that the majority of the studies were conducted in high-volume, specialized centers, it was a

real challenge to organize prospective studies for highly specific research questions over the limited time of my doctorate degree study.

Achievements from this work are directly related to the passion, energy and dedication of each of the people involved. My supervisors Professor Ho Yik-Hong and Professor Steven D. Wexner have provided invaluable guidance, support, technical expertise and encouragement to me during this work.

Contributors and my role

	Study component		Art Hiranyakas	Co-authors	Professor Yik-Hong Ho	Professor Steven D Wexner
Chapter 2 Overview in colorectal cancer treatment	Design	12.5%	80%	0%	20%	0%
	Funding	12.5%	0%	0%	0%	0%
	Ethics and permissions	12.5%	80%	0%	20%	0%
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	Drafted manuscript	12.5%	80%	0%	20%	0%
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Chapter 1: Introduction

Cancer is one of the leading causes of death throughout the world. Colorectal cancer is currently one of the major causes of cancer-related death, especially in the developed countries. The incidence of colorectal cancer has also been found to be increasing in developing countries.

Even though a multidisciplinary approach is the best treatment modality for colorectal cancer patients, surgery is still the mainstay for curative colorectal cancer treatment. Colorectal cancer surgery has been developed for decades, but a new paradigm in colorectal cancer surgery in term of laparoscopic technique emerged approximately 25 years ago. The first laparoscopic colon resection was reported in 1991 (1). This procedure presented doubts about adversely affecting the chance of cure for colorectal cancer. Randomized trials have been carefully performed to compare the traditional open surgery with the laparoscopic technique. These studies examined and compared surgical specimens, differences in lymph node harvest and bowel margins. In addition, rates of recurrence and overall survival were also compared. In “The clinical outcome of surgical therapy (COST) study group trial”, there was no difference in median length of bowel margins. Results of nonrandomized trials in 1990s did not detect differences in survival between patients undergoing laparoscopic and open resection. In a single-center trial, published in 2002, Lacy et al. reported an increase in disease-free survival in their laparoscopic arm (2). These results were thought to be related to less metabolic insult on the immune system with a laparoscopic technique, but have not been reproduced. Thus it has been proven that recurrence and survival rate is not compromised by the use of a laparoscopic approach.

Several trials which compared laparoscopic and open surgery have also found small but measurable differences in postoperative pain, return of bowel function, and length of

hospital stay (3). Three large randomized trials have found no differences in operative mortality between the two groups (4-6). Laparoscopic surgery for colon cancer is currently considered a well-accepted alternative to open resection for colon cancer.

Rectal cancer is one of the most difficult management challenges in colorectal surgery. As a result, laparoscopic rectal cancer surgery is much less developed and the results therefore not as certain. For rectal cancer, differences in anatomy, and natural history of disease compared to colon cancer have led to a unique surgical approach and outcome measurement. Total mesorectal excision (TME) has become the surgical treatment of choice for rectal cancer (7). This is a technique which achieves complete resection of the rectum together with its draining lymphatics, along well-defined surgical anatomical planes which results in low rates of cancer recurrence. Prior to the TME era, local recurrence rates of ≥20% were commonly reported. Heald and Ryall showed, through a variety of publications, that local recurrence rates could be decreased to ≤ 5% with TME. More importantly, his concepts could be taught, adopted, and utilized, and similar improvements in local recurrence rates and survival statistics could be achieved (8). Quirke and colleagues also demonstrated that the survival improvements were a result of removing the rectum and the mesorectum as an intact envelope of tissue. This would achieve a negative circumferential resection margin. He also showed that the local recurrence rates of 85% were found in patients who had positive circumferential resection margins in comparison with 3% recurrence rates in patients in whom the radial margins were tumor free (9). Meticulous dissection with careful attention to anatomy and embryologic tissue planes were essential toward a good local control of the disease (10).

Although a difficult technique to master, laparoscopy allows very good exposure of the pelvic cavity because of magnification and seems to facilitate pelvic dissection. Laparoscopy for rectal cancer offers several advantages in compared to open surgery, including postoperative pain, shorter duration of ileus, shorter hospital stay, and less disability (11-15). However, these advantages of laparoscopic TME are beneficial to patients only when the

oncologic cure rate for this technique is at least similar to that of open TME. Several trials found that the oncologic resection using laparoscopic TME is feasible, adequate, and can be as efficacious as open resection (16-18). The CLASICC trial had noticed an increase in circumferential radial margin positivity in the low anterior laparoscopic resection group. The trial had only a small subset of patients with rectal cancer. However, long-term follow-up which was reported in 2013 suggested that long-term local and distant recurrence for rectal cancer treated laparoscopically was comparable to open treatment (19). The COREAN trial compared laparoscopic and open resection of 340 neoadjuvant treated patients with stage II and III mid to low rectal cancer. The early, reported in 2010, showed no difference in short-term outcomes and quality of the oncologic resection (circumferential radial margin, total mesorectal excision completeness, lymph node evaluation, and complication rate). Their recent (2014) report of long-term follow-up also showed no difference in long-term outcome (20, 21). The Colorectal Cancer Laparoscopic or Open Resection II (COLOR II) trial (22) included 1044 patients with stage I to II rectal cancer within 15 cm of the anal verge, randomized 2:1 laparoscopic to open resection. Neoadjuvant therapy was used in only 59% of patients. Pathologic complete response occurred in 8% to 10% of patients. Total mesorectal excision completeness was 92% in laparoscopic-surgery group and 94% in open-surgery group. Distal margin results were all negative. The circumferential radial margin positivity was found in 10% for both laparoscopic and open-surgery group. The circumferential radial margin positivity rate in the low rectum open arm was 22% and only 9% in the laparoscopic arm. Three-year local recurrence was 5%. Disease-free survival rates were 74.8% in the laparoscopic-surgery group and 70.8% in the open-surgery group. Overall survival rates were 86.7% in the laparoscopic-surgery group and 83.6% in the open-surgery group. The conclusion is that laparoscopic resection of rectal cancer is safe and feasible (23).

Interestingly, ACOSOG Z6051 Randomized Clinical Trial (24) aiming to determine if laparoscopic resection is noninferior to open resection for clinical stage II or III rectal cancer

within 12 cm of the anal verge. The multicenter study of 35 institutions in the United States and Canada was reported in 2015. This trial included the group of highly motivated, credentialed, expert laparoscopic rectal surgeons. Two hundred and forty with laparoscopic resection and 222 with open resection were evaluable for analysis of the 486 enrolled patients. All patients underwent neoadjuvant therapy. The study reported successful resection in 81.7% of laparoscopic resection cases (95%CI, 76.8%–86.6%) and 86.9%of open resection cases (95%CI, 82.5%–91.4%). Conversion to open resection was 11.3%. They also found that the operative time was significantly longer for laparoscopic resection (mean, 266.2 vs 220.6 minutes; mean difference, 45.5 minutes; 95%CI, 27.7–63.4; P < .001). The length of stay, readmission within 30 days and severe complications did not differ significantly. Quality of the total mesorectal excision specimen in 462 operated and analyzed surgeries was complete (77%) and nearly complete (16.5%) in 93.5% of the cases. Negative circumferential radial margin was observed in 90% of the overall group (87.9% laparoscopic resection and 92.3% open resection; p = 0.11). Distal margin result was negative in more than 98% of patients irrespective of type of surgery (p = 0.91). Nevertheless, after the calculation for inferiority (primary end points of circumferential radial margin results negative, distal margin results negative, and total mesorectal excision complete or nearly complete), the authors concluded that the use of laparoscopic resection compared with open resection failed to meet the criterion for noninferiority for pathologic outcomes among patients with stage II or III, mid to low rectal cancer.

A cohort of patients in the Academic Department of Surgery at the Townsville Hospital has successfully undergone laparoscopic restorative rectal cancer surgery since 2003. The technique there continues to be refined. Short term and long term outcomes after laparoscopic surgery for rectal cancer will be measured in this prospectively ongoing studied group of patients. There is an opportunity to assess aspects of laparoscopic TME such as the quality of laparoscopic TME specimen, oncological clearance (number of lymph nodes retrieved, tumor clearance, and the integrity of rectal fascia), short term outcomes (like return

to bowel function, return to normal activity / energy levels complications), and long term outcomes (like quality of life, psychological adaptation to having to manage any necessary chemo radiotherapy) for laparoscopic TME patients. These measurements will be important in helping to refine and optimize techniques.

Laparoscopic rectal cancer surgery is, by nature, a more extensive and stressful procedure for the patient, compared to colon cancer surgery. Surgery induces a generalized stage of immunodepression (25). Cytokines produced by cells of the immune system and other tissues act as mediators of immune and acute phase response. C-reactive protein (which rises at 4 to 12 hours after surgery, usually peaks at 24 to 72 hours after surgery, and levels may remain elevated for approximately 2 weeks), tumor necrosis factor-alfa (TNF-alfa), interleukin 1-beta (IL 1-beta), and interleukin 6(IL6, it usually peaks at 4 to 48 hours, median 8 hours, after surgery and falls rapidly thereafter with an uncomplicated postoperative course) are the major mediators of acute-phase response in humans. The postoperative levels of these cytokines have been found to correlate with the magnitude of surgery and the presence of complications. They have, therefore, been accepted as markers of tissue trauma after open surgery (26). However, there remains paucity of data examines how these factors relate to clinical progress after laparoscopic colorectal surgery, especially where it pertains to rectal cancer surgery. A prospective randomized trial found that tissue trauma, as reflected by systemic cytokine response, was less after laparoscopic resection than open resection of rectosigmoid carcinoma(which is different from rectal cancer) (27). In cancer surgery, immunosuppression induced by the disease and the surgery confers a growth advantage to micro metastasis (28). By using laparoscopic surgery, it is hoped that surgical trauma will be reduced, thus preserving the host immunity and improving survival. The effects of reduced systemic cytokine response on long term outcome remain unknown.

Although the objective outcome measures after surgical procedures are an important means of defining patient’s degree of health, the patient’s subjective perception and expectations, including the patient’s hopes, needs to be factored into that objective

assessment to determine the patient's actual quality of life (29, 30). Studies showing the quality of life after laparoscopic colon surgery are scanty, let alone laparoscopic rectal cancer surgery. A benefit in the early postoperative quality of life was reported in patients who underwent laparoscopic colorectal resection (31, 32), whereas a nonrandomized trial comparing long term quality of life after laparoscopic colorectal resection versus open colorectal resection for benign disease did not show a significant difference (33). However, most of the published reports included a heterogeneous group of patients with different diseases undergoing a variety of surgical procedures of different magnitudes. In addition, the patients in these studies mainly underwent laparoscopic colon cancer surgery or had laparoscopic abdominoperineal resection for rectal cancer. After the latter, they were left with a permanent stoma. However, with the recent advent of laparoscopic restorative rectal cancer surgery, the patients do not need a permanent stoma. The quality of life, particularly in this group of patients, has not been studied in any detail.

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Chapter 2: Overview in colorectal cancer treatment

Overview

This chapter will give overview to understand the development of both colon and rectal cancer treatment. The comparison of the conventional open surgery *versus* the minimally invasive surgery was carefully demonstrated in all dimensions. The good understanding of the current updates in colorectal cancer treatment will lead to the critical thinking of more complex knowledge in the following chapter. This review of literature was already published in the peer-review journal.

Surgical Treatment of Colorectal Cancer – a Review.

(Int Surg. 2011; 96(2):120-6)

The rapid in development of surgical technology has had a major effect in surgical treatment of colorectal cancer. Laparoscopic colon cancer surgery has been proven to provide better short-term clinical and oncologic outcomes. However this quickly accepted surgical approach is still performed by a minority of colorectal surgeons. The more technically challenging procedure of laparoscopic rectal cancer surgery is also on its way to demonstrating perhaps similar short-term benefits. This article reviews current evidences of both short-term and long-term outcomes of laparoscopic colorectal cancer surgery, including the overall costs comparison between laparoscopic surgery and conventional open surgery. In addition, different surgical techniques for laparoscopic colon and rectal cancer are compared. Also the relevant future challenge of colorectal cancer robotic surgery is reviewed.

In 1987 (1) the success of laparoscopic surgery for gallbladder disease had a major effect on the development of present day laparoscopic surgery for various organs of benign

and malignant diseases. The first series laparoscopic colonic surgery was reported in 1991 by Jacob et al. (2) Twenty patients with both benign and malignant colorectal diseases were safely resected laparoscopically with acceptable outcomes. With the aim to enhance postoperative recovery, reduce postoperative morbidity, reduce overall cost of treatment, and improve long-term survival for colorectal cancer patients, laparoscopic colorectal surgery had become a popular treatment option for colorectal cancer. A few years later, the interesting results from the first randomized controlled trial in 2002, emphasizing on the late outcomes of laparoscopic surgery for colonic cancer by Barcelona trial, Lacy et al. (3) stated the significant advantages of reduced blood loss, early return of intestinal motility, lower overall morbidity, and shorter duration of hospital stay in the laparoscopic-assisted group. Subgroup analysis from the study also revealed survival benefit that was mainly limited to stage III (Dukes' C) disease. Although this finding might be explained by statistical phenomenon on subgroup analysis, it had already started the hope for this novel surgical approach on potential outcome improvement.

The objective of this review is to describe the comparison of available evidence between the conventional open approach and laparoscopic resection on short-term and long-term outcome of colorectal cancer treatment.

Short-Term Outcome

Laparoscopic colorectal surgery has a steep learning curve due to its unique technique of working in multiple abdominal quadrants, control of vascular structures, creation of anastomosis, as well as retrieving large specimens in some patients (4, 5). Early randomized controlled trials suggest that the short term outcomes of laparoscopic colorectal surgeries are probably marginally better than the traditional open approach. However, after laparoscopic technique had been widely accepted, later reports (6, 7) demonstrated clear superiority of short-term outcome for the laparoscopic approach, including a reduction in

postoperative ileus, less postoperative pain and a concomitant reduction in the need for analgesics, earlier tolerance of diet, shortened hospital stay, quicker return to premorbid functional activity, less wound-related morbidity, improved cosmetic results, and a possible reduction in adhesion formation.

The Clinical Outcomes of Surgical Therapy (COST) study group (8) (1994–2001) reported the outcome from 48 institutions of 872 patients with colon cancer who were randomized to two groups: 435 laparoscopic resections and 437 open resections. The results from experienced surgeons who had done 20 or more laparoscopic resections showed longer operating time, but shorter recovery time and hospital stay, and trend toward lower intraoperative complications. There was no significant difference in morbidity and mortality, tumor recurrence, or overall survival after 4.4 years of follow-up. The COlon cancer Laparoscopic or Open Resection (COLOR) trial (9) is also a multicenter study that enrolled 1248 patients with colon cancer randomized to two groups: 627 laparoscopic resections and 621 open resections. The laparoscopic group had longer operating times but less blood loss, early recovery of bowel function, fewer analgesics requirement, and shorter hospital stay. There was no significant difference in radicality of resection and postoperative morbidity and mortality. The Medical Research Council (MRC) Conventional vs. Laparoscopic-Assisted surgery in Colorectal Cancer (CLASICC) trial (10) included 794 patients who were diagnosed with colon and rectal cancer (526 laparoscopic resections and 268 open resections) from 27 United Kingdom centers between 1996 and 2002. The study concluded that laparoscopic-assisted surgery for cancer of the colon is as effective as open surgery in the short term and is likely to produce similar long-term outcomes. However, there were 34% of conversions from laparoscopic to open surgery among the rectal cancer patients. Patients with converted treatment had raised complication rates. The impaired short-term outcomes after laparoscopic-assisted anterior resection for cancer of the rectum do not yet justify its routine use. The meta-analysis of 12 randomized controlled trials on short-term outcome comparing laparoscopic resection for colorectal cancer to open resection reported by

Abraham et al. (11) in 2004 showed that it took 30% longer to perform the operation in the laparoscopic group, but there was less morbidity, earlier return of bowel function (33%), reduced analgesia requirements (37%), and reduced hospital stay (20%). There was no difference in perioperative mortality or oncologic clearance in either group. The superior short-term outcome with laparoscopic resection is supported by the reports on perioperative immunologic response. A recent prospective study from China (12) on 68 colorectal cancer patients (35 laparoscopic resections and 33 open resections) showed significant earlier return of bowel function and reduction of hospital stay in the laparoscopic resection group. Total lymphocytes, CD4 T cell, and CD8 T cell levels were significantly higher in laparoscopic resection compared with open resection, especially on postoperative day 4. This study confirmed the results from other studies (13–16) for better reserved cellular immune responses in patients undergoing laparoscopic colorectal resections. In addition, more aggressive phenotype of cancers also found with more profound immunosuppression demonstrated after open surgery (17). Milas˘ien et al. (18) also reported that better cellular immunity correlated with higher postoperative survival rates.

Short-term outcomes from the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial (19), a multicenter prospective randomized clinical trial, included 601 colon cancer patients. All the patients were enrolled by 33 surgeons from 31 Australian and New Zealand centers between January 1998 and April 2005. 294 patients were allocated to laparoscopic-assisted surgery. Statistically significant differences in quicker return of gastrointestinal function and shorter hospital stay were demonstrated in favor of laparoscopic-assisted resection. The infective complications increased significantly in cases converted from laparoscopic-assisted to open procedures. There was no statistically significant difference found in postoperative complications, reoperation rate, or perioperative mortality. Interestingly, the quality of life from the ALCCaS trial was recently reported by McCombie AM. et al (20) in 2018. Of the 592 patients enrolled in ALCCaS, 425 completed at least 1 quality-of-life measure at 4 time

points (71.8% of cohort). Symptoms Distress Scale, the Quality of Life Index, and the Global Quality of Life Score were used to measure the patient symptoms and quality of life preoperatively and at 2 days, 2 weeks, and 2 months postoperatively. The study demonstrated a short-term gain in quality of life maintained at 2 months postsurgery for those who received laparoscopic relative to open colonic resection; Symptoms Distress Scale ($p< 0.01$), Quality of Life Index ($p< 0.01$), and Global Quality of Life ($p< 0.01$).

Cost

The concern about potential increased cost of laparoscopic colorectal resections has always been considered. However, laparoscopic colorectal resections were found to be significantly cheaper than conventional open resections because of the reduced hospital stay, despite higher operative spending (21). A report from Australia by Norwood et al. (22) compared hospital cost using Hospital Patient Costing System, including costs from nursing interventions (calculated in minutes). Ninety-seven patients (53 laparoscopic resections, 44 open resections) were analyzed. The median total cost of the procedure was equivalent: AUS$9698/£5631 (AUS$3862–90,397) in the open group and AUS$10,951/£6219 (AUS$2337–66,237) in the laparoscopic group. The laparoscopic group showed more benefit in reduction of nursing intensity (80 versus 58.5 hours), and the significant reduction of nursing intensity was demonstrated after exclusion of laparoscopic patients who underwent conversion (80 versus 54 hours; P=0.01). Furthermore, a large Dutch multicenter trial recently confirmed in 2017 (23) that the laparoscopic approach for colon cancer resection resulted in a significant cost reduction when compared to open resection. Retrospective analyses using a population-based database included all elective resections for a T1-3N0-2M0 stage colorectal cancer, between 2010 and 2012 in 29 Dutch hospitals. Ninety-day hospital costs were measured uniformly in all hospitals based on time-driven activity-based costing. For colon cancer surgery (N = 4202), laparoscopic resection was

significant less expensive than open resection in all subgroups. Particularly in patients ≥75 years and ASA I-II, laparoscopic resection was associated with 46% less mortality (P = 0.05), 41% less severe complications (P < 0.001), 25% less hospital stay (P = 0.013), and 65% less ICU stay (P < 0.001). However, for rectal cancer surgery (N=2328), all laparoscopic subgroups had significantly higher total hospital costs.

Long-Term Outcome

Several evidences from early basic science studies suggested that in the right setting, laparoscopic surgery will result in a better long-term oncologic outcome by more preservation of immunologic functions (24–26). Preservation of the body's immunologic function, particularly cellular immunity immediately after surgery, is an essential defense to potentially prevent cancer recurrence (27). Significantly less physiologic alterations during this critical perioperative period can be achieved by laparoscopic surgery, which is relating to less tissue trauma (24–26). Interestingly, these potential advantages have not been translated into better long-term outcomes in human settings.

Jayne et al. (28) reported the evidence on long-term outcomes of the UK MRC CLASICC trial after 5 years of follow-up. They described no difference in the overall survival, disease-free survival, local or distant recurrence between laparoscopic resection and open resection. Long-term quality of life was also comparable between groups. These data, together with other multicenter randomized trials (9, 10, 29) and meta-analyses (12, 30, 31), are applied not only for colonic caner but also for rectal cancer. As already mentioned, the steep learning curve for laparoscopic colorectal surgery may have a major effect on unimproved oncologic outcomes. Expert surgeons who participated in the trials at that time were relatively inexperienced. Unexpectedly very high conversion rates from the 3 multicenter prospective trials also confirmed this hypothesis: COST, 21%; COLOR, 17%; CLASICC, 29% (32–34). However, the up-to-date trial by more experienced laparoscopic surgeons is

still debatable if better cancer long-term outcome can be expected from laparoscopic colorectal surgery.

There is conflicting data on the conversion rate, which may affect morbidity, mortality, and overall survival. Some studies have suggested that conversion does not influence outcome (35). Casillas et al. (36) reported a case-match study from the Cleveland Clinic with 51 (12%) cases converted to open surgery from 430 laparoscopic colectomies performed between 1999 and 2002. The converted cases were matched for operation and age. They found that conversion does not result in inappropriately prolonged operation times, increased morbidity or length of stay, increased direct costs, or unexpected readmissions compared with similarly complex laparotomies. Other investigators (37, 38) found a correlation between conversion and survival disadvantages. Data from 5 years of follow-up in the CLASICC trial (28) also demonstrated this clear survival disadvantage. The adverse impact of conversion was significant only for overall survival not disease-free survival. This finding is not attributable to a surgeon-related factor. Although advanced cancer pathology, which was cited as the most common reason for conversion, other reasons (e.g., obesity, technical difficulties, complication) appear to have a bad outcome independent of surgical experience.

Port site recurrence had been one of the major concerns for laparoscopic surgery for colorectal cancer. This unusual pattern of recurrence was first reported in 1991 (39, 40). The incidence from case series ranged from 1% to 21%, and 80% of cases presented within 12 months of surgery (41). The incidence from open surgery is 1.1% 61.5% (42). This type of recurrence in laparoscopic colorectal surgery for malignancy might be overstated. Data reported from prospective voluntary audit from 1992 to 1995 showed an incidence of 1.1%, which is similar to open surgery (43). It also appeared that these types of recurrences are not observed in the latest updates from large randomized control trials: COST, 0.5%; COLOR, 1.3%; Barcelona trial, 0.9% (32, 34, 44).

Experimental (45) and clinical data from single center, nonrandomized, and largely heterogeneous studies (46–50) support that adhesion formation was reduced after the laparoscopic procedure. Incisional hernia is also a cause of postoperative morbidity and mortality. Several studies have suggested that the rate of incisional hernia was reduced after laparoscopic colorectal surgery (46, 48) owing to the absence of a large abdominal wound (51, 52). The MRC CLASICC (53) reported long-term complications in 411 patients with adhesive intestinal obstruction and incisional hernia. The results did not confirm that laparoscopic surgery reduced the rate of adhesive intestinal obstruction and incisional hernia after colorectal cancer surgery. Trends suggested that a reduction in conversion to open surgery and elimination of port site hernias may produce such an effect.

Rectal Cancer

According to anatomic limitation, laparoscopic surgery for rectal cancer involves several challenges that lead to a longer learning curve when compared with laparoscopic colonic surgery. Laparoscopic surgery for rectal cancer is limited to specially trained surgeons; as a result the reports for this procedure are scanty. Better visualization with the laparoscopic approach for rectal dissection reduced blood loss and surgical stress, which also leads to faster recovery (54). However, laparoscopic surgery for rectal cancer is still not universally accepted and concerns persist regarding the adequacy of oncologic resection. The CLASICC trial (28) reported a nonsignificant increased rate in radial resection margin positive in patients undergoing laparoscopic anterior resection (6.3% for open resection versus 12.4% for laparoscopic resection). This also did not affect the difference in local recurrence rate at the 5-year follow-up. These data are reassuring—laparoscopic surgery for rectal cancer is feasible with benefits of shorter outcomes and comparable long-term oncologic outcomes.

Many investigators have called for a change in the technical approach of the abdominoperineal resection (APR). The remaining difference in local recurrence rate between rectal cancer treated by an anterior resection and those patients undergoing APR, which carries an 8.8% increased risk, relates to the anatomic location of the tumor. The introduction of cylindrical APR is now well recognized to rectify the situation (55). This difference has been attributed, in part, to the smaller tissue volume around the tumor and the higher rate of cancer at circumferential resection margins (CRM) after APR (56–58). A recent multicenter study reported by West et al. (59) comparing 176 extralevator APR from 11 European colorectal surgeons to 124 standard APR from 1 United Kingdom center demonstrated significant more removed tissue from outside the smooth muscle layer per slide (median area 2120 versus 1259 mm^2; P=0.001) leading to a reduction of circumferential involvement (from 46.6% to 20.3%; P=0.001), and intraoperative perforation (from 28.2% to 8.2%; P=0.001). However, extralevator surgery was associated with an increase in perineal wound complications (from 20% to 38%; P50.019). This is interesting when compared to a report from Memorial Sloan-Kettering in 2007 (60). One hundred nine patients with locally advanced rectal cancer who underwent preoperative chemoradiotherapy followed by total mesorectal excision (TME) were studied. A complete pathologic response was found in 16% of patients. In patients with residual tumor, the median CRM was 10 mm. This was similar to the patients undergoing either low anterior resection or standard APR. There were only 2% of patients who had CRM of less than 1 mm. Genitourinary dysfunction results in significant morbidity when it occurs after rectal resection. Studies comparing differences in rates of genitourinary dysfunction after laparoscopically assisted or open rectal cancer resections are limited. Quah et al. (61) reported no statistically significant difference in bladder dysfunction between laparoscopically assisted and open TME for rectal cancer. However, impotence and ejaculation dysfunction had significantly higher rates with the laparoscopic resection. A study from the United Kingdom (62) also reported a trend toward male sexual dysfunction. However, it was also stated that laparoscopic rectal resection did not adversely affect bladder function. Nerve identification during resection may reduce the

rate of postoperative genitourinary dysfunction (63–65). Junginger et al. (63) demonstrated in their study of 150 patients who underwent TME for rectal cancer that intraoperative visual inspection of the pelvic autonomic nervous system was achieved 72% of the time. Patients who had complete identification of the pelvic autonomic nerves experienced a significant reduction in postoperative urinary dysfunction.

Interestingly, local failures have still been a problem. Despite of total mesorectal excision and preoperative radiation therapy, abdominoperineal resection (APR) was reported to have significantly worse results than anterior resection with more circumferential resection margin positivity and local recurrences. Both anatomic aspects of the advanced tumor within a challenge location and technical difficulties associated with standard APR (66-68). During “standard” APR, the reduced volume of mesorectum in the lower rectum increased the chance of reaching the anal sphincters at the circumferential margin, leaving a “waist” in the specimens. In a “call for a change of approach,” Nagtegaal et al (67) described the poor prognosis of patients who had undergone standard APR leading to a high frequency of circumferential margin involvement either by the tumor itself or the perforation, or both during the dissection. For these reasons, an alternative approach using a wide perineal resection has been proposed. Holm et al (69-70) reported the extralevator APR which was optimally performed in the prone jackknife position. It was recommended that the rectum should be mobilized from the abdomen until the seminal vesicles in men and upper vagina in women. The stoma was then made and the abdominal closure was performed. The patient was turned to a ventral position. The extended rectal excision was performed under direct vision. The coccyx excision was recommended to facilitate an adequate visualization of the posterior pelvis that was previously dissected through the abdomen. Lateral dissection was extended to the origin of the levator muscles at the pelvic sidewall. The technique aimed to remove more surrounding tissue around the tumor and thus decrease perforations and rates of circumferential resection margin involvement. Furthermore, adequate and direct visualization could enhance a better dissection through the correct anatomic planes to

prevent intraoperative tumor perforation. More recently, West et al (68) had confirmed that extralevator APR using prone jackknife position led to a reduction in circumferential resection margin positivity and intraoperative perforations.

Chemotherapy and Radiotherapy

Surgery for locally advanced rectal cancer (LARC) has a significant impact on the patient, and severe complications occur in up to 22% of patients (71). In addition, sphincter preservation is possible in only 50% of patients with low-rectal cancer (72). Organ-preserving strategies and quality of live improvement have become major interests within this group of patients. The guidelines of the National Comprehensive Cancer Network (NCCN) for LARC recommend a multidisciplinary approach with neoadjuvant chemo radiotherapy (CRT), surgery using TME principles, and adjuvant chemotherapy (73). Neoadjuvant CRT was defined as standard mainly because of its potential to decrease 5- and 10-year pelvic recurrence rates (74). However, whether long- or short-course radiotherapy is preferable remains matter of debate.

A wide range of drugs, including oxaliplatin as an adjunct to CRT, failed to demonstrate clear benefits in several high-quality studies and this was due mainly to increased toxicity (75-76). However, more recent data showed improved disease-free survival when adding oxaliplatin to both preoperative CRT and postoperative chemotherapy (77). Several further phase II trials showed similar promising results without jeopardizing planned CRT or increasing surgical complications (78-81), labelling the concept of total neoadjuvant chemotherapy as safe and feasible. Splitting of adjuvant chemotherapy by delivering at least some cycles before CRT and the remaining post-surgery has also been described as an alternative (82-83). A randomized trial in North America (NRG GI002) is accruing patients for a total neoadjuvant approach.

Furthermore, the combination of long-term morbidity with pelvic irradiation and widespread application of TME principles to decrease local recurrence, a subset of patients may be eligible to avoid preoperative radiation and to undergo solely neoadjuvant systemic chemotherapy. Large studies are ongoing (84) and today this approach is used primarily in trial settings. The randomized phase III PROSPECT (Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME) trial is assessing this strategy in patients with uncompromised CRM (ClinicalTrials.gov Identifier: NCT01515787).

Robotic Surgery

Limitations inherent in conventional laparoscopic surgery can be overcome by the use of robot. The clear advantages of robot are increased dexterity of instruments, precision, 3-dimensional visuals, a steady camera, and intuitive movements that may help obtain better oncologic and overall surgical outcomes (86, 87). It has been well documented that robotic surgery has passed its infancy for some subspecialties (e.g., urology and gynecology). The data have shown the equality and sometimes superiority of robotic surgery versus conventional laparoscopic surgery (88–92).

Reports on robotic surgery for colorectal cancer are still limited. Potential advantages of the robot in colorectal surgery are similar to those in other fields: less operative blood loss, better oncologic technical dissection in rectal cases, and increased ease of dissection in a confined space. Laparoscopic TME is limited both by the rigidity of the instruments and the restricted range of motion for the surgeon. The robot overcomes these limitations and allows for more precise oncologic dissection (93). The high conversion rate of laparoscopic surgery for rectal cancer ($\leq$30%) may have an advantage in implementing robot surgery (10). Three-dimensional visualization also is providing the ability of better nerve sparing TME (91). Baik et al. (95) reported on a randomized controlled trial of 36 patients: 18 who underwent robotic

low anterior resection using the da Vinci Surgical System, and 18 patients who underwent conventional laparoscopic low anterior resection. No difference was found in operating time, hemoglobin level change, conversion rate, or quality of the specimen between the 2 groups. The significant difference was demonstrated in the average length of stay (6.9 61.3 days in robotic resection group; 8.7 61.3 days in laparoscopic group; P<0.001).

Repositioning is a major obstacle for robotic surgery when more than 1 field of dissection is required. The hybrid procedure laparoscopic splenic flexure mobilization and vascular pedicle transection combined with robotic total mesorectal excision may be 1 solution to be considered. However, operative time may be reduced by an experienced team or by using the nonrepositioning technique, as reported by Hellan et al. (95).

The most important study in the field was published recently: The ROLARR study, an international multicenter prospective trial, randomly assigned 471 patients to either conventional laparoscopic or robotic-assisted resections (96). The study failed to demonstrate significant benefits of robotic surgery regarding the main outcomes of CRM positivity, TME quality, intra- and postoperative complications, and 30-day mortality. However, the wide range of experience among operating surgeons was criticized.

In conclusion, laparoscopic surgery for colorectal cancer has become popular among patients and surgeons. In recent years, it has been confirmed that laparoscopic surgery for colon cancer demonstrates better short-term outcome, oncologic safety, and equivalent long-term outcome. For rectal cancer, laparoscopic surgery can be more complex depending on the tumor location. TME, sphincter preservation, and autonomic pelvic nerve preservation provide even more challenge for colorectal surgeons to minimize local recurrence, and at the same time, to maximize quality of life for the patients. Unlike laparoscopic surgery for colon cancer, there is not enough evidence to reach any conclusion on its long-term oncologic outcome. Large randomized control trials need to be conducted to assess the long-term outcome of laparoscopic surgery for rectal cancer to reach the same conclusions.

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Chapter 3: Laparoscopic surgery for rectal cancer

Overview

This chapter contains the most important part of the thesis. This was the first published data comparing laparoscopic ultralow anterior resection *versus* laparoscopic pull-through with coloanal anastomosis for rectal cancers. The rational of combining transanal dissection with the routine transabdominal TME was explained in detail. The preoperative, intraoperative and postoperative parameters were collected and analyzed. The proposed technique may overcome the challenge in rectal cancer dissection in deep and narrow pelvis.

Laparoscopic Ultralow Anterior Resection *versus* Laparoscopic Pull-through with Coloanal Anastomosis for Rectal Cancers – a Comparative Study.

(Am J Surg. 2011; 202(3):291-7)

BACKGROUND: Ultralow anterior resection for mid and distal rectal cancers has been reported routinely performed using either a laparoscopic ultralow anterior resection (LAR) or laparoscopic pull-through with coloanal anastomosis (LPT). This study evaluated the postoperative and functional outcomes. METHODS: Between January 2007 and December 2008, 40 consecutive patients had laparoscopic surgery for rectal cancers. The data were prospectively collected. RESULTS: There were 21 patients (21 men; mean age 61.2±3.2 years standard error of the mean (SEM)) in the LAR group and 19 (16 men; mean age 61.4±2.4 years SEM) in the LPT group. Tumor characteristics, adjuvant therapy given, mean follow-up (overall 33.5±1.4 months SEM), intraoperative time, blood loss, mesorectum quality, conversion rate (LAR n=2, LPT n=1), pain score, time for ileostomy to function, subsequent incontinence scores,

and complication rates (LAR n=7, LPT n=9) were not different between groups, but benign anastomotic strictures were higher after LPT (n=4, LAR n=0, P=0.042). The latter was associated with chemoradiotherapy (P=0.015). There were 2 systemic cancer recurrences both in the LPT group but no local recurrences to date. CONCLUSIONS: The LAR technique may have less risk of anastomotic strictures, particularly with adjuvant therapy. LPT may be considered selectively for a bulky distal rectal tumor in a small pelvis with comparable functional results.

Laparoscopic colectomy for colon cancer has recently been confirmed to provide equivalent oncologic results to traditional open surgery with advantages of early feeding, less pain, shorter hospital stay, earlier return to normal daily activities, and perhaps lower long-term risks of incisional hernias and adhesions (1– 4). Even though laparoscopic rectal cancer surgery is technically more challenging compared with laparoscopic colon surgery because it involves total mesorectal excision (TME) in a limited pelvic cavity, it has recently been reported to be feasible and safe and offers the advantages of laparoscopic surgery (5–7); however, long-term follow-up of local recurrence, disease-free survival, and overall survival have not yet been consistently confirmed. Various laparoscopic-assisted and laparoscopic rectal cancer surgery techniques have been introduced including (1) mobilization of splenic flexure and ligation of the inferior mesenteric vessels laparoscopically and then performing the pelvic dissection through a small transverse supra- pubic incision, (8, 9) (2) using a hand port technique to assist the laparoscopic procedure, (10, 11) and (3) performing the entire abdominal and pelvic procedure laparoscopically (12). The last technique has the advantage of better visualization of the mesorectum, nearby nerves, and other vital structures during deep pelvic dissection with the magnification of the laparoscope (12). With the total laparoscopic approach, 2 techniques of distal pelvic dissection, resection of specimen, route of specimen extraction, and subsequent coloanal anastomosis have been reported.

First, with the laparoscopic ultralow anterior resection (LAR), the entire pelvic dissection and division of the distal rectum is performed with an abdominal laparoscopic technique. The specimen is then extracted through a protected lower abdominal wound or defunctioning ileostomy site, (12) and coloanal anastomosis is performed (at anorectal junction) with a laparoscopic intracorporeal double-cross staple. In the second laparoscopic pull-through coloanal anastomosis (LPT) approach, a transanal approach is used to complete the distal pelvic dissection, extract the specimen, and perform a hand-sewn coloanal anastomosis (at the dentate line) (13–15). Both techniques may incorporate a colonic pouch or coloplasty to improve postoperative bowel function (16). The conceivable advantages of LAR include more control in specimen extraction against tumor spillage using commercially available wound protectors and better preservation of anorectal function (17, 18). By contrast, LPT facilitates difficult distal pelvic dissection via the transanal approach and extracts the specimen through a natural orifice although an incision for a defunctioning stoma may still be required.

To date, there have not been any studies that have compared the outcomes of LAR and LPT when both were performed routinely. A prospective comparative study was conducted to assess the early postoperative and functional outcome of the 2 techniques.

Methods

Between January 2006 and December 2008, patients with rectal cancer operated on by a single surgeon were included in a prospective comparative study that was approved by the Institutional Review Board. Patients undergoing laparoscopic abdominoperineal resection and those who had a tumor invading an adjacent organ, high anterior resection, and associated disease (eg, polyposis, ulcerative colitis, and secondary cancer) necessitating proctocolectomy were excluded. The preoperative assessment included physical examination, colonoscopy with biopsy, endorectal ultrasonography, abdominopelvic

computed tomography (CT) scan, serum carcinoembryonic antigen (CEA), a chest x-ray, and pelvic magnetic resonance imaging. Patients with pelvic magnetic resonance imaging showing a locally advanced tumor; a tumor penetrating through the rectal wall (T3), and/or a tumor with lymph node involvement without any evidence of distant metastases were given the option of preoperative chemoradiotherapy (45 Gy). Otherwise, patients with confirmed inadequate radial resection margin (less than 3 mm) and/or specimen-confirmed lymph node metastases were offered postoperative adjuvant chemoradiotherapy as appropriate. Although offered neoadjuvant therapy, most patients in this reporting regional service draining a large distant rural population preferred to have chemoradiotherapy only after it was proven to be indicated on the histopathology report. The LAR or LPT technique was selected by alternating allocation by sequence on the day of surgery. Tumors were staged postoperatively using the 6th edition of the American Joint Committee on Cancer clinical tumor node metastasis (TNM) classification.

Surgical technique

Surgery was performed 6 to 8 weeks after chemoradiotherapy as appropriate. Patients were operated on by 1 colorectal surgeon experienced in laparoscopy. All patients had epidural analgesia as well as fast-track multimodal perioperative management except for bowel preparation. Our technique for LAR has previously been described with video (12). In the LPT technique, port placement was similar except that a 5.5-mm port was used instead of the 15-mm port in the right lower quadrant. The operative technique has been described previously by Person et al. (15) A loop ileostomy was matured, and a pelvic suction drain was used selectively in both groups. Ileostomy reversal was scheduled 12 weeks later or after the completion of chemoradiotherapy; confirmation of anastomosis integrity was performed with a Gastrografin enema (Bayer New Zealand Limited, North Shore, Auckland).

Quality of surgery

The rectal specimen was examined in the operating room by a trained independent observer to assess the completeness of mesorectal excision and the distal resection margin. For pathological assessment, the surface of mesorectum was inked before slicing to assess the circumferential resection margin. Microscopic assessment was performed to define the extent of tumor infiltration through the bowel wall (pT/ypT), lymph node involvement (pN/ypN), and distal and circumferential resection margins.

Definition of conversion and morbidity

Conversion to an open operation was defined as extension of the extraction incision over 5-cm long (including conventional midline laparotomy or the need to perform any part of the procedure besides maturing of the ileostomy through the incision). The reasons for conversion were recorded. Patients in either groups who subsequently needed abdominoperineal resection or any procedural changes that violated the allocation (eg, changing from LAR to LPT) were also classified as conversions. Morbidity was defined as a surgical postoperative complication of grade III, IV, and V as classified by Dindo et al. (19) Grade III included postoperative complications that required surgical, endoscopic, or radiologic intervention with or without general anesthesia. Grade IV included life-threatening complications requiring intensive care unit management. Grade V complications caused postoperative death. Pelvic sepsis was defined as clinical pelvic infection (ie, anastomosis leakage, pouch leakage, or isolated pelvic abscess) but not asymptomatic radiologic leaks. Any infection suspected on the basis of fever, abdominal pain, gas, pus or fecal discharge from the drain, rectal discharge, or rectovaginal fistula was confirmed by an immediate pelvic CT scan with water soluble contrast enema.

Data collection, follow-up, and statistical analysis

Data were prospectively collected for age; sex; body mass index; American Society of Anesthesiologists grade; incision length; tumor stage; indication for surgery; duration of operation; amount of blood loss; tumor location; tumor size; distal margin; TME quality (Quirke classification) (20); pelvic size; conversion; and postoperative data including passage of flatus, hospital stay, morbidity, and mortality. Patients were asked to score their maximum pain experienced on a visual analog pain score of 0 to 10 at the time of discharge, 10 being the worst pain. Functional outcome assessment was with the Wexner incontinence score (21) at 3 months after ileostomy closure. Sexual function was also asked at the same visit. All patients had an office rigid sigmoidoscopy at 3 months after surgery. An anastomotic stricture was defined as failure to pass the rigid sigmoidoscope through the anastomosis.

Patients were followed up at 3 monthly intervals for 2 years and 6 monthly intervals for the subsequent 3 years. Serum CEA levels were measured before each visit and the patients underwent a thorough clinical examination including digital rectal examination and/or rigid sigmoidoscopy. A CT scan of the abdomen, pelvis, and thorax was performed annually. Patients also underwent a follow-up colonoscopy at 1 year, earlier if the colon had not been completely screened before surgery. Further appropriate investigations were otherwise performed based on symptoms, clinical findings, and serum CEA levels.

Statistical analysis was performed by using the Fisher exact probability test, the chi-square test, and the Mann Whitney U test for differences between the groups. To minimize the statistical discrepancies caused by small sample size, the exact significance was calculated by using the SPSSR Exact Test (SPSS, Inc, Chicago, IL), and statistical significance was assigned to any P value < 0.05.

Results

Forty consecutive patients who underwent LAR and LPT for rectal cancer were prospectively evaluated (Table 1). No patients meeting criteria were excluded. Every patient had good control of bowel movements preoperatively evaluated by a detailed history and precise proctologic examination. There were no significant differences between the mean age, sex, body mass index, American Society of Anesthesiologists grade, location of the tumor above the anal verge, tumor size, tumor stage, tumor grading, distal resection margin, and resected mesorectum quality (20) between the LAR and LPT groups. All the specimens in both groups had adequate circumferential resection margins. The proportions of patients who received adjuvant chemoradiotherapy were also not significantly different.

Table 1 Patient demographics in patients who had LAR and LPT

	LAR (n=21)	LPT (n=19)
Age (y)*	61.3±2.40	61.2±3.15
Male/female ratio	21/0	16/3
Body mass index (kg/m^2)*	26.1±0.8	26.7±1.6
ASA score†	2 (1–3)	2 (1–3)
Lower margin of tumor from anal verge‡		
• <8 cm	11 (52.4)	10 (52.6)
• 8–12 cm	10 (47.6)	9 (47.4)
Tumor greatest diameter‡		
• <4 cm	15 (71.4)	15 (78.9)
• >4 cm	6 (28.6)	4 (21.0)
Tumor stage‡		
• pT/ypT0	1 (4.8)	0 (0)
• pT/ypT1	2 (9.5)	2 (10.5)
• pT/ypT2	8 (38.1)	4 (21.1)
• pT/ypT3	10 (47.6)	13 (68.4)
Nodal stage‡		
• pN/ypN0	12 (57.1)	13 (68.4)
• pN/ypN1	9 (42.8)	6 (31.6)
Liver metastasis	2 (9.5)	1 (5.3)
Tumor differentiation‡		
• Well differentiated	6 (28.6)	2 (10.5)
• Moderately differentiated	13 (61.9)	13 (68.4)
• Poorly differentiated	0 (0)	4 (21.1)
Quirke mesorectum quality‡		
• Grade 1	1 (4.8)	3 (15.8)
• Grade 2	6 (28.6)	7 (36.8)
• Grade 3	14 (66.7)	9 (47.4)
Distal resection margin‡		
• 1–1.9 cm	7 (33.3)	5 (26.3)
• 2–5 cm	12 (57.1)	10 (52.6)
• >5 cm	2 (9.5)	4 (21.0)
Preoperative radiation‡	3 (14.3)	0 (0)
Postoperative radiation‡	6 (28.6)	7 (36.8)

There were no significant differences between LPT and LAR using the Mann-WhitneyUtest and the Fischer exact test as appropriate. ASA, American Society of Anesthesiologists. *Values in mean (SEM). †Values in median (range). ‡Values are n (percentage).

All LAR and LPT patients had 5-cm colonic j-pouches. The operating times, extraction wound size, estimated blood loss, and conversion rates showed no significant differences between the 2 groups (Table 2). Two conversions in the LAR group were because the operating table failed to tilt adequately despite normal testing before the procedure and because of inadequate blood supply of the proximal colon after extraction and excision of the segment with rectal cancer. Conversion to a laparotomy ensured a well-vascularized distal transverse colon successfully brought down for anastomosis. The LPT patient who needed conversion had persistent hypotension upon induction of the pneumoperitoneum.

Table 2 Operative parameters in patients who underwent LAR and LPT

	LAR (n=21)	**LPT (n=19)**
Operating time (h)*	2.7±0.2	2.9±0.1
Extraction wound size (cm)*	3.1±0.3	NA
Estimated blood loss (mL)*	46.2±9.2	78.6±18.3
Conversion†	2 (9.5)	1 (5.3)

There were no conversions of LAR to LPT because of technical difficulties. There were also no conversions to abdominoperineal resection in both groups. No significant differences between the LAR and LPT groups using the Mann-Whitney U and Fischer exact test where appropriate. *Values in mean (SEM). †Values are n (percentage).

Table 3 shows that the postoperative pain scores, time for ileostomy to function, hospital stay, postileostomy closure bowel movements, and incontinence scores were not different between LAR and LPT patients. One patient in the LAR group and 4 patients in the LPT group had ileus of 5 days duration or longer; all ileuses resolved within 6 days in the

LAR group and 7 days in the LPT group (P=not significant). The mean length of hospital stay was longer in the LPT group (11.5 vs 6 .8 days) although not statistically significant. This was likely related to the higher but again not significant incidence of failed fast-track feeding/prolonged ileus in the LPT group. Interestingly, at the 2-year follow-up (mean follow-up 24.41.3 months SEM; LAR and 24.51.5 months SEM; LPT, P=not significant), the LPT group showed a trend of better control in bowel movement (Wexner incontinence score of 1.3 vs 3.3). Improvement in bowel function was found in both groups over time (Wexner incontinence score of 1.0 vs 1.1, mean follow-up 33.4±1.3 months SEM; LAR and 33.51.5 months SEM; LPT, P=not significant).Table 4shows that there were no significant differences in the total complications rates between the LAR (n=7) and LPT (n=9) patients. The only mortality was in a high-risk patient who died of a cerebrovascular accident after LPT. The other medical complications were chest infections and urinary tract infections. There were no anastomotic leaks as detected clinically or by the Gastrografin enema before closure of the ileostomy. However, the incidence of anastomotic strictures was significantly higher in the LPT group. These strictures all developed late, occurring at a median of 14 (range 6 –28) weeks after surgery. There was a significant association with postoperative chemoradiotherapy in this group (P=0.015). All did not respond to the dilatation and required reoperation; 1 patient preferred to have a completion abdominoperineal resection, and anastomotic revisions were successful in 2 patients who had their ileostomies closed eventually. The revision of the anastomosis failed in 1 patient because of inadequate colonic vascular supply resulting in permanent colostomy. Two patients with pelvic collections detected on a CT scan because of prolonged ileus/failure of fast-track feeding improved with antibiotics, intravenous fluids, and nasogastric tube suction.

Table 3 Postoperative outcome measures comparing LAR with LPT

	LAR (n=21)	LPT (n=19)
Pain score*†	5.9 (7.6)	6.4 (1.6)
Time for ileostomy to start function*	2.6 (0.3)	3.6 (0.6)
Hospital stay*	6.8 (0.7)	11.5 (3.7)
At the 2-year follow-up		
Bowel movements*‡	3.5 (0.9)	2.4 (0.6)
Wexner incontinence score*‡	3.3 (2)	1.3 (0.8)
At the last follow up (mean, mo)	33.4±1.3 SEM	33.5±1.5 SEM
Bowel movements*‡	2.6 (0.8)	2.2 (0.5)
Wexner incontinence score*‡	1.0 (1)	1.1 (0.8)

No statistically significant differences between LAR and LPT patients using the Mann-Whitney U test. *Values are in n (percentage). †Visual analog scale with 0 minimum 10 maximum used. ‡Assessed after ileostomy closure at the last follow-up.

A repeat CT scan confirmed resolution of the collections. One LPT patient had a drain left in for 7 days for persistent blood stained serous discharge, but small bowel contents appeared. Gastrografin studies confirmed a small bowel fistula, which closed after 1 week of total parental nutrition. Late complications were found in 2 LAR patients, with incisional hernias at the ileostomy closure site, who subsequently underwent laparoscopic hernia mesh repair. All patients were routinely asked about genitourinary function at the follow-up; 1 LAR patient who also underwent postoperative chemoradiotherapy had persistent impotence that had not been present before surgery.

The mean follow-up was 33.4±1.3 months SEM in the LAR patients and 33.5±1.5 months SEM in the LPT (P=not significant). Two LPT patients developed liver metastases 3

and 18 months after surgery. There were no patients to date with any local recurrences detected.

Table 4 Postoperative complications

	LAR (n=21)	LPT (n=19)
Medical complications		
• Cerebrovascular accident and death	0 (0)	1 (5.3)
• Chest infection	1 (4.8)	2 (10.5)
• Urinary tract infection	2 (9.5)	0 (0)
Surgical complications		
• Anastomotic stricture*	0 (0)	4 (21.0)
• Intra-abdominal collection	1 (4.8)	1 (4.8)
• Impotence	1 (5.3)	0 (0)
• Drain erosion to bowel	0 (0)	1 (4.8)
• Incisional hernia	2 (9.5)	0 (0)

Values are in n (percentage of complication over the number of patients in the group). *P0.042, statistical significance was tested using the Mann-Whitney U or Fischer exact test where appropriate.

Comments

Laparoscopic surgery for rectal cancer can be associated with relatively high morbidity and conversion rates, especially when TME with sphincter preservation is performed (12, 16, 22, 23). Because of these technical difficulties, reports on laparoscopic rectal cancer surgery are scanty compared with laparoscopic colon surgery. However, the technique has been gradually refined and proven to be feasible (16, 24, 25). Most series reporting on the short-term and long-term outcome for laparoscopic rectal cancer surgery have included patients who underwent laparoscopic high anterior resection and laparoscopic abdominoperineal resection. Our results including operative time, blood loss, conversion rate, and postoperative complications were comparable to those previously published (Tables 5 and 6). Most complications were medically related to high-risk elderly patients.

In our study, neither LAR nor LPT offered any technical advantage over the other as measured by operative time, blood loss, conversion rate, and overall complications. The patient and cancer characteristics were not significantly different between the 2 groups, particularly the tumor site. There were more T3 lesions in the LPT group (68.4% vs 47.6%), but these were relatively early non-bulky T3 lesions and the tumor size was comparable between groups. In addition, more patients in the LAR patients had neoadjuvant therapy, and, hence, the postoperative specimens were likely downgraded. LPT did not result in less pain although a smaller port was used and the specimen was extracted from the anus probably because an abdominal incision was still required for the defunctioning ileostomy. Another explanation for this might be our technique of extracting the specimen through the protected eventual ileostomy site in the LAR group, (25) which was also likely to have reduced postoperative pain by saving on the abdominal incisions made. In addition, the routine use of perioperative epidural analgesia in all patients after laparoscopic surgery would have significantly reduced postoperative discomfort (31). Sonoda et al. (32) reported no significant difference between those who underwent standard laparoscopic surgery versus hand-assisted surgery where obviously more incision-length differences were compared. The creation of ileostomy with coloanal anastomosis is supported by a recent meta-analysis that confirms that a diverting stoma reduces the risks of anastomotic dehiscence complications (33).

Table 5 Laparoscopic low anterior resection: operative times and blood loss reported

	N	Operative time (h)	Blood loss (mL)
Chen, et al. (20)	8	3.5	250
Selvindos et al. (13)	55	3.0	53.5
Tjandra, et al. (12)	31	3.0	153
Palanivelu, et al. (26)	170	2.3	40
Present series	40	2.8	62.2

Fecal incontinence is more likely in patients with a resection less than 6 to 8 cm from the anal verge, often a part of anterior resection syndrome, which has multifactorial causes (34) such as loss of the rectal reservoir, iatrogenic injuries of the anal sphincter, (35) or damage to autonomic nerve (36). Chemoradiation (37) and/or pelvic floor disease before surgery (31) may also play a role. Its incidence has been reported in up to 60% of such patients (38). Our series is the first to compare the functional outcome between LPT and LAR. Even though the specimen extraction and hand-sewn anastomosis were performed through the anal sphincter in LPT patients, there is no significant difference in functional outcome compared with LAR patients although the numbers are relatively small. This might possibly be related to the anal procedure performed with gentle, minimal, and intermittent dilatation (39).

Table 6 Outcomes parameter: postoperative conversion rate and complication

	N	Conversion rate (%)	Complication* (%)
Laurent, et al. (18)	117	25	15.5
Selvindos, et al. (12)	55	5	8.0
Tjandra, et al. (11)	31	0	25.8
Palanivelu, et al. (26)	170	0	13.5
Leroy, et al. (27)	102	3	27.0
Barlehner, et al. (28)	145	1	18.6
Morino and Giraudo (29)	98	18.4	18.4
Scheidbach, et al. (30)	231	6.1	37.6
Dulucq, et al. (24)	218	12	21.0
Present series	40	7.5	27.5

*Overall complications are the percentage of the patients with complications because some complications occurred in the same patients and were probably related. This was also the method of reporting in the other series.

We decided to use the adequately validated Wexner incontinence score for functional evaluation in this study because of its unique correlation with clinical evaluation, reproducibility, and sensitivity to change produced by definitive treatment. It is also the first easy-to-use incontinence scoring system to take into account usage of pads and lifestyle alteration as well as the consistency and frequency of incontinence (21). Electrophysiologic studies are generally not well correlated with clinical function especially with relatively small numbers of patients and therefore not being used (or prescribed) routinely as an investigation. It was selectively used in some cases (31).

In conventional open surgery, the coloanal pull-through hand-sewn anastomosis for rectal cancer (40) had become less commonly performed after the evolution of the stapling devices, which routinely enable distal rectal anastomosis deep in the pelvis. Nonetheless, it continues to have a role when the pelvis is narrow, the forward angle of distal rectum and when the rectal cancer is very distal particularly with intersphincteric resection (20, 41, 42). Laparoscopic rectal cancer surgery is hampered by inadequate articulation of endoscopic staplers for distal rectal transection near the level of the anorectal ring. This might result in a long oblique stapler line on the anorectal stump, which requires multiple applications of the stapler compromising adequate distal margin or anastomotic integrity. Another challenge of both laparoscopic and open surgery is that the distal tumor margin may not always be correctly identified. The bulk of the mesorectum may obscure the precise localization of the tumor; moreover, obtaining a reliable distal margin may be even more difficult in patients who have undergone neoadjuvant chemoradiotherapy, because the residual tumor may be small or absent (43). LPT may be used routinely to overcome these technical difficulties, (44) but theoretic concerns with wound contamination from specimen extraction remain although this is not proven with results available to date. However, we found in this study and with previous experience that LAR is usually possible without excessive problems after incision of Waldeyer’s fascia (27). The latter step can be easily performed laparoscopically with

inversion of the 30° camera in the pelvis, allowing the rectum to be brought proximally and forward to facilitate stapler transaction (45). It is likely that improvements in stapler technology including the powered staplers may further assist this (46).

Four patients all in the LPT group developed severe anastomotic strictures after the completion of radiochemotherapy. Previously reported factors that may be associated with anastomotic stricture include ischemia, anastomotic dehiscence, (47–49) obesity, pelvic sepsis, radiotherapy, and diverting proximal ostomy (50, 51). The late strictures found in our study were significantly related to the effect of postoperative radiotherapy. Hence, it is suggested that LAR be the routinely preferred technique particularly if the patient is likely to have chemotherapy radiotherapy. LPT could be considered as when a hand-sewn coloanal anastomosis is indicated for open surgery that is when difficulties are encountered with distal bulky tumors in patients with narrow tight pelvis.

The limitations of this study include the relatively small sample size and the medium not long-term follow-up particularly addressing oncologic issues. Planned randomized controlled trials addressing this issue with a larger sample size and long-term follow-up should be performed to consider the possible higher risk of delayed anastomotic structuring after LPT.

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Chapter 4: Factors influencing rectal cancer treatment outcomes

Overview

Circumferential resection margin has been considered and repeatedly reported as one of the most important factors in locoregional control of rectal cancer treatment. This chapter contains the relevant data on factors considered to influence circumferential resection margin positivity during rectal cancer surgery. High-quality TME with negative circumferential resection margin will certainly lead to longer disease-free survival and overall survival.

Factors Influencing Circumferential Resection Margin in Rectal Cancer.

(Colorectal Dis. 2013; 15(3): 298-303)

BACKGROUND: Abdominoperineal excision (APR) has been associated with higher circumferential resection margin (CRM) involvement and local recurrence rates than extralevator APR for low rectal cancer. This study aimed to evaluate the CRMs in APR and low anterior resection (LAR) specimens and to identify factors influencing CRM involvement. METHOD: All pathological specimens from consecutive patients with rectal cancer who underwent curative resection at the Cleveland Clinic Florida, from January 2000 to July 2010, were reviewed by two pathologists. Demographics, tumour characteristics, operative data, postoperative pathology and Dworak's tumour regression grade were compared between specimens with positive and negative CRMs. RESULTS: One-hundred and fifty-four patients underwent curative APR (n=65) or LAR (n=69). Mean tumour size was 3.6 cm, and mean distance from the dentate line was 5.4 cm. Nine (6.8%) patients had a positive CRM (n=6 APR, n=3 LAR), which was associated with tumour size > 5.9 cm (P= 0.002), a distance of £2.6 cm from the

dentate line (P= 0.013), microvascular invasion (P= 0.009), perineural invasion (P< 0.001), number of positive lymph nodes (P= 0.046) and incomplete total mesorectal excision (TME) (P< 0.001). APR specimens were three times more likely than LAR specimens to have an incomplete mesorectum (9.8% vs 2.9%, P= 0.322). CONCLUSIONS: Factors associated with a positive CRM were tumour size > 5.9 cm, a distance of £2.6 cm from the dentate line, incomplete TME, number of positive nodes and microvascular and perineural invasion. The incidence of a positive CRM was not significantly different between LAR and APR (n= 3 LAR and n=6 APR).

The adequacy of local control is an essential goal in the treatment of rectal cancer. The introduction of advances in rectal cancer surgery, such as total mesorectal excision (TME), which provides complete resection of the tumour together with its lymphatic and venous drainage (1,2), and neoadjuvant chemoradiotherapy have drastically reduced the reported rates of local recurrence (3, 4). Interestingly, the improvement in overall treatment outcomes of distal rectal cancer has not reached the same level as obtained for mid or proximal lesions (5). Specifically, a higher rate of suboptimal circumferential resection margins (CRMs) has been found in patients undergoing abdominoperineal excision (APR) when compared with patients undergoing anterior resection (41% vs 12%). This CRM-positivity rate has, at least in part, led to higher local recurrence (36.5% vs 22.3%) and lower survival (52.3% vs 65.8%). In addition, CRM status has been reported to be a strong prognosticator for local and distant recurrence and for survival (6).

A better understanding of the factors influencing CRM positivity is important and will help in the design of risk-adapted treatment of rectal cancer patients. The purpose of this study was to analyze the CRMs in APR and low anterior resection (LAR) specimens and to identify factors influencing CRM involvement.

Method

After Institutional Review Board approval, patients at the Cleveland Clinic Florida who had a primary diagnosis of adenocarcinoma of the rectum and underwent curative LAR or APR from January 2000 to July 2010 were identified from a prospectively collected colorectal surgery database. Patients with a pT4tumour, Stage IV disease, and those who had had a complete pathological response (ypT0N0) were excluded. Pathological specimens were reviewed by two experienced gastrointestinal pathologists. The patients' demographics, tumour characteristics, operative data, postoperative pathology, quality of total mesorectal excision (2) and Dworak's tumour regression grade (TRG) (7) were compared between specimens with a positive and a negative CRM. Pathological staging was performed using the International Union Against Cancer TNM system, fifth edition (8). CRM involvement was defined as the presence of tumour cells located 1 mm or less from the painted resection margin, as determined by microscopic evaluation.

Neoadjuvant therapy

Neoadjuvant chemoradiotherapy was administered to all T3 or N-positive mid- and low rectal adenocarcinomas evaluated by endorectal ultrasound and/or MRI. Radiotherapy was given over 5–6 weeks with a total dose of 45 Gy to the pelvis and a boost to the rectum to a total of 50.4 Gy over 28 fractions. 5-Fluorouracil was administered concurrently as a continuous infusion of 225 mg/m^2 per day. Standard TME (9) was performed 6–8 weeks after chemoradiotherapy in the supine modified lithotomy position in all cases.

Statistical analysis

Statistical analyses were performed using Fisher's exact test, the Mann–Whitney U-test, the log-likelihood ratio test or the Student's t-test, as appropriate. The log likelihood ratio x^2

test was applied in the special situation in which there was no relationship between the two categorical variables and the expected value in any cell of a contingency table was <5. P<0.05 was considered statistically significant.

Results

After the exclusion of pT4 and Stage IV patients, 154 patients who underwent curative APR or LAR for midrectal cancer between January 2000 and July 2010 were identified. Ninety-three patients (59%) received neoadjuvant chemoradiotherapy. Twenty (18%) of these patients had a histopathological complete response and were excluded from the study. From a total of 134 patients, 65 underwent APR and 69 underwent LAR. The mean tumour size was 3.6 cm, and the mean distance from the dentate line was 5.4 cm. Nine (6.8%) patients had a positive CRM (n=6 APR, n=3 LAR), and 125 (94%) patients had a negative CRM (n=59 APR, n=66 LAR). There was no significant difference in the age, gender, body mass index (BMI), type of surgery, type of procedure, site of tumour, tumour location and use of neoadjuvant chemoradiotherapy between the positive and negative CRM groups (Table 1).

The mean operative time was 214.4±71.3 min (positive CRM group) vs 203.7±70.5 min (negative CRM group), and estimated blood loss was 283.3±163.3 ml (positive CRM group) vs 334.1±335.1 ml (negative CRM group); there was no significant difference between the groups, suggesting no difference in the degree of technical difficulty during TME (Table 2). Pathological stage did not vary significantly between the two groups. The number of harvested lymph nodes (27.9±13.4, positive CRM group vs 21.613.6, negative CRM group; P= 0.108) and Dworak's TRG were similar in both cohorts (Table 3). Intra-operative tumour perforation was not found in any specimen, and the distal resection margin was free of tumour in all patients.

Table 1 Patients' demographic data

	CRM		
	Positive(n=9) (6.8%)	**Negative(n=125) (93.2%)**	**P-value**
Age (years)	68±18.2	62±14.1	0.280*
Gender			0.483+
• Male	7 (77.8)	77 (61.6)	
• Female	2 (22.2)	48 (38.4)	
ASA	2	2	0.886‡
Obesity			0.446
• BMI<30kg/m^2	8 (88.9)	91 (72.8)	
• BMI≥30 kg/m^2	1 (11.1)	34 (27.2)	
Neoadjuvant chemoradiotherapy			0.184+
• Yes	3 (33.3)	72 (57.6)	
• No	6 (66.7)	53 (42.4)	
Type of surgery			0.701+
• Laparoscopic	3 (33.3)	33 (26.4)	
• Open	6 (66.7)	92 (73.6)	
Type of procedure			0.315+
• APR	6 (66.7)	59 (47.2)	
• LAR	3 (33.3)	66 (52.8)	
Tumour site (mm) (level from anal verge)	44.7±46.6	54.8±38.2	0.171‡
Tumour location			1.000+
• Anterior	1 (14.3)	18 (24)	
• Others	6 (85.7)	57 (76)	

Values are given as median, mean±SD or n(%). APR, abdominoperineal resection; ASA, American Society of Anesthesiology; BMI, body mass index; CRM, circumferential margin; LAR, low anterior resection. *Student's t-test. +Fisher's exact test. ‡Mann–Whitney U-test

The study demonstrated a significant association between CRM positivity and tumour size > 5.9 cm (P= 0.002), a distance of < 2.6 cm from the dentate line (P= 0.013), incomplete TME (P< 0.001) and a greater number of positive lymph nodes (P= 0.046; Table 3). In addition, the presence of an incomplete mesorectum was three times higher in APR specimens compared with LAR specimens (9.8%vs2.9%); nevertheless, this finding did not reach statistical significance. There was a significant correlation between positive CRM and both microvascular invasion (P=0.010) and perineural invasion (P= 0.009), while no association was seen with tumour grade, mucin production, lymphatic invasion and the presence of signet ring cell (Table 4).

Table 2 Operative outcome

	CRM		
	Positive (n=9)	**Negative (n=125)**	**P-value**
Operative time (min)	214.4±71.3	203.7±70.5	0.575*
Operative blood loss (ml)	283.3±163.3	334.1±335.1	0.984*
Postoperative stage			0.020+,**
• Stage I	0	45 (36.3)	
• Stage II	3 (33.3)	28 (22.6)	
• Stage III	6 (66.7)	51 (41.1)	

Values are given as mean±SD or n(%). CRM, circumferential margin. *Mann–WhitneyU-test. +Log likelihood ratio test. **Statistically significant.

Discussion

The study has shown a significant association for CRM positivity in rectal cancer specimens with tumour size (P= 0.002), distance of the tumour from the dentate line (P= 0.013), presence of lymph node metastasis (P= 0.046), microvascular invasion (P= 0.009), perineural invasion (P<0.001) and an incomplete mesorectum (P= 0.018). Well-performed TMEs with a resection margin at the mesorectal plane had a lower CRM positivity rate than did specimens in which an incomplete TME had been performed (10, 11).

Table 3 Pathological parameter and tumour staging

	CRM		
	Positive (n=9)	**Negative (n=125)**	**P-value**
T stage			0.005*,**
• T1	0	15 (12)	
• T2	0	42 (33.6)	
• T3	9 (100)	68 (54.4)	
Nodal stage			0.046*,**
• N0	3 (33.3)	72 (57.6)	
• N1	2 (22.2)	40 (32)	
• N2	4 (44.4)	13 (10.4)	
Tumour size (mm)	59.2±22.6	34.7±19.6	0.002+,**
Number of harvested lymph nodes	27.9±13.4	21.6±3.6	0.108+
TRG (Dworak)			1.000‡
• Grade 1–2	1 (33.3)	29 (40)	
• Grade 3–5	2 (66.7)	43 (60)	
TME quality			< 0.001‡,**
• Complete	3 (33.3)	98 (94.5)	
• Incomplete	6 (66.7)	6 (5.5)	

Table 3 Pathological parameter and tumour staging (continued)

	CRM		
	Positive (n=9)	**Negative (n=125)**	**P-value**
Tumour distance from dentate line			0.013‡,**
• ≤26 mm	6 (66.7)	28 (24.3)	
• > 26 mm	3 (33.3)	87 (75.7)	

Values are given as mean±SD or n(%). CRM, circumferential margin; TME, total mesorectal excision; TRG, tumour regression grade. *Log-likelihood ratio test. +Mann-Whitney U-test. ‡Fisher's exact test. **Statistically significant.

The reported incidence of CRM positivity between mid and low rectal cancer varies from 8% to 41% (5, 12, 13). Our finding of an overall CRM involvement of 6% appeared to be low when compared with other published rates. Such a difference could perhaps be explained by the different methodology and⁄or study design, including neoadjuvant regimen, the exclusion of T4 lesions, as well as surgical approach. The fact that all surgery in our study was performed by highly experienced specialized colorectal surgeons might be an important factor contributing to this better outcome. Similarly to other studies (5, 12, 14), a significant correlation between CRM positivity and tumour location ≤2.6 cm from the dentate line (P=0.014) was also demonstrated. Moreover, we found that CRM involvement was twice as common in the APR group as in the LAR group (66.7% vs 33%). Similarly, other studies have found higher CRM positivity and intra-operative perforation rates in patients who underwent APR compared with patients who underwent LAR (5, 12, 14–17). Guillou et al. (17) performed a multicenter randomized controlled trial in 794 patients with colorectal cancer in 27 UK centres. Overall, rectal cancer patients who underwent APR demonstrated a two-fold increased incidence of CRM involvement when compared with patients who underwent anterior resection (20 (23%) of 75 vs17 (10%) of 193). From a multicentre study of 1036 rectal cancer patients, Tekkis et al. (16) found that those who underwent APR showed significantly higher CRM positivity compared with patients who had anterior

resection (16.7% vs 7.5%, P< 0.001). The authors concluded that surgical technique with wide perineal dissection and the use of neoadjuvant therapy may reduce CRM involvement in patients with rectal cancer following APR. It is therefore also notable that there were no tumour perforations and a CRM positivity rate of only 10.8% achieved in the supine modified lithotomy position. These findings are in sharp contrast to the reports by Holm, West and Quirke, who propose that such low CRM positivity rates can only be achieved in the prone jack-knife position. However, Lavery and coworkers have recently refuted this claim, citing findings similar to those results reported in the current study (18). Nagtegaal et al. (6) suggested that the main causes of CRM positivity may be related to suboptimal surgical technique and to the special anatomy of the lower rectum and anal canal. This is characterized by a reduction in the volume of mesorectal tissue when following the mesorectal plane to the anorectal junction. This fact may be responsible for less extrarectal tissue around a low-lying tumour, leading to an increase in the likelihood of CRM involvement and of intra-operative perforation (5). Similarly to the original Miles' procedure (19), extralevator APR has recently been introduced to reduce the rates of CRM involvement and intra-operative perforation found with 'standard' APR (20, 21). Extralevator APR, which was proposed by Holm et al. (21)

Table 4 Histological characteristics

	CRM		
	Positive (n=9)	**Negative (n=125)**	**P-value**
Tumour grade			0.620*
• Low grade	6 (75)	93 (83.8)	
• High grade	2 (25)	18 (16.2)	
Mucin			0.168*
• Positive	3 (33.3)	18 (15.3)	
• Negative	6 (66.7)	100 (84.7)	
Lymphatic invasion			0.178*
• Positive	3 (37.5)	22 (17.9)	
• Negative	5 (62.5)	101 (82.1)	
Microvascular invasion			0.009*,**
• Positive	6 (66.7)	28 (22.8)	
• Negative	3 (33.3)	95 (77.2)	
Signet ring cell			0.174*
• Positive	1 (12.5)	2 (1.6)	
• Negative	7 (87.5)	121 (98.4)	
Perineural invasion			< 0.001*,**
• Positive	6 (66.7)	15 (12.2)	
• Negative	3 (33.3)	108 (87.8)	

Values are given as mean±SD or n(%). CRM, circumferential margin. *Fisher's exact test. **Statistically significant.

in 2007, demonstrated the important modification of not dissecting the mesorectum from the levator muscle. It is recommended that the rectum should be mobilized from the abdomen until the seminal vesicles in men and upper vagina in women. For better exposure and visualization, the authors preferred a prone jack-knife position for the perineal part of the operation. The dissection was continued just outside the subcutaneous portion of the external anal sphincter; the levator muscle was then identified. The dissection was continued along the outer surface of the levator muscles proximally until the insertion onto the pelvic side wall. Furthermore, the coccyx excision should be done to facilitate visualization of the posterior pelvis previously dissected through the abdomen. More recently, West et al. (20) confirmed that extralevator APR in the prone position removes more tissue around the tumor and leads to a reduction in circumferential resection margin involvement and intraoperative perforations. This concept has, however, been challenged by authors who practice meticulous standard APR surgery with outcomes equivalent to those following anterior resection (22, 23).

Several tumour-related factors have been correlated with CRM positivity. Advanced TNM stage had an obvious relationship with a higher possibility of CRM involvement (2, 10, 15, 16, 24–26). Other than direct tumour extension, involvement of the CRM may occur as a result of the presence of metastatic lymph node, foci of microvascular invasion or tumour budding.

Our results demonstrated a significant correlation between a positive CRM and an increased number of involved lymph nodes (P=0.031); however, the depth of tumour invasion (T stage) did not impact CRM involvement. This finding might be explained by the exclusion of T4 lesions and careful patient selection for neoadjuvant therapy. Larger tumours, and lesions with an ulcerative or a stenosing growth pattern, correlated with a higher likelihood of a positive CRM (24). The present study demonstrated a significant association between tumours larger than 5.9 cm and CRM involvement (P= 0.002).

In the current study, microvascular (P= 0.009) and perineural (P< 0.001) invasion were significantly related to an involved CRM. Similar findings have been previously reported in other studies (27, 28). In addition, many authors showed that a positive CRM is significantly associated with an infiltrating margin [2] and poor histological differentiation (2, 27, 28). Ueno et al. (27) showed that poor differentiation in submucosal transanal biopsies was predictive for CRM involvement (OR = 10.8; 95% CI, 1.7–67.1), as was microvascular invasion (OR = 16.1; 95% CI, 1.9–139.2).

We acknowledge that this study had low statistical power owing to the low numbers of CRM events. Moreover, because it was a retrospective study, some preoperative factors, such as pre-neoadjuvant tumour characteristics, which might be directly related to CRM positivity, were not analysed. Despite these limitations, we were able to identify tumour-related factors associated with a positive CRM, which could potentially impact on surgical planning for the achievement of a negative CRM and consequently improve patients' outcomes.

Despite the limitation of the low number of patients with a positive CRM, significant associations between CRM positivity and tumour size > 5.9 cm, a distance £2.6 cm from the dentate line, incomplete TME, number of positive nodes, and microvascular and perineural invasion were identified. The incidence of a positive CRM did not differ significantly between LAR and APR; however, an incomplete mesorectum was more commonly seen following APR, suggesting an inadequate plane of dissection with this technique. Furthermore, an overall CRM positivity rate of 6.8% has been achieved with routine use of the modified lithotomy position.

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Chapter 5: Technique to avoid postsurgical complication

Overview

It has been criticized for the necessity of high ligation of inferior mesenteric vessels and splenic flexure take down during rectal resection with anastomosis. The direct experience working in tertiary referral center had brought up the question of how to avoid this difficult to treat postoperative complication, anastomosis stricture. The detail of this published data can guide the colorectal surgeons to carefully consider these additional steps to prevent re-surgery. The tips can certainly be applied to rectal cancer patients for uneventful recovery and better quality of live.

Colorectal Anastomotic Stricture: Is it associated with inadequate Colonic Mobilization?

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BACKGROUND: Anastomotic stricture or stenosis is a well described complication of intestinal anastomosis. The incidence of stricture after colorectal anastomosis ranges from 0 to 30 %. The aim of this study was to identify possible factors related to postoperative colorectal anastomotic stricture and to indicate reoperative surgery outcomes. METHODS: After institutional review board approval, medical records were reviewed for patients who underwent surgery for colorectal anastomotic stricture at Cleveland Clinic Florida between January 2001 and December 2010. The main outcome measures were demographics, indications for initial surgery, body mass index, comorbidities, previous treatment, level of anastomosis, history of radiotherapy, and operative data for the reoperative surgery. RESULTS: Nineteen patients (15 males) were eligible for the study. Nine patients had a diagnosis of cancer, 7 of whom received radiotherapy. The initial surgeries were low anterior resection (n=9; 47.4 %), high anterior resection (n=9;

47.4 %), and sigmoidectomy (n=1; 5.2 %). Six patients (31.6 %) had anastomotic leak after initial surgery. The majority of the patients (n=17; 89.5 %) had an intact splenic flexure, inferior mesenteric artery, and inferior mesenteric vein. In all patients, full mobilization of the splenic flexure and high ligation of the mesenteric vessels was performed. Seven patients (36 %) developed postoperative complications. Over a mean follow-up of 24.3 months, there was no recurrence of anastomotic stricture. CONCLUSIONS: An intact splenic flexure and mesenteric vessels were the most prevalent in patients who underwent reoperation at our institution. Full mobilization of the splenic flexure, high ligation of the mesenteric vessels, anastomotic stricture resection, and re-anastomosis can be successfully performed with satisfactory outcomes.

The incidence of stricture after colorectal anastomosis ranges from 0 to 30 %, although only 5 % of patients become symptomatic (1–11). The heterogeneous surgical indications, types of surgical and anastomotic procedures, and definitions of anastomotic stricture may explain the wide range in incidence. Although strictures are thought to be related to various factors, including radiation (12), anastomotic ischemia or leak (13, 14), or technique (7, 15, 16), there is a lack of adequate information regarding the etiology of stricture formation and its risk factors. The aim of this study was to identify possible factors related to postoperative colorectal anastomotic stricture and reoperative surgery outcomes.

Methods

The medical records of all patients who underwent surgical resection for a colorectal anastomotic stricture at Cleveland Clinic Florida between January 2001 and December 2010 were reviewed after institutional review board (IRB) approval. Anastomotic stricture was defined as the inability to freely pass a 12-mm sigmoidoscope through the anastomosis in a patient with symptoms including left iliac fossa pain when passing stool and/or gas, abdominal distention, fractionated evacuation, constipation, and/or when thin stools were noted. Other causes of anastomotic stricture such as malignancy, inflammatory bowel disease, and diverticulitis were excluded. Patient demographics, indications for initial surgery, body mass index (BMI), comorbidities, previous treatments for anastomotic stricture, distance of anastomosis from the dentate line, history of radiotherapy, operative data, and functional outcomes were collected. Obesity was defined as BMI $\geq$ 30 kg/m^2 (17).

Surgical technique

All patients without ileostomies underwent mechanical colonic preparation. Antibiotic prophylaxis was administered within 1 h prior to the incision. Intraoperative bilateral ureteric catheters were utilized in all cases.

The proximal colon was mobilized by freeing the left colon and splenic flexure from the peritoneal attachments and dividing the inferior mesenteric artery (IMA) at its origin from the aorta and the inferior mesenteric vein (IMV) at the lower border of the pancreas. The strictured anastomosis was resected, and a redo tension-free colorectal anastomosis was performed using double-stapled technique or hand-sewn coloanal anastomosis. A 33-mm circular stapler was routinely used to perform stapled anastomosis. Subsequent intraoperative endoscopic assessment of the anastomosis was routinely performed to ensure continuity of the anastomosis, mucosal viability, and

anastomotic hemostasis. If not already presented, temporary loop ileostomy was performed in patients in whom the anastomosis was created within 4 cm from the anal verge.

Results

Nineteen patients, including 15 males and 4 females of a mean age of 59 years (SD 11.6; range 29–78 years), were treated for postoperative anastomotic stricture. Seventeen (89.5 %) patients had the initial surgery performed at other hospitals and were subsequently referred to our institution for treatment. The majority were non-smokers (n=8; 42.1 %) or ex-smokers (n=8; 42.1 %); and 3 (15.8 %) were smokers. The mean BMI was 26.5 kg/m^2 (SD 4.4; range 13.5–34.2 kg/m^2). Four patients (21.1 %) were obese. Twelve patients (63.2 %) had comorbidities, including cardiac problems (n=5; 41.7 %), hypertension (n=4; 33.3 %), diabetes (n=2; 16.7 %), and renal problems (n=1; 8.3 %). The mean American Society of Anesthesiologists (ASA) score was 2.

Initial surgery

The indications for the index surgery were rectal cancer (n=9; 47.4 %), diverticulitis (n=9; 47.4 %), and a gunshot wound (n=1; 5.2 %). Among the patients with rectal cancer, 7 (77.8 %) underwent radiotherapy, 4 (57.1 %) preoperatively, and 3 (42.9 %) postoperatively. The initial procedures included low anterior resection (n=9; 47.4 %), high anterior resection (n=9; 47.4 %), and sigmoidectomy (n=1; 5.2 %). Seventeen of the surgeries were performed by open laparotomy, 1 by laparoscopy, and 1 hand-assisted. None of the 19 operative reports included specific information about high IMA and IMV ligation or splenic flexure mobilization. The mean distance of the anastomosis from the dentate line was 11.9 cm (SD 7.5; range 0–25 cm). Most of the original anastomoses

were located within 20 cm from the dentate line. Only 1 patient who underwent sigmoidectomy for acute diverticulitis had an anastomosis 25 cm from the dentate line. There were 6 anastomotic leaks, 3 of which were successfully treated with bowel rest, percutaneous drainage, total parenteral nutrition, and intravenous antibiotics. Fecal diversion was required in the other 3 patients. Attempts at endoscopic balloon dilations of the strictured anastomosis were performed in 7 patients (36.8 %), resulting in 1 perforation of a strictured anastomosis 6 cm cephalad to the dentate line. One patient failed multiple anastomotic dilatations using Hegar dilators.

Reoperative surgery

The mean time to the reoperative surgery was 14.3 months (SD 10.9; range 4–48 months). The procedures included anterior resection in 18 patients (94.7 %) and abdominoperineal resection (APR) in 1 patient (5.3 %). The latter operation was performed in a rectal cancer patient who had initially undergone a low anterior resection and postoperative radiotherapy. A nonfunctioning fibrotic anal sphincter together with a severe anastomotic stricture precluded restorative surgery. Sixteen anastomoses were performed using the double-stapled technique, while hand-sewn coloanal anastomosis was undertaken in 2 patients. The mean distance of the new anastomosis was 4.5 cm from the dentate line. In 17 patients (89.5 %), neither the splenic flexure nor the IMA or IMV had been mobilized and divided at the time of the index procedures. Only 2 patients (12.5 %) with rectal cancer had the splenic flexure mobilized along with the high division of the mesenteric vessels. The levels of these anastomoses were at 4 and 5 cm from the dentate line, respectively. Colonic J-pouches were fashioned in 5 patients. The mean operative time was 232.8 min (SD 68.3; range 50–360 min), and the mean operative blood loss was 250 mL (SD 70; range 100–1,500 mL). A temporary loop ileostomy was performed in 11 patients (57.9 %). No intraoperative complications occurred.

Postoperative complications were observed in 7 patients (36.8 %), including wound infection, wound dehiscence, pulmonary embolism, urinary retention, pneumonia, ileus, and myocardial infarction. There were no anastomotic complications or mortality. The mean hospital stay was 12.1 days (SD 8.5; range 4–34 days). The mean time until loop ileostomy reversal was 3.6 months. No recurrent stricture occurred at a mean follow-up of 24.3 months, and all 18 patients were continent; 2 patients reported urgency (11.1 %), and 4 patients (22.2 %) had more than 3 bowel movements per day.

Discussion

Despite the unclear pathophysiology of anastomotic stricture (1, 12), multiple techniques have been used for its management, including staplers and cutting devices (18), steroid injections (19), the combined use of electrocautery and photoablation (20–22), manual or instrumental dilatation using a balloon, bougie, or pneumatic dilator (23–28), and surgical resection and re-anastomosis (12, 29). Similar to other reported studies (12, 29), our study demonstrated that the rectum was the most common site of stricture. In this study, the most common treatment prior to surgical intervention was endoscopic balloon dilatation (7 of the 19 patients; 36.8 %). This simple rapid procedure, with a reported success rate of 75 % (23–25, 30), may be adequate for a short anastomotic stricture (23, 25). However, if more than 3 sessions are required, this method is likely to result in poor bowel function (24).

Resection of the stricture site and re-anastomosis are usually performed for long segment strictures, following anastomotic leak, radiation therapy, or failure of other methods (12, 29, 31). To perform an anastomosis following a distal colorectal resection, it is important to have sufficient length of proximal colon to avoid tension at the suture line. The current case series found that 17 of the 19 patients (89.5 %) with anastomotic stricture had an intact splenic flexure as well as inferior mesenteric vessels. These

findings represented the single most important factors related to anastomotic stricture. Tension-free anastomosis is facilitated by freeing the left colon and splenic flexure from the peritoneal attachments, and dividing the IMA and IMV.

Maximal length can be obtained by dividing the IMA at its origin from the aorta, rather than below the origin of the left colic artery, together with the division of the IMV at the lower border of the pancreas. This ‘‘high tie’’ leaves the colon proximal to the anastomosis reliant on the marginal artery and shifts the blood supply from the inferior mesenteric axis to the superior mesenteric axis. However, some authors have suggested a ‘‘low tie’’ technique, in which the division of IMA is performed below the origin of the left colic artery to gain better blood supply to the colon proximal to anastomosis (32). In addition, there has been little evidence to support any oncological or survival benefit among cancer patients from more radical lymph node clearance using the ‘‘high tie’’ technique (33–35).

Hall et al. (36) measured tissue oxygen tension proximal to the resection margin before and after either low or high division of the IMA in 62 patients who underwent elective colorectal resections. Oxygen tension improved when the transverse and descending colon were used for anastomosis but diminished for sigmoid anastomosis. Changes in oxygenation were significantly affected by the location of the proximal resection site but not by choice of high or low tie. The results suggested that the sigmoid colon is not suitable for anastomosis; however, the middle colic artery via the marginal artery can maintain a viable blood supply to a pelvic anastomosis when the transverse or descending colon is used. The authors concluded that the sigmoid colon should be sacrificed and there should be no hesitation in performing a high tie and routine splenic flexure mobilization for maximal length to avoid tension in low pelvic anastomosis. This finding has been confirmed by other authors (37, 38).

Arguments have arisen as to whether the IMA should be divided during operations performed for benign disease and, if so, at which level. In a prospective study of elective laparoscopic sigmoidectomy for diverticular disease, Ambrosetti et al. (11) found that arterial preservation did not prevent anastomotic stricture. Eleven of the 55 patients (20 %) whose IMA was preserved had anastomotic stenosis compared with 1 of the 13 patients (7.7 %) whose IMA was not preserved. Similar findings have been also described by other authors (18, 39, 40).

This study demonstrated that redo-operation with resection of the previous anastomosis and colorectal/coloanal anastomosis is feasible and safe. Even though the operations tend to be difficult because they are redo procedures and because of increased operative times, blood loss, and length of hospital stay, acceptable rates of complications and postoperative recovery confirmed the feasibility and safety of the procedure.

Other risk factors for anastomotic stricture, including anastomotic dehiscence, pelvic sepsis, ischemia, inflammatory bowel disease and radiotherapy, have been reported (8, 12, 41). In our study, 6 of the 19 patients had a clinical anastomotic leak after initial surgery, and 31.6 % of these leaks resulted in subsequent stricture. One of the main factors associated with anastomotic dehiscence is how far distal the anastomosis is. The more distal the anastomosis, the higher is the risk of dehiscence. We observed 11.9 cm as the mean distance from the anastomosis to the dentate line. We also found that the majority of patients who had anastomotic stricture were male (79 %). This finding is perhaps related to the more technical challenge of performing the anastomosis in the deep narrow male pelvis. In addition, 7 of the 9 rectal cancer patients (77.8 %) underwent either preoperative or postoperative radiotherapy. Four of the 19 patients (21.1 %) were obese.

Furthermore, Law et al. (42) and Rullier et al. (43) demonstrated a higher leak rate following stapled anastomosis compared to hand-sewn. They attributed this to the difficulty of the cases undergoing stapled astomosis. However, a systematic review of nine randomized controlled trials could not find any significant difference in leak rates between the two groups (44).

This study is limited by a small sample size. In addition, some preoperative factors that might be directly related to anastomotic stricture, such as incomplete doughnuts (12) and anastomotic technique (16), could not be analyzed due to the fact that all the collected data were based solely on the review of medical records.

Conclusions

A correlation seems to exist between failure to mobilize the splenic flexure as well as failure to divide the IMA and IMV and colorectal anastomotic stricture. Full mobilization of the splenic flexure with high division of the IMA and IMV together with resection of the stenosis and re-anastomosis can be successfully performed with satisfactory outcomes to treat colorectal anastomotic stricture.

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Chapter 6: Protocols for rapid recovery

Overview

All the surgeons are currently facing surgical correctable health issues among elderly population. Colorectal surgeons are also challenged by cancer diagnosed in elderly patients. This published review will be helpful in the decision making, patient selection and to consider physical age rather than chronological age for adequate plan for treatment. Furthermore, the review in management of postoperative ileus in the elderly will facilitate the uneventful and rapid recovery for this group of patients.

Epidemiology, Pathophysiology and Medical Management of Postoperative Ileus in the Elderly.

(Drugs Aging. 2011; 28(2):107-18)

As the population of the Western world ages, the number of major surgical procedures performed in the elderly population will by necessity increase. Within virtually every surgical specialty, studies have shown that patients should not be denied surgery on the basis of chronological age alone. It has recently been recognized that physiological age is far more important within the decision-making algorithm as to whether or not to proceed with major surgery in the septuagenarian and octogenarian populations and beyond. Not unexpectedly, not only the results of these operations, but also the associated morbidities, are similar in older and younger populations. Therefore, it is not surprising that postoperative ileus (POI) affects patients of all ages. POI is a multifactorial condition that is exacerbated by opioid analgesics, bed rest and other conditions that may be rather prevalent in the postoperative elderly patient. Therefore, as major surgical interventions are considered in this population, appropriate

assessment and, ideally, correction of any physiological disturbances should be undertaken along with implementation of standardized enhanced recovery protocols. Ideally, through this combined approach, an appreciable impact can be made on reducing POI while controlling postoperative pain and limiting postoperative thromboembolic, cardiopulmonary, cerebral and infectious complications. This article reviews the potential impact of pharmacological agents, laparoscopy and other maneuvers on POI in the elderly.

Introduction

The 20th century has been characterized by the steepest rise in the world's population and the sharpest increase in human life span ever seen. Life expectancy in developed countries for the last 100 years has almost doubled and now ranges from 76 to 80 years (1, 2). Every year in France, life expectancy increases by 3 months (3). It has been recognized that chronological age does not necessarily correlate with physiological aging; thus, the assignment of terms such as 'elderly' or 'old' to all patients aged $\geq$ 65 years during workup and evaluation should be more flexible and dependent on criteria other than chronological age. The most widely used system divides these individuals into the 'young-old' (aged 65–74 years), the 'old-old' (aged 75–84 years), and the 'oldest-old' (aged $\geq$ 85 years) (4).

In 2000, those aged $\geq$ 65 years comprised 35 million people (or 12%of the US population) (5). Within this group, 18.5 million people (53%) were young-old, 12.3 million (35%) were old-old and 4.2 million (12%) were oldest-old. Among these three groups, the oldest-old group is the fastest growing population. Further aging is predicted to increase the population aged $\geq$ 65 years from 35 million in 2000 to 40 million in 2010 (a 14%increase) and then to 55 million in 2020 (a 38%increase for that decade). It is predicted that by 2030 the population of people aged $\geq$ 65 years will reach 72 million,

which is almost twice the number in 2007 (6). In Finland, the percentage of people aged ≥ 65 years by the end of the 20th century was 12%and is projected to double by 2030 (7). The current healthcare system would need to deal with results similar to the demographic phenomenon that happened after World War II, called the 'baby boom' generation. There is a cohort of 74 million people born in the years 1946–64 currently reaching age 45–63 years in the US alone (8).

Change of Surgical Dogma Regarding Age as a Relative Contraindication to Surgery

The aging of the population has forced a significant trend towards an increase in hospitalizations for all groups of the elderly, with many varied and often challenging problems (9-14). New medical sub-specializations with geriatric research interests are emerging in all medical fields, such as geriatric oncology and geriatric anesthesiology (3, 15, 16). It is common knowledge that more than 50% of all cancers are diagnosed in the population of patients aged ≥ 70 years (17). The growth in the proportion of patients with cancer in older age groups has been accompanied by a constant increase in the volume of elderly patients in surgical oncology. A recent study from Portland, Oregon, USA, showed that nearly one third of colon cancers in the state of Oregon are diagnosed in patients aged > 80 years (18). Most of these cancers are surgically managed and tumour eradication is required with minimal denial of surgery on the basis of patients' age. Advances in anesthesia, intensive care and perioperative care unit support have significantly decreased the surgical threshold, which in turn allows acceptance of the older population not only for emergent (7, 19) but also for elective surgical procedures (20).

Despite reports of more frequent multi-morbidity in patients aged >75 years and a higher rate of postoperative complications (21-24), there is a general consensus that

advanced age is in itself not a contraindication to colorectal surgery (24-29). It is not chronological age but rather co-morbidities that define the outcomes of surgery (30-33). Several reports state that intraoperative complications are no more frequent in the older patient than in the younger patient (24, 34-36). A popular surgical aphorism is that ‘‘all postoperative complications begin in the operating room” (37). This applies equally to all specific postoperative complications, including ileus, transit disorders, wound healing, after-bleeds and anastomotic leakage (24, 34, 35). As a logical result of this, decisions about life-saving procedures, such as cancer surgery, and about procedures related to diseases with a major impact on patients’ quality of life, such as rectal prolapse, should not be influenced by patients’ chronological age but perhaps should be tailored to individual preoperative co-morbidities, particularly cardiopulmonary and respiratory diseases (21, 22, 24, 34, 36), which are the underlying basis for general postoperative morbidity.

Postoperative Ileus (POI) in the Elderly

With the great advances in medicine in the 20th century, the risks of infection, anastomotic complications, bleeding and thromboembolic events have been successfully reduced (38-41). By contrast, neither the incidence nor the clinical impacts of postoperative ileus (POI) have significantly changed as yet. This can be explained by the characteristics of POI, which is not life-threatening and somewhat unpreventable. However, its negative impact in terms of prolonging length of hospital stay has been estimated to cost $US1.46 billion annually in the US (year of costing 2002) (42). The difficulty in performing pharmacoeconomic analyses of treatment for POI stems from the absence of a clearly identified population by administrative datasets. Confusion arises when patients without any precipitating complication (primary POI) are grouped with patients who have precipitating complications (secondary POI) (43). As described by

Kehlet and Holte (44), POI is a temporary impairment of gastrointestinal tract function and motility, mostly found after abdominal surgery. This delay in the coordinated movements of the gastrointestinal tract is different to the inevitable response to surgical trauma, from which patients typically recover within 3–5 days after surgery (45). It is comprised of a combination of various signs such as abdominal distension, lack of bowel sounds, accumulation of gas and fluids in the bowel lumen and delayed passage of flatus and stool. The symptoms range from cramping and abdominal pain to nausea and vomiting.

POI has multifactorial etiologies and its pathophysiology is not yet completely understood. Correlation with the degree of surgical trauma, the site of surgical intervention, the patient's preoperative medical condition, the length of the operation, the stimulation of gut opioid receptors by endogenous and exogenous opioid analgesics, the presence of surgical infection and many other factors has been reported in animal models (46). Modern views on POI pathogenesis are based on studies that show that activation of the sympathetic nervous system (SNS) by surgical stress plays a significant role (45). Also significant is the release of inflammatory mediators and the immigration of leucocytes into the intestinal wall, both of which contribute to the paralysis of intestinal smooth muscle tissue (46, 47). Moreover, excess perioperative intravenous fluid can impair bowel motility as a consequence of edema of the intestinal wall (48).

Aging alone is associated with gradual loss of reserve capacity, even in the individual without co-morbidities (49). This also reduces the older patient's ability to tolerate stress (49). While the pathogenesis of POI is still unknown, there should be no difference in its pathogenesis between elderly and younger patients, regardless of reoperative co-morbidities. The level of stress arising from surgical trauma plays an important role in increasing or decreasing the incidence of POI. Hong et al. (50) and Asgeirsson et al. (51) demonstrated that laparoscopy reduces the risk of POI compared with laparotomy but does not eliminate the risk. Table I shows a trend for higher incidence of POI in elderly

patients. However, most reports are limited by the accuracy of clinical documentation, inconsistency of billing and coding, and definitional differences among clinicians (51). The elderly population in general is characterized by changes in several physiological parameters that may be responsible for a higher incidence of POI. With respect to renal function, it is known that older patients tend to have decreased filtration area of the glomerular basement membrane with a concomitant decrease in glomerular filtration rate of about 40–50%; decreased permeability of the basement membrane; decreased tubular function; and decreased urine concentration (17). Liver function is also affected, with a decrease in hepatic blood flow and decreased serum albumin concentration and cytochrome P450 enzyme function. In terms of cardiovascular function, there is a greater incidence of occlusive disease of coronary, carotid and vertebral arteries; a higher risk of myocardial infarction or stroke; more frequent peripheral vascular disease; a greater likelihood of abdominal or visceral aneurysm; and an increased prevalence of hypertension that requires more medical management. Pulmonary function in the elderly is characterized by less pulmonary reserve and a higher incidence of chronic obstructive pulmonary disease or lung malignancies. The elderly population also has a higher prevalence of risk factors and other comorbidities, such as past or current diabetes mellitus, tobacco use, alcoholism, malignancies, arthritis and orthopedic procedures. Finally, there is a greater risk of under-nutrition or malnutrition in this age group (17).

Table 1 Postoperative ileus (POI) following colorectal surgery

Study	n	Surgery type	Younger patients		Elderly patients	
			age (y)	POI (%)	age (y)	POI (%)
Scheidbach et al. (52) 2005.	49	lap	<75	0.8	≥75	1.8
Chautard et al. (53), 2008.	178	lap	<70	4.9	≥70	9.3
Person et al. (54]), 2008.	291	open	<65	7.9	≥65	7.8
	264	lap	<65	3.8	≥65	3.7
	86	conv	<65	6.6	≥65	16.0
Louis et al. (20), 2009.	157	lap+open	NA	NA	≥80	8.9
Lian et al. (55), 2010.	97	open	NA	NA	≥80	19.6
	97	lap	NA	NA	≥80	17.5

Note: conv=conversion (from laparoscopic to open surgery);lap=laparoscopy; NA=not applicable

Although there have been improvements in perioperative care during the last 3 decades, these have not dramatically affected the prognosis of elderly patients who require emergency surgery (56). Elective surgery, together with careful preoperative evaluation and correction, is preferred to limit the impact of naturally decreased functional reserve in each organ system after surgery. There is no universally accepted tool for the measurement of medical co-morbidities among elderly patients; scales vary between individual surgeons, groups and institutions (57). The most commonly used method is probably the American Society of Anesthesiologists (ASA) system of classifying preoperative risk. A recent report from Illinois, USA, also confirmed that emergency status and ASA class are useful predictors of perioperative morbidity, including POI (20).

Fast-Track and Enhanced Recovery Protocol

POI treatment has historically been of a mostly supportive, retroactive nature. The idea of a 'stress- and pain-free operation' was first introduced as the 'fast-track protocol' in the mid-1990s by Kehlet and Wilmore (58). The fast track protocol includes recommendations for preoperative, perioperative and postoperative care. Recommendations for preoperative care include counselling, feeding, administration of antibacterial, no bowel preparation, no pre-medication and fluid restriction (59). The recommended perioperative measures are high O2 concentrations, active prevention of hypothermia, epidural analgesia and minimally invasive surgery/transverse incisions. Recommendations for postoperative care include selective use of nasogastric (NG) tubes, avoidance of drains, enforced mobilization, enforced early oral feeding, avoidance of systemic use of opioids, use of standard laxatives and early removal of urinary catheters (59).

Gastrointestinal tract motility is controlled by three nervous systems (60): the parasympathetic nervous system (PNS) and the SNS (which together make up the extrinsic nervous system), and the intrinsic nervous system (45, 61). The PNS acts to increase intestinal motility, whereas activation of the SNS inhibits bowel function. POI is believed to be related to the longevity of a high sympathetic state activated by surgical stress (45, 62). Because the contraction and motility of the colonic cells are more dependent on the extrinsic nervous system (PNS and SNS), unlike the cells of the small intestine, a longer duration of high sympathetic outflow would prolong the duration of POI. In addition, the colon relies on the presence of material in the lumen to stimulate its function in the absence of the migrating motor complex, which is located specifically in the stomach and small bowel (45, 63). Routine preoperative fasting may further prolong recovery of the colon. Better understanding of the pathophysiological events occurring during and after surgery has made the fast-track protocol possible.

Early application of these principles showed a decrease in hospital stay after open colectomy in a group of patients (median age 71 years) to a median of 2 (range 2–6) days (64). Polle et al. (65) demonstrated that implementing a mean 7.4 of the 13 previously listed fast-track modalities resulted in a significant reduction in length of primary hospital stay in the fast-track group compared with the traditional-care group (4.5 vs 8 days, $p=0.02$) without any increase in morbidity. Gouvas et al. (59), in a meta-analysis published in 2009, evaluated 11 studies involving 1021 patients who were divided into a fast-track group (526 patients) and a standard-care group (495 patients). Results showed significantly shorter primary and total hospital stays and lower immediate postoperative morbidity rates for the fast-track group in comparison with the standard-care group (all $p<0.00001$). The analysis found no differences in readmission rates or mortality rates between the two groups. The investigators concluded that there is good evidence that fast-track programs should form the mainstay of patient care for elective colorectal surgery. Successful implementation of fast-track programs requires a joint effort by a committed well trained and experienced multidisciplinary team of anesthesiologists, surgeons, dieticians, physiotherapists, pharmacologists and appropriately trained and dedicated nurses, coupled with the understanding and compliance of the patient and his or her family as well (59). Characteristic bottlenecks may be encountered initially as surgical dogmas need to be debunked and new ideas, such as early rather than delayed mobilization, preoperative feeding instead of preoperative fasting, avoidance of NG tubes and drains, fluid restriction, and the introduction of laparoscopic surgery, are adopted (65).

Disbrow et al. (66) reported an interesting result of preoperative psychological suggestion that may impact postoperative outcome. These investigators demonstrated that patients given preoperative information on the early return of gastrointestinal activity had a significant decrease in the length of POI (2.6 vs 4.1 days) and earlier time to hospital discharge (6.5 vs 8.1 days), compared with patients not given this information.

Traditional use of NG tubes has been challenged in the past, with several reports failing to show the advantage of routine NG tube insertion (67, 68). Use of an NG tube did not shorten the time to first bowel movement or effective oral intake; furthermore, routine use of an NG tube was associated with more episodes of fever, atelectasis and pneumonia as well as slower return to oral intake. Although patients who were not treated with an NG tube had an increased incidence of abdominal bloating and vomiting, no overall increase in postoperative complications was seen. Similarly, the traditional belief that early ambulation may stimulate gastrointestinal tract motility has not been proven in studies. Conversely, early ambulation has indisputably been shown to help prevent atelectasis, pneumonia and deep venous thrombosis (69).

Restrictive fluid administration aimed at maintaining normovolemia provides adequate organ perfusion, whereas overloaded fluid administration may adversely affect perioperative organ function, e.g. by causing intestinal edema that might prolong the duration of POI (especially if the fluid excess involves a large volume of saline) and delay recovery (70-72). A fast-track protocol has implications for perioperative fluid management because patients are allowed to eat and drink freely immediately after the operation, thus minimizing use of postoperative intravenous fluid administration. A recent randomized, controlled, double-blind trial conducted in Denmark found that the restrictive fluid regimen of fast-track surgery led to improvements in pulmonary function and postoperative hypoxaemia, whereas no differences in POI, exercise capacity or other recovery measures were found (73).

Minimally invasive surgery and laparoscopy play significant roles in decreasing the incidence, length and severity of POI. It is thought that laparoscopic surgery is associated with decreased surgical trauma with better preservation of immune function, decreased inflammatory responses and decreased pain and catabolism compared with open surgery (58, 73-75). These benefits are manifested by a decreased incidence of POI, faster recovery and increased patient satisfaction. The 2005 Cochrane review of the

short-term benefits of laparoscopic colorectal resection concluded that the intensity of postoperative pain (evaluated by a visual analogue scale) was lower and that the mean duration of POI was 0.9 days shorter after laparoscopic colorectal resection than after open surgery (76). These authors also found that postoperative pulmonary function (forced vital capacity) improved more rapidly after a laparoscopic approach.

Laparoscopy has also proven its benefits in high-risk patients, defined by Marks et al. (77) as being aged >80 years, morbidly obese (body mass index >30 kg/m^2), having an elevated ASA class of 3 or 4, or having a history of previous radiation. Their experience of 190 high-risk patients (median age 66 years) showed that laparoscopic colorectal resection, in the hand of experienced surgeons, could be performed safely and result in decreased morbidity and shorter hospital stay than open surgery. These investigators suggested that increased age, morbid obesity, high ASA class or preoperative radiation should not be contraindications to laparoscopic colorectal surgery. Data from a prospective, observational, multicentre study of patients aged <75 or $\geq$75 years undergoing open or laparoscopic colectomy in 105 hospitals in Germany, Austria, Switzerland and Italy showed a highly statistically significant difference between the two age groups for virtually all of the individual complications and mortality with no significant difference in complications directly associated with the procedure necessitating re-operation (bleeding, anastomotic leak, POI) (52). The investigators noted that the use of age as a consideration for laparoscopic surgery should be individualized. They also concluded that the surgeon should consider preferential use of laparoscopy in colorectal surgery because of the advantages of the laparoscopic approach with regard to the postoperative course.

Fast-Track Protocol in Geriatric Patients

In addition to the ordinary fast-track protocol, a modified geriatric fast-track program is a reasonable option for the provision of elderly-oriented surgical care. Such a program needs to include additional points of care in relation to postoperative delirium, which can be present in up to 53%of elderly post-surgical patients (78). On this point, it is interesting to note that between 32% and 96% of patients with new onset symptoms of delirium leave the hospital without resolution of these symptoms, which may take weeks or months to resolve (78). The traditional fast-track philosophy of providing a quick guided tour around the hospital has particular benefit in the geriatric-modified protocol. A preoperative tour of the medical facility to familiarize the older patient with his or her future ward, floor and building might be potentially helpful in decreasing the incidence and severity of postoperative delirium. Gurlit and Mollmann (79) listed the following environmental risks that contribute to the development of delirium in elderly surgical patients: confusion associated with an overnight stay in a new place; noisy situations; absence of reading glasses, hearing aids and clocks/watches; introduction of new medications; use of psychoactive drugs to induce sleep at night; scheduling of diagnostic interventions at mealtimes; and sleep deprivation (79).

Demeure and Fain (78) have suggested several valuable recommendations for decreasing delirium manifestations in the elderly population after surgery. These include early return of hearing aids and eyeglasses as soon as patients are able to use them; provision of large-dial clocks, menus and newspapers with large print; allowing a family member to stay with the patient or having the patient bring familiar articles, such as framed photographs, from the home into the hospital room; facilitating access to radio and other audio/ video modalities that the patient is comfortable with; providing room lighting that matches the normal daily rhythm of waking and sleeping hours; and minimization, as much as possible, of night-time disturbances of sleep, such as hall noises and the waking of patients to measure routine vital signs (78).

A combination of all these measures should decrease the level of postoperative cognitive dysfunction, which is described as a cognitive impairment of executive functions (concentration/processing speed/self-monitoring), learning, memory, visuospatial abstraction, language comprehension and verbal memory (80-82). The available evidence shows that older adults have longerlasting cognitive impairment after major surgeries and that postsurgical cognitive impairment may herald greater mortality (80-82).

Co-management of older surgical patients by surgeons and other doctors specializing in hospital medicine (hospitalists) is one way of establishing the initial fast-track team (83). Providing a designated geriatric nurse who can become a 'constant companion', a well-known face amongst all the patient's hospital relationships, is a very helpful measure in optimizing surgical care (79). Kehlet and Wilmore (84) described an algorithm for the initiation and implementation of an enhanced postoperative recovery program that starts with a simple interest in the program. The algorithm consists of several steps and emphasizes the importance of team meetings, writing and discussing protocols and developing care plans.

Pharmacological Treatment of POI

Successful pharmacological treatment of POI has been a long-awaited dream for surgeons. The desire for a single 'magic pill' that would eliminate the frustration of ileus in postoperative recovery resulted in the trial of various pharmacological agents (85). However, since POI is multifactorial, it is somewhat unrealistic to expect total elimination of the condition with one medication. Nevertheless, the combination of a fast-track protocol with a dedicated team and a clinical pharmacologist may result in some benefit.

The Cochrane systematic review published in 2008 analyzed data from 39 randomized, controlled trials involving 4615 patients who underwent major abdominal

surgery, major abdominal-vascular surgery or major abdominal urological and gynecological surgery (48). The main endpoint of the review was to evaluate the effects of systemic prokinetic pharmacological treatments for POI. The authors evaluated the following medications that were commonly used to treat POI: cholinergic receptor agonists (bethanechol chloride, neostigmine), benzamides (cisapride, metoclopramide, bromopride), dopamine receptor antagonists (domperidone), peptide hormones (cholecystokinin, ceruletide, vasopressin), Beta-adrenoceptor antagonists (propranolol), macrolide antibacterial (erythromycin), ergotamine derivates (dihydroergotamine mesilate), systemic administration of local anesthetics, prostaglandins, vitamins (calcium pantothenate [pantothenic acid], dexpanthenol) and selective gastrointestinal opioid receptor antagonists. However, with the exception of two u-opioid receptor antagonists, none of these medications are US FDA approved for the treatment of POI. In addition, in 2000, cisapride was withdrawn from the medical market in many countries, including the US, because of serious cardiac events.

The review found that the prokinetic activities of erythromycin, cholecystokinin, cisapride, dopamine receptor antagonists, propranolol and vasopressin are not effective in the treatment of POI (48). Although intravenous lidocaine (lignocaine) and neostigmine might be beneficial, further well designed studies are required to provide proof.

Opioids are widely used in postoperative pain management. Their pain control mechanism is realized though Mu-opioid receptors in the CNS. The same Mu-opioid receptors are also present in the gastrointestinal tract and activation of these peripherally located receptors impairs bowel motility. Peripheral selective gastrointestinal opioid receptor antagonists that can block these receptors without reversing the central analgesic effects of Mu-opioid receptor agonists would be a desirable mechanism of POI-reducing medications.

A more specific Cochrane systematic review of Mu-opioid receptor antagonists for opioid-induced bowel dysfunction included 23 studies involving 2,871 patients (86). The authors reviewed the effects of alvimopan (nine studies), methylnaltrexone bromide (six studies), naloxone (seven studies) and nalbuphine (one study). Meta-analysis of these anti-POI medications included combined endpoints such as time to flatus/bowel movement, time to flatus/bowel movement/solid food and time to solid food/bowel movement. The results showed that methylnaltrexone bromide and alvimopan were both superior to placebo at reversing opioid-induced increased gastrointestinal transit time and constipation, and that alvimopan appears to be safe and efficacious in treating POI. The review also found that the incidence of adverse events with opioid receptor antagonists was similar to that with placebo and that these events were generally reported as mild or moderate. The authors concluded that although alvimopan and methylnaltrexone bromide have shown promise in the treatment of constipation as well as POI, further data are required to fully assess the place of these medications in therapy.

Alvimopan

Alvimopan is the first FDA-approved drug (in May 2008) that has been proven to accelerate the time to upper and lower gastrointestinal recovery following partial large or small bowel resection surgery with primary anastomosis in the US (87). Alvimopan antagonizes the peripheral effects of opioids on gastrointestinal motility and secretion by competitively binding to gastrointestinal tract Mu-opioid receptors (88). In clinical trials, alvimopan did not reverse opioid analgesia, as measured by visual analogue scale pain intensity scores and/or the amount of postoperative opioids administered. Alvimopan is an antagonist of cloned human Mu-opioid receptors (Ki [inhibition constant] 0.4 nmol/L [0.2 ng/mL]) with a median time to reach maximum plasma concentration of 2 hours, a bioavailability of ~6%, 65% biliary and 35% renal excretion, a mean terminal half-life of

10–17 hours and no measurable opioid-receptor agonist effects in standard pharmacological assays (88).

Alvimopan is currently approved only for short-term use in hospitalized patients. Only hospitals that have registered with the manufacturer and have met all of the requirements for the Entereg^{R} Access Support and Education (EASE^{TM}) program may use alvimopan at this time. The recommended adult dosage of alvimopan is 12 mg administered 30 minutes to 5 hours prior to surgery followed by 12 mg twice daily beginning the day after surgery for a maximum of 7 days or until discharge (88). Patients should not receive more than 15 doses during their hospital stay. Alvimopan is contraindicated in patients who have taken therapeutic doses of opioids for more than 7 consecutive days immediately prior to taking alvimopan (89). Alvimopan is not recommended for use in patients with severe hepatic impairment or end-stage renal disease, or in patients undergoing surgery for correction of complete bowel obstruction.

Table 2 Laboratory tests for healthy patients undergoing major surgery at Cleveland Clinic Florida

Age (y)	Laboratory test	
	Men	Women
<40	Hct or Hgb	Hct or Hgb
	T&S	T&S
40–49	Hct or Hgb	Hct or Hgb
	T&S	T&S
	ECG	
50–64	Hct or Hgb	Hct or Hgb
	T&S	T&S
	ECG	ECG
65–74	Hct or Hgb	Hct or Hgb
	T&S	T&S
	ECG	ECG
	BUN or Cr	BUN or Cr
≥75	Hct or Hgb	Hct or Hgb
	T&S	T&S
	ECG	ECG
	BUN or Cr	BUN or Cr
	Glucose	Glucose
	CXR	CXR

BUN=blood urea nitrogen; Cr=creatinine; CXR=chest x-ray; Hct=hematocrit; Hgb=hemoglobin; T&S=type and screen.

Methylnaltrexone Bromide

Currently, methylnaltrexone bromide is approved by the FDA as a subcutaneous formulation for the treatment of opioid-induced bowel dysfunction (constipation) as part of palliative care for patients with advanced illnesses such as incurable cancer, AIDS or

end-stage heart or lung disease, for methadone users, and for patients with chronic pain (88). Use of methylnaltrexone bromide has never been specifically assessed in the geriatric population.

Gum Chewing

Vagal cholinergic tone in the gastrointestinal tract can be simply and effectively stimulated by gum chewing (90, 91). This type of sham feeding also elicits the release of gastrin, pancreatic polypeptide and neurotensin, all of which affect gastrointestinal motility (90, 91). A systematic review and meta-analysis that evaluated 437 patients from nine eligible trials demonstrated that chewing sugarless gum following elective intestinal resection is associated with improved outcomes (a lower incidence of POI) (92). Asao et al. (93) conducted a randomized, prospective study of gum chewing as a method to stimulate bowel motility after laparoscopic colectomy for colorectal cancer. These investigators found that the passage of first flatus was a mean 1.1 days earlier in the gum-chewing group than in the control group (occurring on day 2.1 vs 3.2, respectively). The time to first defecation was also significantly earlier in the gum-chewing patients than in controls (on postoperative day 3 vs 5.8, respectively). However, the mean length of hospital stay was not significantly different between the two groups (13.5 vs 14.5 days, respectively) (93).

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended by enhanced recovery protocols after elective colorectal surgery (94). The opioid-sparing and anti-inflammatory properties of NSAIDs are attractive in the postoperative setting. NSAIDs can be considered as alternative analgesia to avoid undesirable effects of opioid, such

as constipation, sedation, and respiratory depression. Their anti-inflammatory properties may also be valuable for accelerating the recovery of bowel function by inhibiting the synthesis of prostaglandins and reducing neuromuscular dysfunction (95). On the other hand, the use of NSAIDs after colorectal surgery is controversial. Their nephrotoxic properties increase the risk of acute kidney injury, which is associated with increased 1-year mortality after noncardiac surgery (96). They may also be associated with an increased risk of anastomotic leak according to some observational studies (97, 98).

NSAIDs exert their anti-inflammatory effects through inhibition of COX-1 and COX-2, subsequently leading to inhibition of prostaglandins. This is relevant in the days after surgery, where the effects of ileus are probably mediated by a cascade of mast cells, macrophages, and inflammatory cytokines involving the bowel muscularis (95).Previous research has shown that this inflammatory response is safely mitigated using pharmacological and nonpharmacological interventions, and, in doing so, the return of GI function can be accelerated (99). On this notion, NSAIDs may represent a cost-effective and accessible intervention to improve GI recovery while also providing effective postoperative analgesia.

TZP-101

TZP-101 is a selective, small molecule ghrelin agonist in clinical development as a treatment for gastric dysmotility disorders. Ghrelin is the natural ligand for growth hormone secretagogue receptors (GHSR-1a), and both ghrelin and GHSR-1a are colocalized in the proximal gastrointestinal tract (100). The ghrelin receptor pathway mediates multiple gastrointestinal functions, including motility, gastric emptying, and induction of migrating motor complexes (MMCs) (101). Compared with ghrelin, TZP-101 has enhanced metabolic stability and high affinity (Ki22 nM) for the human type 1a GHSR, (102) and shows prokinetic activity in animal models of POI (103, 104) and in

patients with gastroparesis (105). While all TZP-101 doses decreased the time to recovery of first bowel movement (or time to first toleration of solid food), the most notable effects were consistently in the 480g/kg dose group. These results were supported by the secondary gastrointestinal recovery end points such as time to first flatus, time to toleration of solid food, and time to eligibility for discharge, which were all statistically significant at that dose. For these reasons, 480g/kg was identified as the most effective dose (106).

Patient Evaluation and Enhanced Recovery Protocol at Cleveland Clinic Florida

Healthy surgical patients treated at Cleveland Clinic Florida (Weston, FL, USA) undergo individualized preoperative evaluations depending on their chronological age and co-morbidities (table II). The adjusted enhanced recovery protocol used at Cleveland Clinic Florida is shown in table III.

Conclusions

As the population of developed countries ages, a wider acceptance of people aged >65 years for surgical procedures has become routine. Studies show that chronological age is no longer a limiting factor for surgical treatment. This shift of surgical dogma has potentially led to the increase in the incidence of POI associated with major surgery. POI is a multifactorial condition, requiring prophylaxis at every step in the preoperative, perioperative and postoperative periods. Assessment and correction of physiological disturbances in older patients with implementation of enhanced recovery protocols may lead to significant reductions in POI and pain levels, as well as decreases in cardiopulmonary, thromboembolic, infectious and cerebral/cognitive complications. Laparoscopy has shown significant benefits in this elderly population. In addition, there are new pharmacological agents with proven effects in relation to shortening the duration of POI, although not specifically in the geriatric population.

Table 3: Enhanced recovery protocol for patients undergoing colorectal surgery at Cleveland Clinic Florida

Operative period	Visit/perioperative day	Activity
Preoperative	Initial office visit	-Discussion of aspects of surgery, potential risks, complications and alternatives. Description of the range of required preoperative tests (internal medicine or cardiology clearance, blood work, etc.) -Giving out handouts to patients defining expectations of early ambulation, return of bowel function, projected discharge criteria. -Giving out handouts to patients listing medications to avoid prior to surgery to prevent intra- or postoperative bleeding. -If a stoma is considered a possibility, education by dedicated stoma nurses regarding care andmanagement; preoperative marking.
Perioperative	0	-Subcutaneous heparin (5000 units); pneumatic stockings.

		-May receive spinal anesthesia. -Oro/nasogastric tube removed at extubation.
Postoperative	1	-Enforced early postoperative mobilization (5 laps in the hallway, approximately 100 m). -Clear liquid diet, ice chips -Subcutaneous heparin (5000 units every 8 hours during hospital stay); pneumatic stockings. -Incentive spirometry exercises (to prevent respiratory problems).
	2	-Awaiting flatus or bowel movement. -Removal of dressing. -Removal of bladder catheter.
	3	-If flatus or bowel movement present, advance to full liquid diet. -Hep-Lock intravenous fluids. -Discontinue patient-controlled analgesia pump. -Oral pain medication.
	4	-Advance to low-residue diet unless distended. -Anticipate discharge home

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Chapter 7: Closure of the ileostomy

Overview

This chapter will broaden the understanding of the indications, clinical course and potential complication for temporary loop ileostomy after mid to low rectal cancer surgery and its reversal. The critical knowledge explained by the published data is essential in the comprehensive care of rectal cancer patients.

Loop ileostomy Closure after Laparoscopic vs. Open Surgery: Is There a Difference?

(Surg Endosc. 2013 ;27(1):90-4)

BACKGROUND: Temporary loop ileostomy is commonly performed to protect the distal anastomosis during both open and laparoscopic colectomies. This study aimed to evaluate the impact of initial open and laparoscopic colorectal resection on the outcomes of ileostomy closure. METHODS: After institutional review board approval, all patients who underwent loop ileostomy closure from January 2008 to July 2012 were identified. The patients' demographics, diagnosis, American Society of Anesthesiology (ASA) classification, type of resection, approach (laparoscopic [LS] or open [OS] surgery), use of antiadhesion barrier, and ileostomy closure outcomes were obtained from a chart review. The outcomes of ileostomy closure after LS and OS colorectal resections were compared using Chi-square for categorical variables and Student's t test for continuous variables. RESULTS: The study identified 351 patients with a mean age of 51 years: 145 patients (41.2 %) in the LS group and 206 patients (58.8 %) in the OS group. The most common procedures performed were total proctocolectomy with ileal J pouch anal anastomosis (109 patients: 49 LS, 60 OS) and restorative proctectomy (99 patients: 34 LS, 65 OS). At the time of ileostomy closure,

the patients in the LS group had a significantly shorter mean operative time (LS 60.9 vs OS 82.6 min; p<0.001) and a shorter hospital stay (LS 4.9 vs OS 5.8 days; p=0.042). The overall complication rate was 20.1 % (70 patients), and the rate in the OS group was significantly higher (p=0.028). The most common complications were postoperative ileus (41 patients: 13 LS vs 28 OS) and enterocutaneous fistula (5 patients, all in the OS group). CONCLUSIONS: Loop ileostomy closure after laparoscopic colorectal surgery is associated with a significantly shorter operative time and hospital stay as well as a lower rate of postoperative complications. Superior outcomes after loop ileostomy closure lend further support to the use of laparoscopy.

Temporary loop ileostomy is commonly performed in colorectal surgery to attenuate the potential adverse sequelae of anastomotic leakage (1–6) after construction of a distal pelvic anastomosis during both open and laparoscopic proctectomies. Subsequent reversal of loop ileostomy to restore bowel continuity and to improve patients' quality of life generally is undertaken 12 weeks after the index surgery.

However, although loop ileostomy closure is a potentially simple and relatively safe procedure (7), it is not always completely innocuous. Besides dehydration and electrolyte abnormality secondary to high stomal output, the difficulty during creation and closure of loop ileostomy may lead to serious complications (8–10). A recent review of 26 studies by Kaidar-Person et al. (11) reported rates of small bowel obstruction (0–15 %), wound infection (0–18.3 %), anastomotic leak (0–8 %), and enterocutaneous fistula (0.5–7 %) resulting from ileostomy closure after both open and laparoscopic surgeries.

The technical difficulty during stoma closure is strongly related to the degree of adhesion formed around the ileostomy site. To date, no good evidence exists to demonstrate the differences in degree of adhesion formation after laparoscopic versus open colorectal surgery (12, 13). A recent report from the Conventional versus Laparoscopic Assisted Surgery in Colorectal Cancer (CLASICC) trial (14) on adhesion-induced intestinal obstruction

showed no differences between these two approaches. This study aimed to evaluate the impact of initial open and laparoscopic colorectal resection on the outcomes of ileostomy closure.

Patients and methods

After institutional review board approval, all patients who had undergone loop ileostomy closure at Cleveland Clinic Florida between January 2008 and July 2010 were identified from a prospectively collected colorectal surgery database. The exclusion criteria for the study ruled out patients who had undergone reversal as part of multiple procedures and patients who had experienced intraabdominal complications after their initial surgeries. The patients' demographics including age, gender, diagnosis, American Society of Anesthesiologists (ASA) classification, type of previous surgical procedure (laparoscopic [LS] or open [OS] surgery), use of anti-adhesion barrier (Seprafilm; Genzyme Corp., Cambridge, MA, USA), and ileostomy closure outcomes were obtained from a chart review.

For the patients who received an anti-adhesion barrier (Seprafilm), the barrier was applied under the midline incision and around the stoma. The perioperative outcomes of ileostomy closure after LS and OS colorectal resections were compared using Chi-square for categorical variables and Student's t test for continuous variables. A p-value lower than 0.05 was considered statistically significant. Postoperative ileus was defined as more than three episodes of emesis in 24 h and a return to nothing by mouth or to insertion of an nasogastric tube (15). Enterocutaneous fistula was defined as enteric drainage emanating from the incision wound without a sign of sepsis or generalized peritonitis (16).

Surgical technique

After radiographic and endoscopic confirmation of adequate anastomotic healing, all the patients were scheduled for loop ileostomy reversal. The choice of an open or laparoscopic approach and the use of Seprafilm at the index operation were at the preference of the surgeon.

A parastomal incision was performed, and the loop ileostomy was dissected from the surrounding subcutaneous tissues, rectus fascia, and peritoneum. Adequate length of small bowel was mobilized from intraabdominal adhesions. Wound extension was undertaken as necessary, and conversion to a midline incision was required if small bowel mobilization could not be achieved safely through the parastomal incision. Careful inspection together with betadine irrigation into each small bowel limb then was performed to assess for any possible seromuscular injuries. Standard stapled side-to-side bowel closure technique was used as previously described [17]. Absorbable subcuticular purse-string suture was performed, and loose betadinesoaked gauze packing was applied to the surgical site after fascial closure. Prophylactic antibiotics were continued for 24 h postoperatively.

Statistical analysis

Statistical analyses were performed using Fisher's exact test, a likelihood ratio Chi-square test, or Student's t test as appropriate. Allpvalues lower 0.05 were considered statistically significant.

Results

The study identified 351 patients (160 males, 191 females) with a median age of 51 years (range, 14–89 years): 145 (41.2 %) in the LS group and 206 (58.8 %) in the OS group.

The groups had comparable demographics as follows: median body mass index (BMI) (LS: 24.4 kg/m^2; range, 15.3–48.9 kg/m^2 vs OS: 25.0 kg/m^2; range, 14.1–96.5 kg/m^2), ASA classification (91 % ASA 2), nature of diagnosis (malignant or benign), and number of patients who received preoperative radiotherapy (36 LS [81.8 %] vs 54 OS [84.3 %]). The time from the original surgery to the reversal of ileostomy was significantly longer in the OS group (18.1±8.4 weeks) than in the LS group (16.1± 4.6 weeks) (p=0.005). Table1 shows the demographic characteristics of the patients in both groups.

The most common procedures performed were restorative proctocolectomy with ileal J pouch anal anastomosis (109 patients [31 %]: 49 LS patients [33.8 %] vs 60 OS patients [29.1 %], nonsignificant difference) followed by restorative proctectomy with colonic J pouch anal anastomosis (99 patients [28 %]: 34 LS patients [23.4 %] vs 65 OS patients [31.6 %], nonsignificant difference). The two groups did not differ significantly in the use of an antiadhesion barrier (Seprafilm) around the ileostomy (4 LS vs 16 OS).

At the time of ileostomy closure, the patients in the LS group had a significantly shorter mean operative time (LS 60.9±22.1 vs OS 82.6±61.8 min; p<0.001) and hospital stay (LS 4.9±3.8 vs OS 5.8±4.8 days; p=0.042). The intraoperative blood loss was minimal in all cases.

Table 1 Demographic data

	LS (n=145) n(%)	OS (n=206) n(%)	p Value
Median age: years (range)	**50 (14–89)**	**52 (16–85)**	**0.064**
Gender			**0.110**
• **Male**	**60 (40)**	**100 (48.5)**	
• **Female**	**90 (60)**	**106 (51.5)**	
Median BMI: kg/m^2 (range)	**24.4 (15.3–48.9)**	**25.0 (14.1–96.5)**	**0.352**
ASA			**0.737**
• **1**	**10 (6.7)**	**18 (8.7)**	
• **2**	**138 (92)**	**186 (90.3)**	
• **3**	**2 (1.3)**	**2 (1)**	
• **4**	**0**	**0**	
Diagnosis			**0.703**
• **Benign**	**101 (41.6)**	**142 (57.3)**	
• **Malignant**	**44 (40.7)**	**64 (59.3)**	
Preoperative radiotherapy	**36 (81.8)**	**54 (84.3)**	**0.73**
Mean time to ileostomy reversal (weeks)	**16.1±4.6**	**18.1±8.4**	**0.005**

LS laparoscopic surgery, OS open surgery, BMI body mass index, ASA, American Society of Anesthesiology

Conversion to a midline incision was performed for one patient (0.7 %) in the LS group compared with five patients (2.4 %) in the OS group. Table 2lists the surgery-related information.

The overall complication rate was 20.1 % (70 patients), and the LS group had a lower complication rate (14.5 %) than the OS group (24.5 %) (p=0.028). The most common

complications were postoperative ileus (41 patients: 13 LS patients [9 %] vs 28 OS patients [13.6 %]), urinary

Table 2 Operative outcomes

	LS (n=145) n(%)	OS (n=206) n(%)	p Value
Procedure			**0.259**
• **RPC/IPAA**	**49 (33.8)**	**60 (29.1)**	
• **RP/CPAA**	**34 (23.4)**	**65 (31.6)**	
• **Others**	**62 (42.8)**	**81 (39.3)**	
Mean operative time (min)	**60.9±22.1**	**82.6±61.8**	**<0.001**
Conversion to midline incision	**1(0.7)**	**5(2.4)**	**0.407**
Anti-adhesion barrier (Seprafilm)	**4 (2.8)**	**11 (7.6)**	**0.063**
Mean hospital stay (days)	**4.9±3.8**	**5.8±4.8**	**0.042**

LS laparoscopic surgery, OS open surgery, RPC/IPAA restorative proctocolectomy with ileal J pouch anal anastomosis, RP/CPAA restorative proctectomy with colonic J pouch anal anastomosis

retention (6 patients: 2 LS patients [1.4 %] vs 4 OS patients [1.9 %]), and enterocutaneous fistula (ECF) (5 patients [2.4 %], all in the OS group).

Two of the patients with ECF also had intraabdominal collections, which were successfully drained percutaneously under radiologic guidance. No isolated surgery site infection, postoperative adhesion-induced intestinal obstruction, or postoperative mortality was identified. All complications were treated conservatively without the need for surgical intervention. Table 3 lists the postoperative complications in both groups.

Discussion

Although closure of loop ileostomy may be considered a simple and minor procedure, it has been associated with a morbidity rate reaching 33 %, with a significant adverse impact on patient outcomes (18).

Table 3 Complications

	LS (n=145) n(%)	OS (n=206) n(%)	p Value
Overall complications	**21 (14.5)**	**49 (24)**	**0.028**
Postoperative ileus	**13**	**28**	
ECF	**0**	**5**	
Wound dehiscence	**0**	**1**	
Urinary retention	**2**	**4**	
Pulmonary complications	**1**	**2**	
Cardiac complications	**1**	**0**	
Others	**4**	**9**	

LS laparoscopic surgery, OS open surgery, ECF enterocutaneous fistula

The amount of adhesion formation around the ileostomy is associated with different degrees of technical difficulty. Extensive adhesiolysis may lead to a variety of intraoperative complications such as seromyotomy and enterotomy, as well as postoperative complications including ileus, obstruction, and fistula.

In the current study, the overall complication rate was 20.1 %, including surgical complications such as postop erative ileus (11.7 %), ECF (1.4 %), and wound dehiscence

(1.4 %). These findings are comparable with complication rates reported in the literature (8–11).

Seprafilm is a sodium hyaluronate/carboxymethylcellulose absorbable barrier used to prevent adhesion formation in intraabdominal procedures. Salum et al. (19) reported interesting results from a multicenter trial comparing patients who received Seprafilm at the time of loop ileostomy construction with patients who did not. Seprafilm significantly decreased adhesion formation around the stoma but not operative time, intraoperative morbidities including myotomy and enterotomy, or postoperative complications.

Laparoscopic surgery may be associated with less adhesion formation than open surgery, but the results in the literature are contradictory. The current study showed a significantly shorter operative time for ileostomy closure in patients who underwent prior laparoscopic surgery compared with open procedures. This fact may reflect less difficulty with mobilization due to fewer and far less dense adhesions, leading to significantly fewer postoperative complications and a shorter hospital stay. The threefold greater chance of a midline conversion and the 2.4 % ECF rate found only in the open group also suggest increased technical difficulty and likely a higher degree of more dense adhesions among these patients.

A recent case-control study reported by Li, et al. (20) comparing the stoma-related morbidity between the ileostomy closure < 3 months post formation and $\geq$ 3 months post formation. A total of 358 patients were analyzed (179 patients in each group). No difference was observed in estimated blood loss (EBL), operative time (OT) and length of stay (LOS) (all $p > 0.05$). Postoperative outcomes including wound infection, post-operative bleeding, intra-abdominal abscess, ileus, small bowel obstruction (SBO), anastomotic leak, reoperation, surgery related readmission, postoperative transfusion were also similar among the groups ($p > 0.05$).

The omission of a temporary ileostomy is proposed to limit the need for hospital admission, avoid potential sphincter atrophy during the period of diversion, and avoid the complications of ileostomy closure. Additionally, in the case of ileal pouch surgery, a defunctioning ileostomy may theoretically compromise blood flow to the distal small bowel, thus increasing the risk of pouch ischemia (21). However, these potential benefits must be balanced with consequences of anastomosis leakage such as significant short- and long-term morbidity, a reduced quality of life, poor subsequent bowel function, increased risk of cancer recurrence, and increased mortality (22–25).

A metaanalysis performed by Chow et al. (26) demonstrated that the consequences of stoma reversal often are underestimated. These authors also recommended that patients be selected carefully for defunctioning ileostomy and that they be counseled before the original surgery to spare the potential morbidity of stoma reversal. In addition to poor surgical technique with tension in the anastomosis (27), male gender, malnutrition, preoperative weight loss, cardiovascular disease, steroid use, preoperative vascular disease, preoperative alcohol abuse, perioperative blood transfusion, advanced age, obesity, previous radiation, and low anastomosis closer to the anus are known factors that may increase the risk of anastomosis leakage (5, 22, 28–34).

The limitation of this study was its retrospective design. As such, conversion to a midline incision and strict parameters for stoma-site incision enlargement were not analyzed. Similarly, no objective assessment of the extent or density of adhesions was undertaken. Furthermore, the choice of surgical access, open or laparoscopic, and the use of Seprafilm were at the discretion and preference of the surgeon. Despite these limitations, our results indicate that closure of loop ileostomy after open colectomy is technically more challenging than laparoscopic procedures secondary to adhesion formation. Surgeons should be aware of the significant existing morbidities associated with diverting ileostomy and provide appropriate patient counseling before the reversal, particularly after an open procedure.

Conclusion

Loop ileostomy closure after laparoscopic colorectal surgery is associated with a significantly shorter operative time and hospital stay, as well as with lower rates of postoperative complications than open surgery. Superior outcomes after loop ileostomy closure lend further support to the use of laparoscopy.

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Chapter 8: Treatment of common stomal complication

Overview

This chapter involves the proposed minimally invasive treatment for the most common stomal complication that can be diagnosed in low rectal cancer patient with extensive anal sphincters involvement and underwent abdominoperineal resection. This also includes other detail about the risk of developing parastomal hernia on each type of the stoma, and alternative procedure to overcome the complication.

Laparoscopic Parastoma Hernia Repair, Multi-media Article.

(Dis Colon Rectum 2010; 53(9):1334-6)

Parastomal hernia is a common complication after stoma formation. Its reported incidence varies from 30% to 50%. Loop ileostomy has the lowest risk (0%– 6.2%), followed by end ileostomy, and loop colostomy with a similar risk of 28% to 30%. End colostomy carries the highest risk for parastomal hernia of 48%. Even though most hernias occur within the first 2 years after stoma construction, the risk of herniation extends up to 20 years. Theoretically, parastomal hernia occurs as a result of mechanical factors, an intrinsic defect in collagen metabolism, and wound repair. Parastomal hernia is asymptomatic most of the time, but it may be associated with serious complications such as strangulation and perforation; hence, elective repair is mandatory for carefully selected cases and surgical approaches. Primary closure of the aponeurosis at the hernia site, either via peristomal approach or through midline incision, is a simple procedure, but it carries a recurrence rate of 38% to 100%. Stoma relocation may result in a zero recurrence rate at the same hernia site, but the risk of a parastomal hernia after new stoma formation is still expected. In addition, an

incisional hernia at the previous colostomy site closure may also occur. Similar to other sites of hernia repair, prosthetic mesh has been used to reinforce the hernia defect intraperitoneally through open incision and recently via the laparoscopic approach. Mesh repair has demonstrated the lowest risk of recurrence for parastomal hernia of 0% to 33%.

Parastomal hernia is a common complication after stoma formation, with an incidence varying from 30% to 50% (1– 8). The risk depends on the type of stoma; loop ileostomy has the lowest risk (0%– 6.2%), followed by end ileostomy, loop colostomy (28%–30%), and end colostomy (48%) (2). Most parastomal hernias occur within the first 2 years after stoma construction, but the risk of herniation extends up to 20 years (9, 10). Etiological factors include mechanical stress, an intrinsic defect in collagen metabolism, and wound repair (2, 11). Although parastomal hernias are mostly asymptomatic (3, 7), serious complications such as strangulation and perforation (2) may occasionally occur. Therefore, elective repair should be considered if the hernia is symptomatic, in particular, when there is an impending risk of complications occurring. Different surgical approaches for repair of parastomal hernias have been described. Direct primary closure of the aponeurosis at the hernia site via either peristomal or midline incision carries a reported recurrence rate of 38% to 100% (7). Stoma relocation does not remove the risk of parastomal hernia developing at the new stoma site, and incisional hernias may also develop at the previous stoma closure site. Other techniques have been explored because of these recurrences, which may be related to biological disease rather than simple mechanical rupture (12–14), as well as to the increased morbidity associated with recurrent repairs (15–17). In the repair of other types of hernia, prosthetic mesh has been used to reinforce the defect intraperitoneally (18–21); placed through an open incision, or more recently by a laparoscopic approach (22, 23). When mesh was used for repair of parastomal hernias with an open approach, a relatively low recurrence rate of 0% to 33% was reported (22). This dynamic article presents a novel technique in

which the parastomal hernia is repaired laparoscopically with the use of prosthetic mesh. A relatively large parastomal hernia is demonstrated to show the technique more clearly, but obviously this method can be applied effectively to the more common smaller parastomal hernias.

Technique and Results

We have used this technique in 3 patients with parastomal hernias after abdominoperineal resection for anorectal cancer. Abdominoperineal resection had been performed with a lower midline incision in 1 patient and laparoscopically in the other 2, all after neoadjuvant chemoradiotherapy. These were 2 men with a median age of 75 (range, 62– 83) years. All parastomal hernias were located on one side of the stoma. A PROCEED (laminated oxidized regenerated cellulose fabric and polypropylene; Ethicon, Livingston, Scotland, UK) mesh was trimmed to cover the defect with 5 cm of overlap (Fig.1).

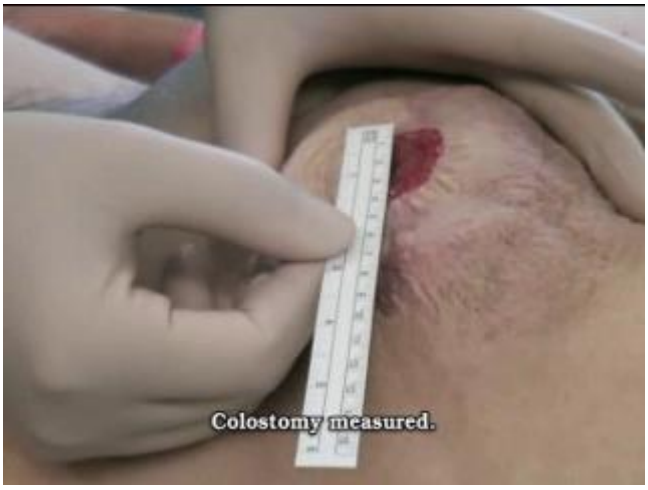

Figure 1 The parastomal hernia was measured. Mesh size was calculated.

A slit was made at one edge leading to a circle measured to fit around the stoma. The slit was aligned to cover the peritoneal surface where the stoma was attached, away from the parastomal hernia. After placement of the mesh, which included passing the slit around the colostomy so that the latter fitted into the cut circle (Fig. 2), the dome-shaped anterior

abdominal wall naturally allowed the edges of the mesh slit to overlap adequately for securing with laparoscopic tacks (Fig.3). These steps are shown in the video (see Video, Supplemental Digital Content 1, http://links. lww.com/DCR/A40).

Figure 2 Mesh positioning using 2/0 Prolene brought out to the hernia apex.

Figure 3 Laparoscopic tacks were used to secure the mesh to the abdominal wall.

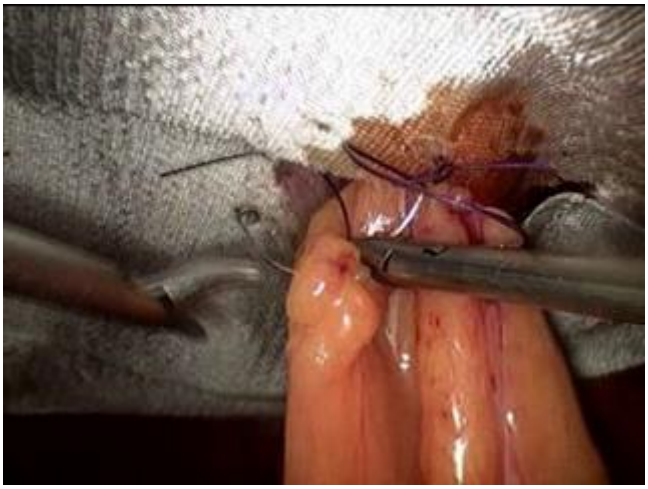

Figure 4 Laparoscopic stitches were put to ensure the adequate repair of the hernia.

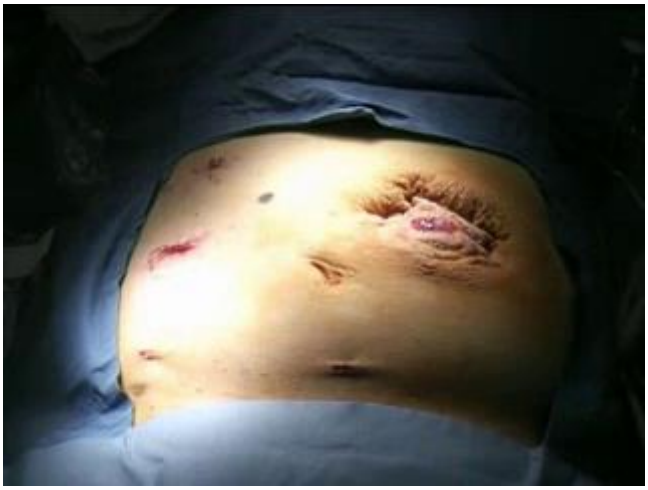

Figure 5 The mesh was successfully placed

The prolene stitch used to position the mesh for laparoscopic tacking actually anchored the center of the mesh to the apex of the hernia defect and, when tied in, helped in securing the position of the mesh (Fig. 4). The small skin incision overlying the knot was closed with an absorbable suture (Fig. 5). The median operating time was 43 (range, 32– 60) minutes and blood loss was 50 (range, 30– 70) mL. All of the patients tolerated a full diet on the 2nd postoperative day and were discharged 1 day later with minimal analgesic requirements. At a median 12 (range, 8–16) months follow-up, none of the patients had any complications,

stoma application problems, or recurrences (Fig. 6). In particular, the skin redundancy over the mesh repair seen in the demonstration was asymptomatic, did not affect stoma management, and had improved further at the latest follow-up.

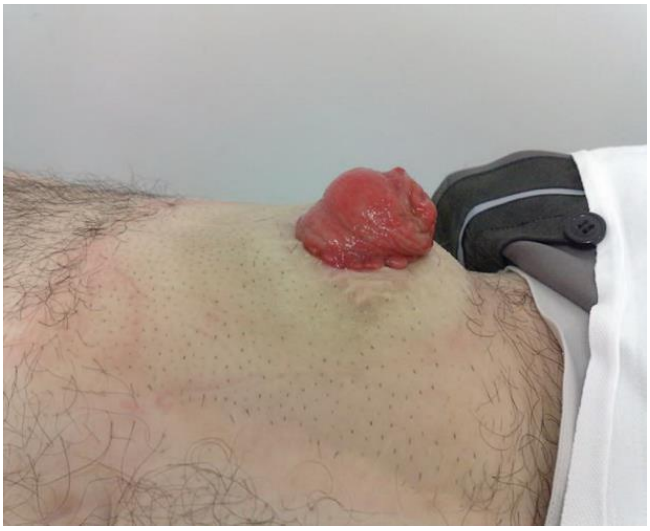

Figure 6 At 6 months' follow-up after laparoscopic parastomal hernia repair.

Discussion

A laparoscopic prosthetic mesh parastomal hernia repair technique was presented. The advantages of the laparoscopic method for mesh repair of nonparastomal ventral hernias include reduced analgesic requirements, reduced length of hospital stay, minimized abdominal wall trauma, and more rapid recovery. Decreased rates of wound and mesh infections have been reported previously (24). Uniquely for parastomal hernias, an important theoretical consideration, as addressed by our techniques, would be to avoid an incision close to the stoma where bowel contents could potentially seep through the wound onto the underlying mesh with predictably disastrous results. Some controversy has arisen from the available experience in open parastomal hernia mesh repair (25–28). A slit prosthetic mesh to accommodate the bowel exiting at the stoma has been reported to fail with the slit widening over time (25). A nonslit prosthetic mesh technique has been described where the bowel wall is first secured against the lateral abdominal wall and the mesh is then placed to

cover the remaining defect (26). In our technique, the laparoscopic tacking of the overlapping slit edges, which were also placed away from the hernia site, would potentially address this issue. Separation between the stoma and the surrounding key hole prosthesis is another cause of concern for recurrence. We placed intracorporeal sutures to attach the mesh to the bowel serosa to address this possible problem (27). Although nonabsorbable prosthetic mesh such as polypropylene has been reported to result in pain, obstruction, and erosion (28), this has not occurred in any of our patients, possibly because our technique tailored the size of the mesh aperture to provide a correct fit around the stoma.

To prevent mesh-related complications, such as fistula formation, adhesions, septic complications, and seroma formation, optimal mesh selection should be considered (28). For the intraperitoneal onlay mesh technique, the mesh surface facing the abdominal wall should be nonabsorbable material, inducing tissue response and allowing for integration of the mesh within the abdominal wall. The mesh surface facing abdominal contents also should be nonreactive material, causing a low or negligible inflammatory response, so that adhesions and subsequent erosion, septic complications, and fistulas do not develop (29).

Conclusion

The advantages of laparoscopic surgery can be applied to parastomal hernia repair with encouraging early results (27). We demonstrated a method using mesh to address the various technical issues involved. It would be appropriate to consider randomized controlled trials with long-term follow-up to assess the optimal surgical management of parastomal hernias.

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Chapter 9: Conclusion, outcomes and future research directions

Total mesorectal excision (TME) (1) has brought the revolution and the improvement of outcomes measured in both oncologic and functional outcomes that includes bowel, urinary, and sexual function. It has developed to become a standard procedure for rectal cancer surgery. However, to achieve a complete TME specimen, surgeons around the world have searched and studied to find the optimal tools and/or techniques to overcome the challenge in difficult dissection along the natural curve of human pelvis.

Laparoscopy in the management of rectal cancer has gained popularity. Multiple randomized trials (2, 3) have shown the equivalent in short-term outcomes and perioperative morbidity and mortality of laparoscopic proctectomy as compared to open surgery. Long-term oncologic outcomes also reported to be comparable between laparoscopic rectal cancer surgery and conventional open surgery (3-5). However, laparoscopic rectal cancer surgery remained a challenge with higher conversion rates (6). Technical challenge of poor ergonomic, coning and fulcrum effect was reported as the limitations of the procedure. Proctectomy can be even more difficult to work in the deep pelvis with in-line rigid instruments from angles that require complicated maneuvers to reach the extremes of the pelvis. On the other hand, 2 recent randomized trials failed to demonstrate noninferiority of laparoscopic rectal surgery to open surgery for oncologically successful resection in regard to circumferential and distal resection margins and total mesorectal excision (TME) completeness (7, 8). It is possible that modification of instruments or a different platform such as robotics will improve efficacy of minimally invasive techniques (8). Several authors (9-11) reported 3D high definition vision, wrist-like movement of instruments (endowrist^{TM}), stable camera holding, motion filter for tremor-free surgery and improved ergonomics as major improvements in rectal surgery. Robotic rectal cancer surgery has been reported to

be feasible, safe and providing short-term outcomes comparable to conventional laparoscopic surgery (12, 13). Robotic surgery for rectal cancer is expected to have superiority in terms of oncologic and functional aspects theoretically because of the potential for meticulous TME dissection and nerve preservation (14, 15). Kim J., *et al.* recently demonstrated comparable long-term survival to laparoscopic TME. In addition, the authors also showed that robotic rectal surgery was a good prognostic factor for overall survival and cancer-specific survival, suggesting potential oncologic benefits. However, it seems that these expensive technological benefits have not reflected superiority in clinical outcomes. The preliminary results of an ongoing randomized control trial; “Robotic vs. Laparoscopic Resection for Rectal Cancer: The ROLARR Trial”, presented by Pigazzi A. at the American Society of Colon and Rectal Surgeons, Annual Meeting in 2015 including 471 rectal cancer patients (237 patients; robotic surgery, 234 patients; laparoscopic surgery) from 29 hospitals in 10 countries. The results showed no statistically significant advantages to robotic TME regarding to number of nodes, quality of TME specimens, involvement of circumferential margins and 30 day morbidity. The study also failed to demonstrate any statistically significant advantage relative to conversion rate (8.15%; robotic group, 12.2%; laparoscopic group). A similar short term oncologic outcome for both robotic group and laparoscopic group was also reported.

We introduced laparoscopic pull-through with coloanal anastomosis approach (the published manuscript in chapter 3) to facilitate mobilization of the most distal rectum and to overcome the inherent shortcomings of laparoscopic TME (16). As described clearly in chapter 3, the short-term perioperative outcomes and the quality of the specimens from laparoscopic pull-through with coloanal anastomosis was at least comparable to those who underwent laparoscopic low anterior resection. However, transanal dissection during laparoscopic pull-through with coloanal anastomosis allowed a better visualization for surgeons to complete sharp TME transanally. The study concluded that transanal dissection became very useful when the pelvis was narrow and when the rectal cancer was very distal.

In order to make a complete conclusion of the thesis which emphasized mainly on our proposed procedure, the data of long-term oncological outcomes from the same group of patients (unpublished data) is presenting below.

Thirty patients were enrolled in laparoscopic pull-through with coloanal anastomosis (LPT) group while 147 patients were enrolled in laparoscopic low anterior resection (LAR) group (Table 1). Approximately a third of the patients in both groups received neoadjuvant chemoradiotherapy. Low rectal tumor was found significantly more in laparoscopic pull-through with coloanal anastomosis group (73%; LPT, 49%; LAR, p=0.149). The median tumor diameter was 4 cm. in both groups. Operative time was significantly longer in laparoscopic pull-through with coloanal anastomosis group (164.8 mins; LPT, 130.4; LAR, p<0.0001) (table 2). Comparable intraoperative blood loss, conversion rates, quality of the specimens including; the quality of TME, distal resected margin and circumferential margin positivity and perioperative short-term outcomes including; time to return to bowel function and hospital stays were demonstrated.

Table1 Demographic Data

	LPT (n=30) n (%)	LAR (n=147) n (%)	P-value
Neoadjuvant Chemoradiotherapy	9 (31.0%)	61 (43.3%)	0.2230
Tumor site			0.0149*
• Mid rectum	8 (26.7%)	75 (51.0%)	
• Low rectum	22 (73.3%)	72 (49.0%)	
Tumor size (median, cm.)	4	4	0.2649

LPT laparoscopic pull-through procedure, LAR laparoscopic low anterior resection, * statistically significant

Table 2 Operative outcomes

	LPT (n=30) n (%)	LAR (n=147) n (%)	P-value
Operative time (mins)	164.8	130.4	<0.0001*
Blood loss (mL)	96.4	70.9	0.3569
Conversion	3 (10.0%)	12 (8.2%)	0.7221
Complete mesorectum	9 (50.0%)	66 (76.7%)	0.0608
Distal resection margin (cm)	2.9	4.4	0.0920
Positive CRM	1 (3.3%)	4 (3.6%)	0.3569
Return to bowel function (days)	4.9	4.5	0.5746
Hospital stay (days)	11.3	7.7	0.0726

LPT laparoscopic pull-through procedure, LAR laparoscopic low anterior resection, * statistically significant, CRM circumferential margin

Table 3 long-term outcomes

	LPT (n=30) n (%)	LAR (n=147) n (%)	P-value
Follow-up time (months)	46.4	37.4	0.5610
Overall survival	75.0%	89.1%	0.0627
Local recurrence	1 (3.3%)	1 (0.7%)	0.3127
Systemic recurrence	5 (16.7%)	17 (11.6%)	0.5427

LPT laparoscopic pull-through procedure, LAR laparoscopic low anterior resection, * statistically significant

The patients were followed for 46.4 months in laparoscopic pull-through with coloanal anastomosis group and 37.4 months in laparoscopic low anterior resection group. No significant different in overall survival was found among both groups. The comparable local recurrence and systemic recurrence was also demonstrated.

Several surgical platforms and techniques have been reported and claimed to be the treatment of choice for rectal cancer patients. The key toward a successful treatment for this particular group of patients needs to be tailored by well-trained and highly experienced group of multidisciplinary team (MDT) specialists. It has become increasingly clear that some patients belong to a particularly high-risk group, and a one-size-fits-all strategy is not optimal. The approach of the surgeon, radiologist, medical oncologist and pathologist is essential to maximize the potential for success in the management of rectal cancer, especially in locally advanced disease. Preoperative imaging study using high-quality pelvic MRI, recommended by the MURCURY study group (17-19), should currently be the gold standard to provide relevant details on rectal cancer characteristics. MDT should be carefully decide which patients would be beneficial for neoadjuvant treatment (20) rather than only a good-quality TME. The best possible outcomes will eventually be focused on the combination of careful preoperative staging, the appropriate application of neoadjuvant

treatment, less intraoperative and perioperative complications, sphincter-saving technique, rapid recovery, good short and long term oncological outcomes, acceptable functional outcomes and excellent patient satisfaction.

To become a reasonably well-trained academic colorectal surgeon who is competent to provide a standard of care for rectal cancer patients, I strongly believe that the individual requires standard training background, an adequate number of patients, continuous educations and the ability to conduct scientific methodology to find answers for relevant clinical challenge. The thesis intentionally combined chapters that some of them contained original ideas to solve the critical thinking and some of them were set as a review of the up-to-date specific knowledge. The combination of all the presented chapters certainly added up the more understanding of the important points and answers to improve rectal cancer patient care.

Not only the surgeons who will continue to develop and conduct reliable surgical techniques and clinical studies to overcome the challenges in rectal cancer surgery. PROSPECT Trial's (21) been currently enrolling rectal cancer patients to provide the data on the effectiveness of neoadjuvant chemotherapy *versus* the standard neoadjuvant chemoradiation. On the other hand, the scientists also continue to study and try to understand more in the molecular level aiming to find the predictive and prognostic molecular biomarkers for response to neoadjuvant chemoradiation in rectal cancer which perhaps will be the key to the success in the future treatment (22).

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