Journal of Gastrointestinal Surgery (2019) 23:433–442
https://doi.org/10.1007/s11605-018-3965-9

SSAT STATE-OF-THE-ART CONFERENCE

SSAT State-of-the-Art Conference: Advances in the Management of Rectal Cancer

Evie Carchman[1] · Daniel I. Chu[2] · Gregory D. Kennedy[2] · Melanie Morris[2] · Marc Dakermandji[3] · John R. T. Monson[3] · Laura Melina Fernandez[4] · Rodrigo Oliva Perez[4,5,6] · Alessandro Fichera[7] · Marco E. Allaix[8] · David Liska[9]

Received: 12 June 2018 / Accepted: 3 September 2018 / Published online: 13 September 2018

Keywords Rectal cancer

Introduction

The treatment of rectal cancer has evolved significantly since the early days of total mesorectal excision (TME).[1] Modern management now includes a variety of new surgical techniques, treatment modalities, and oncologic principles. Guidelines from key organizations such as the National Comprehensive Cancer Network (NCCN) help surgeons and providers navigate these many options, but reviews of the current state of these affairs is needed. In 2018, the Society for Surgery of the Alimentary Tract (SSAT) convened a State-of-the-Art Conference on Advances in the Management of Rectal Cancer with international experts and emerging leaders in the field of rectal cancer treatment. Four important topics in rectal cancer management were covered: (1) Gregory Kennedy, MD, PhD from the University of Alabama at Birmingham (UAB), USA, discussed the use of surgical techniques for rectal cancer (open, laparoscopic, or robotic), (2) Rodrigo Perez, MD, PhD, from the University of Sao Paulo School of Medicine, Brazil, discussed the use of "watch-and-wait" when there is a complete clinical response from neoadjuvant chemotherapy, (3) John Monson, MD, from Florida Hospital, USA, discussed the use of transanal total mesorectal excision (TaTME) in rectal cancer surgery, and (4) Alessandro Fichera, MD, from the University of North Carolina Chapel Hill, USA, presented the indications for extended lymphadenectomy in rectal cancer. Each of these important topics will be summarized in this manuscript.

This review comprises summary papers from presentations given at the State-of-the-Art Conference during the 59th Annual Meeting of the Society for Surgery of the Alimentary Tract, Washington DC, June 2018.

✉ Evie Carchman
carchman@surgery.wisc.edu

1 Department of Surgery, Section of Colorectal Surgery, University of Wisconsin- Madison, Madison, WI, USA

2 Department of Surgery, Division of Gastrointestinal Surgery, University of Alabama at Birmingham, Birmingham, AL, USA

3 Center for Colon & Rectal Surgery, Florida Hospital, Orlando, FL, USA

4 Angelita & Joaquim Gama Institute, São Paulo, Brazil

5 Colorectal Surgery Division, University of São Paulo School of Medicine, São Paulo, Brazil

6 Ludwig Institute for Cancer Research, São Paulo Branch, São Paulo, Brazil

7 Department of Surgery, University of North Carolina, Chapel Hill, NC, USA

8 Department of Surgical Sciences, University of Torino, Torino, Italy

9 Department of Colorectal Surgery, Cleveland Clinic, Cleveland, OH, USA

Surgical Techniques for Rectal Cancer—Which Approach to Use? Open vs. Minimally Invasive

Despite years of research and large improvements in treatment, rectal cancer continues to pose significant clinical problems. Roughly 25% of all cancers in the large intestine originate in the rectum and we are continually searching for the best way to treat the disease. From preoperative treatment with chemotherapy ± radiation therapy, to radical surgery, to no surgery, we are continually striving to improve outcomes of patients with this disease. Surgery remains a cornerstone of the treatment algorithm of patients with locally advanced rectal cancer. Despite our best intentions, surgical therapy results in postoperative complication rates that can be as high as 30%.[2] These complications have multiple implications including short-term survival, quality of life, and perhaps even long-term survival. For these reasons, we must continually strive to improve our surgical outcomes.[2–4]

The Principles of Rectal Cancer Surgery

First and foremost, we must stay true to a cancer operation. This includes a thorough abdominal exploration, high ligation of the inferior mesenteric artery, careful dissection in the bloodless, retro-rectal space, and distal margin of at least 1–2 cm. Sphincter preservation should be practiced in those patients who are clearly candidates for this procedure. Proximal diversion with a temporary ostomy should be considered in those patients with an anastomosis to the lower 1/3 of the rectum and in whom have received preoperative chemoradiation.[5]

Surgical therapy remains the standard of care for patients with locally advanced rectal cancer. However, the postoperative complication rate of pelvic surgery can be as high as 30%. These complications have direct implications to patient function, quality of life, and cost of care. In addition, there are indications that short-term outcomes may impact long-term survival in patients with cancer. In one series, patients with complications were less likely to receive adjuvant chemotherapy in a timely fashion and had a decreased overall 5-year survival.[4]

Because of these negative implications, significant effort has gone into reducing postoperative complication rates. Bowel preparation, wound infection reduction bundles, and enhanced recovery after surgery protocols have been implemented and correlate with decreased rates of complications in some series.[6–9] However, perhaps the most important strategy to reduce complications is the utilization of minimally invasive surgery.[2]

Efficacy of Minimally Invasive Surgery for the Treatment of Rectal Cancer

The principles of TME surgery must be followed regardless of the approach. Many have demonstrated that these principles can be followed with the MIS approach. While there are aspects of the principles that are easily accomplished with the MIS approach (high ligation, distal margin, and anastomosis), the integrity of the circumferential resection margin has been a concern in some studies.[10–12] In fact, one of the first studies to look at laparoscopy in the surgical treatment of rectal cancer was the MRC CLASICC trial out of the UK.[12] This study was complicated by the fact it was not focused on rectal cancer, but rather it was examining the outcomes of laparoscopy versus open surgery in patients undergoing surgery for the treatment of either colon or rectal cancer. Unfortunately, the rectal cancer cohort treated with a MIS approach did have an increase in the rate of the circumferential resection margin (CRM) positivity.[12] Interestingly, this did not result in an increase in the local recurrence rate calling into question the importance of such an outcome.[13]

Multiple other studies have examined the outcomes in patients with rectal cancer treated with either a laparoscopic or open operation through randomized controlled trials. For example, the COREAN and COLOR II trials were both performed in a randomized fashion and neither found differences in the circumferential margin.[14,15] These studies went on to examine local recurrence rates and found no differences in relatively short time frames. In addition to these randomized controlled trials, many institutional series have been performed and have found no differences in recurrence rates. However, the ACOSOG and ALaCaRT trials have recently been published and have failed to show noninferiority of a MIS approach compared to the open approach for CRM positivity.[10,11] Given these conflicting results, we await long-term results from these trials to make definitive conclusions. In the meantime, minimally invasive surgical approaches should be used only by those surgeons with significant expertise and experience with these techniques in the pelvis. Furthermore, oncologic parameters and short-term complications should be tracked by these surgeons and continually assessed to ensure acceptable outcomes.

Short-term Outcomes

The postoperative complication rate of pelvic surgery in patients with rectal cancer can be as high as 30%. These complications clearly have short-term implications, and patients suffering complications in the postoperative period have been shown to have a decreased quality of life after surgery. These differences in QoL scores persist even after the complications have resolved. Perhaps even more important than the QoL scores, short-term outcomes may impact long-term survival. While the exact mechanism by which long-term survival is impacted by short-term complications is unknown, studies have consistently shown that long-term survival is negatively impacted by postoperative complications and these results are consistent regardless of tumor type.[4,16,17]

Given the many negative implications of postoperative complications, most strive to improve outcomes with multipronged approaches. Many interventions have been shown to decrease specific complications, but few have been shown to reduce almost all complications. A minimally invasive approach has been correlated with a reduction in almost all complications.[2] The studies supporting these reductions have been comparative effectiveness studies looking retrospectively at large prospective databases, and all have found an MIS approach to be correlated with a decreased rate of postoperative complications. Many of these studies have found up to 50% reductions in postoperative complications. However, outcomes from randomized controlled trials have not necessarily found complication rates to be lower in the MIS groups.

The reasons for the discrepancy between randomized controlled trials and the retrospective studies are complicated. The obvious reason is the intrinsic bias that exists in a retrospective study and the nonrandom assignment of treatment type. Several of the retrospective studies have aimed to control for this bias using advanced statistical techniques including the use of propensity scores. Still, their findings must be interpreted carefully taking into account the database used, the quality of the data, and the statistical approach used to control for inherent bias.

It would be easy for us to conclude that there are no differences in short-term outcomes between minimally invasive and open surgical approaches for rectal cancer and the majority have found no differences in outcomes between these approaches. Of course, we are taught to believe that randomized controlled trials are the gold standard and conclusions from these are difficult to refute. However, it is important to put these studies into the context of real-world practice. In fact, while a randomized trial is designed to try to limit bias of approach allocation, the inclusion criteria may limit the generalizability of the findings to all patients undergoing surgery for rectal cancer. For example, to be included in the ACOSOG Z6051 trial, patients had to have a BMI of 34 or less.[10] Many patients at risk for the worst complications will have not been included in this study thereby introducing significant selection bias. In addition, most of these randomized trials have not been powered to detect differences in the short-term outcomes introducing potential Type I and II error, limiting the implications of these findings. Given the inherent bias of these randomized controlled trials, it is difficult to conclude that the short-term outcomes are equivalent. These results have to be placed into context of the other well-done comparative effectiveness studies, all of which conclude MIS to provide superior outcomes compared to open surgery.

Differences in Minimally Invasive Approaches?

In the opinion of many, minimally invasive approach to colorectal cancer should be considered the standard of care. However, the question of platform continues to be a debate. Is robotic surgery better than laparoscopic surgery? In fact, a recent randomized controlled trial examined this issue.[18] In this study, MIS experts randomized patients to either a laparoscopic or robotic approach to rectal cancer surgery. Not surprisingly, they found no differences in conversion to open, complications, or CRM positivity between the two groups.[18] While there may be benefits to robotic surgery, expert laparoscopic surgeons will not see a measurable benefit in their patient outcomes. That is not to say the surgeon will not see a benefit. In fact, there may be significant benefit appreciated in the ergonomics of the operation.[19] Such benefit may decrease rates of back injury, hand/arm/shoulder injury, and result in a longer, pain-free career. However, these benefits remain to be demonstrated.

Another potential benefit is the extension of the minimally invasive approach to surgeons who have not adopted laparoscopy. A laparoscopic rectal operation is difficult. There is evidence indicating the ideal number of cases to overcome the learning curve is over 50 operations.[20] However, there are other data indicating that outcomes continue to change and improve even over 100 operations.[20] This type of data indicates the laparoscopic pelvic dissection is not for the occasional pelvic surgeon. The learning curve for the robotic approach is much lower and has two parts.[21] The first part seems to relate to both the institution and the surgeon while the second part is only that of the surgeon. Once the institutional curve is met, the surgeon learning curve seems to be significantly reduced from around 75 to less than 30.[21]

Innovation remains ripe in rectal cancer surgery, and a search for new techniques that can either improve oncologic outcomes or reduce complication rates is underway. For mid and low rectal cancers, transanal total mesorectal excision (TaTME) has emerged as a new minimally invasive approach to reduce CRM positivity, but is not without its own learning curve and potential complications.[22] Careful evaluation of such new techniques is needed to better understand their appropriate applications.[23]

Surgery for rectal cancer remains fraught with complications. A minimally invasive approach is safe and effective and appears to improve short-term outcomes. While long-term oncologic outcome from some studies is pending, many have found no differences in local recurrence or disease-free survival. While there are clear positives to a minimally invasive operation, oncologic outcomes must be the top priority. Therefore, the approach to the treatment of rectal cancer should be based on the experience of the surgeon. For those who feel comfortable with a minimally invasive approach, the platform of choice appears to make no difference to outcomes.

The Complete Clinical Response: Watch & Wait?

Incorporation of new treatment modalities has significantly increased complexity in the management of rectal cancer. Although surgical treatment is still the main pillar in the management of rectal cancer by proctectomy and total mesorectal excision (TME), there has been increased interest in organ preservation strategies in the last few years. Neoadjuvant chemoradiation (nCRT) may lead to significant tumor regression that can be observed not only in the primary tumor but also in perirectal nodes. Ultimately, the effect of nCRT may be so significant that complete tumor regression may develop in 16–42% of patients depending on baseline staging and the actual treatment regimen.[24]

Rationale

Traditional management would suggest that all patients require total mesorectal excision (TME) regardless of tumor response following nCRT and even patients that develop complete pathological response (pCR) are associated with improved oncological outcomes.[25] However, radical resection is associated with significant postoperative morbidity, including long-term urinary and sexual dysfunction, fecal incontinence, and the need for temporary or definitive stomas. Also, depending on associated comorbidities and patient's age, postoperative mortality rate could reach from 2 to 3% to as high as 16%.[26] Therefore, in selected patients with clinical and radiological evidence of complete tumor regression (complete clinical response—cCR), no immediate surgical treatment and strict surveillance (also known as the "Watch & Wait" strategy—WW) has been suggested.[27]

Assessment of Response

In order to consider organ preservation strategies such as WW, assessment of response is crucial.

Timing of Assessment

The optimal timing for assessment of response after nCRT completion remains controversial. Many retrospective studies (including systematic reviews) have suggested that longer interval periods (≥ 11–12 weeks) were significantly associated with higher rates of complete tumor regression.[28] More recently, a randomized clinical trial has failed to confirm the expected higher rates of pCR between 11 and 7 weeks after completion of nCRT.[29] However, newer nCRT regimens with radiation therapy dose escalation and consolidation chemotherapy have suggested that longer interval periods may be safe and provide higher rates of tumor response to treatment.[30,31]

Tools in the Assessment of Response

The criteria to consider a complete clinical response (cCR) includes the absence of any irregularity, mass, ulceration, or stenosis during DRE. The surface has to be regular and smooth with only mild induration and subtle loss in the pliability of the rectal wall being acceptable findings consistent with a cCR.[32] Endoscopically, a flat white scar and telangiectasia are common findings and usually do not warrant endoscopic biopsies. In fact, even in the setting of an incomplete CR, endoscopic biopsies should be interpreted with caution. The presence of a negative biopsy, per se, does not rule out residual disease as negative predictive values may be as low as 21%.[33]

Radiological studies should also be routinely performed. High-resolution magnetic resonance (MR) is considered as the method of choice for the assessment of tumor response. Typical findings of complete tumor regression include the presence of low-signal intensity areas in the area previously harboring the rectal cancer with multiple patterns.[34] More recently, a grading system has been proposed to estimate pathological tumor regression grade (TRG) with the use of MR (mrTRG1-5) and aid in the selection of patients that are ideal candidates for organ-preservation strategies (mrTRG1).[35]

Diffusion-weighted magnetic resonance imaging (DWI-MR) may add significant functional information and further improve the accuracy of detection of a complete tumor regression to standard MR imaging.[36]

PET/CT imaging may provide additional information to standard radiological features by providing an estimate of tumor metabolism. The variation in standard uptake values (SUV) and metabolic tumor volume reduction between pre- and post-treatment may provide one of the best predictors of a complete tumor regression among patients with rectal cancer.[37]

Ultimately, the combination of multiple studies may increase the accuracy in the detection of complete tumor response to nCRT.[38]

Excisional Biopsies or Transanal Local Excisions

Excisional biopsies with the use of currently available transanal endoscopic microsurgical platforms (TEMs) have been an attractive tool for the assessment of primary tumor response to nCRT.[39] However, in the setting of nCRT, TEMs seem to be associated with higher rates of primary wound dehiscence leading to significant immediate postoperative pain and hospital readmission rates.[40] Ultimately, considerable postoperative scarring and frequent wound separation may also have detrimental functional consequences.[41] Finally, significant distortion of the rectal wall may lead to considerable difficulties in ruling out residual disease or the presence of local recurrence by clinical and even radiological studies.[42] These difficulties may lead to delayed diagnosis of locally recurrent disease with significant impact in surgical outcomes of salvage therapies.[43]

Altogether, patients with clinical and radiological evidence of cCR should preferably be managed by no immediate surgery (including avoidance of excisional biopsies) and frequent reassessment of response. Follow-up visits are usually recommended every 2–3 months for the first 2 years including DRE, endoscopic, and radiological assessment. After 2 years of follow-up, visits are usually recommended every 6 months until completion of a 5-year follow-up. Considering there is still risk for late local recurrences (≥ 5 years), patients should be advised to remain on follow-up with yearly visits for more prolonged periods.

Outcomes

The observation of no oncological differences between patients with pCR managed by TME and patients with cCR managed by WW led several institutions to consider no immediate surgery after development of a cCR after nCRT.[44] A systematic review of patients undergoing WW has suggested that cCR managed by WW have similar outcomes to patients with pCR managed by radical surgery. Pooled local recurrence rates have been reported to be between 15 and 20%.[45] The vast majority of these local recurrences (nearly 90%) are amenable to salvage treatment and usually with an endoluminal component (rendering them accessible by simple clinical and endoscopic detection provided proper follow-up is performed).[46] Patients with more advanced cT stage at baseline staging appear to be at greater risk for local recurrence after initial cCR and should carefully monitored.[47]

Ultimately, WW has so far been adopted only in selected and highly specialized centers for the management of rectal cancer. The lack of randomized clinical trials and not inclusion of this strategy in most available guidelines may have contributed to this selective adoption process.[48] With increasing number of reported experiences and availability of more robust data from international registries may provide background for its inclusion as a treatment option in future guidelines.[49] In this setting, there is no clear consensus as to when such strategy should be adopted in current clinical practice outside of clinical trials or for patients unsuitable for radical surgery.[48] Still, the availability of a significant amount of data in the literature suggests that this approach should at least be discussed and explained to patients with evidence of a complete clinical response after neoadjuvant CRT.[50]

Perspectives

With the use of nCRT specifically aimed to provide organ preservation for selected patients (including early stage disease), accurate prediction of tumor response with molecular biology studies will become increasingly relevant for clinical management decision.[51,52] In addition, introduction of liquid biopsies for the assessment of tumor response may also represent a clinically useful tool for the management and aid in optimal selection of patients for this approach.[53]

Technological Frontier: TaTME

Obtaining adequate trans-abdominal access to the deep pelvis in mid to low rectal cancer surgery continues to challenge even the most experienced colorectal surgeons. taTME (trans-anal total mesorectal excision) is an innovation that aims to overcome this significant limitation of rectal cancer surgery. Indeed, the worse outcomes of a particular subset of patients (obese male, narrow pelvis, low fixed bulky tumor) would seem to stand to benefit the most from a novel "bottom-up" approach that aims to reduce the associated technical limitations related to access to the pelvis from above. The current available literature would suggest at least a favorable comparison in terms of ability to obtain a negative distal resection margin (DRM), a proper quality TME specimen, and a negative circumferential resection margin (CRM).[23,54] Pathological outcomes and long-term survival data, such as local recurrence, overall survival, and disease-free survival, still remain to be established by adequately powered RCTs.[55]

Two international RCTs, COLOR III and ETAP-GRECCAR 11, are under way, where eligible patients with low and mid rectal cancers are randomized to taTME or laparoscopic TME.[23,56]

taTME finds its roots in the parallel evolution of local excision techniques such as TEM and TAMIS which had already established their oncologic superiority for early rectal cancers through the use of stable transanal endoscopic platforms by allowing precise meticulous dissection. Concurrently, the concepts of TATA (transanal transabdominal) surgery and transanally initiated TME techniques for advanced low rectal cancers both exposed the significant potential advantages of a "bottom-up" approach. Only after the addition of CO2 insufflation and direct endoscopic visualization, by using adapted platforms such as TEM and TEO and subsequently, the less costly TAMIS, did the current form of taTME seem to emerge as the dominant technique.[57–59] Although a number of platforms are used for taTME, by far the commonest is the TAMIS port (GelPOINT® Path Transanal Access Platform, © 2018 Applied Medical Resources Corporation, Rancho Santa Margarita, CA). Conceptually, the TAMIS port, is based on single-port surgery and has been adapted for secure seating within the anal canal but with the added benefit of using conventional laparoscopic instruments (rather than unwieldy articulated instruments). Thus, it significantly expands the potential for widespread use while also reducing cost. The existing issues related to impaired visualization due to billowing of the rectum and poor smoke evacuation, issues well known to transanal endoscopic surgeons, have found renewed interest from industry to develop adapted insufflator technology. The latest smokeless high-flow insufflators have easily, albeit expensively, overcome their ubiquitous traditional laparoscopic counterparts' limitations (AirSeal iFS Intelligent Flow System, © 2018 CONMED Corporation, Utica, NY). Concurrently, capitalizing on this already existing pool of insufflator technology, low-cost insufflator adjuncts (Insufflation Stabilization Bag, GelPOINT® Path Transanal Access Platform, © 2018 Applied Medical Resources Corporation, Rancho Santa Margarita, CA) have also been developed to attempt to render TaTME more accessible across the spectrum of resource availability.[57–59]

The implementation of novel technical and technologic innovations in surgery has often been fraught with unintended consequences. With an emphasis on *safety* and *acceptability of clinical outcomes*, the lessons learned from missteps arising throughout the implementation of minimally invasive surgery to various fields (e.g., bile duct injury) have justifiably led the surgical community to heed the cautionary tales of early adopters of the approach. The technical complexity of the procedure, in addition to the identification of new subtle anatomic landmarks combined with the rediscovery of little-known surgical planes, correct and incorrect alike, alongside the occurrence of otherwise rare complications such as urethral injury, have led the proponents of the technique to attempt to set a framework had through which TaTME could be widely adopted in a responsible manner. Thus, analogous to the timely concept of promoting standardization for improvement of a rectal cancer care paradigm, there has been a concerted effort to rapidly seize on the enthusiasm and popularization of TaTME by the implementation of essential structured learning curricula with cadaveric models as well as expert proctorship opportunities. Concurrently, there is ongoing collection of voluntary data via large-scale registries that have built-in ease of access for self-reporting of outcomes. Established learning strategies such as proctorship and wet-lab courses as well as traditional mediums of knowledge sharing such as peer-reviewed journals and surgical meetings now are complemented by a significant parallel interest in the development of various novel adjuncts that serve to transmit the necessary baseline knowledge to learn TaTME. Either by exploiting the ubiquity and simplicity of handheld smart-devices with app-based learning modules (e.g., iLapp surgery © 2017, iLappSurgery Foundation, Hasselt, Belgium) or by maximizing the use of modern data transmission bandwidth for high-quality video streaming, such as web-based expert video tutorials (e.g., WeBSurg, © IRCAD, Strasbourg, France) and live-case streaming (e.g., Advances In Surgery (AIS) Channel, Antonio Lacy), the currently available technology is integrating in a progressively seamless fashion with surgical practice.

The current available evidence shows an ability to obtain adequate CRM, DRM, and good-quality TME specimens. Overall, recent minimally invasive TME techniques have thus far matched the oncologic standards of open TME, although randomized trials with long-term oncologic and functional data are needed to clearly establish the role that each of these approaches should play in the arsenal of surgical treatments for rectal cancer. Further studies are also needed to evaluate the quality of life, genitourinary function, fecal incontinence, and the evaluation of low anterior resection syndrome in patients undergoing TaTME. In addition, there are also several ongoing challenges faced in the technique. Anastomotic techniques in the pelvis had previously been uniform in their application with variations predominantly centered on type of conduit reconstruction. The access allowed by taTME has now introduced significant variability and thus, corresponding debate about anastomotic technique (stapled vs double purse-string vs hand sewn) specimen extraction methods (trans-anal vs trans-abdominal), and best indications (based on anatomy, stage, and location). The learning curve for taTME has been studied recently. For example, CUSUM analysis reported that the good-quality TME rate reaches an acceptable rate after 51 cases overall, and 45 cases if abdominoperineal resections are excluded which seems bot practical and reasonable.[60]

What has not truly been evaluated is where taTME sits in the spectrum of technology options—for example, laparoscopy, open surgery, or robotic surgery. It would seem intuitively correct to suggest that there will be many cases where a transanal approach is simply not required because the abdominal approach is quite satisfactory. There is no evidence to suggest that the specific abdominal approach used results in a greater or lesser need for the taTME technique. When considering robotic surgery, the only study to date suggests the results are similar when using a matched comparison model.[61]

taTME has seen its use expanded progressively to include proctectomy for benign disease. Moreover, such an approach may also benefit the ability to perform advanced oncologic procedures requiring pelvic exenteration.

Hence, the organic collaboration of several individual influential colorectal surgeons striving to meaningfully contribute to their craft by their willingness to share the lessons learned from their respective high-volume and specialized experience has allowed TaTME to rapidly mature as technical innovation.[62,63] Their willingness to share their successes and failures trough conventional and unconventional media has allowed the surgical community as a whole to witness the pioneering of a procedure, all the while being facilitated and enhanced by the technology that connects them.

Indications for Extended Lymphadenectomy in Rectal Cancer

Neoadjuvant chemoradiation therapy (CRT) followed by total mesorectal excision (TME) represents the standard of care for the treatment of locally advanced extraperitoneal rectal cancer.[1,64,65] However, metastases in the lateral pelvic lymph nodes (LPLN) occur in up to 25% of these patients[66–69] and LPLN involvement is associated with high rates of local recurrence and poor oncologic outcomes after neoadjuvant CRT and TME.[67,70]

To lower the risk of local recurrence and improve long-term survival, TME with LPLN dissection and extended lymphadenectomy (EL) beyond the planes of TME has been widely adopted in Japan even in the absence of enlarged

LPLNs.[71] There is level 1 evidence from a large Japanese RCT that EL has better oncologic outcomes than TME alone, with lower local recurrence rates secondary to lower rates of metastases in the LPLNs.[72] However, the value of this strategy is still debated in the Western countries for several reasons. *First*, even though TME with EL appears to reduce the rate of local recurrence, it does not prevent the occurrence of tumor relapse in the lateral pelvis.[72] *Second*, LPLN metastases are considered distant metastases in the Western literature. *Third*, with neoadjuvant CRT the radiation field includes the LPLNs, thus leading to very low local recurrence rates in the Western series.[73] To date, there are some large non-RCTs that demonstrate that TME with EL does not lead to superior oncologic outcomes than TME following neoadjuvant CRT for locally advanced extraperitoneal rectal cancer.[74–76] Kusters et al.[74] compared the pattern of local relapse in 755 rectal cancer patients selected from the Dutch TME-trial database (379 patients had TME alone and 376 patients underwent neoadjuvant short-course radiotherapy followed by TME) and in 324 patients included in the National Cancer Center Hospital of Tokyo database and treated with rectal resection and EL. Neoadjuvant radiotherapy was associated with a lower rate of recurrence in the LPLNs than surgery alone or surgery with EL (0.8% vs. 2.7% vs. 2.2%), suggesting the potential beneficial role of neoadjuvant radiation therapy in sterilizing the LPLNs. These findings are similar to those reported by Watanabe et al.[76] in a retrospective study that assessed the oncologic outcomes in 115 patients with locally advanced rectal cancer. A significantly better disease-free survival at 5 years was reported after preoperative radiotherapy regardless of the surgical procedure performed (74.6% after neoadjuvant radiotherapy followed by surgery vs. 45.9% after surgery alone, $P = 0.006$); the addition of EL beyond the planes of TME did not bring any advantage in terms of survival in those patients who were treated with neoadjuvant radiotherapy. *Fourth*, early perioperative outcomes are poorer after EL than rectal surgery performed within the planes of the TME: EL is associated with longer operative time and greater intraoperative blood losses. Quality of life and both sexual and urinary functions are poorer than those reported after TME alone.[77,78] During the last few years, the impact of a minimally invasive approach to patients with rectal cancer and enlarged LPLNs has been explored. For instance, Ogura et al.[79] have performed a study aiming at evaluating the feasibility and the clinical benefits of adding laparoscopic EL to TME in patients with advanced lower rectal cancer and enlarged LPLNs treated with preoperative CRT. A total of 107 patients undergoing laparoscopic EL were compared to 220 patients surgically treated without EL. The short-term results confirmed a significantly longer operative time and higher total blood loss in the TME plus EL group even with laparoscopy, with a trend towards a higher rate of major complications (9.3% vs. 5.5%). The rate of recurrence-free survival and local recurrence at 3 years were similar (84.7% vs. 82 and 3.2% vs. 5.2%, respectively). Hence forth, the real benefits from the minimally invasive approach in these patients remain unproven and there have been very few retrospective studies comparing laparoscopic and open EL. For instance. Nagayoshi et al.[80] have recently published a retrospective review of 90 patients with advanced rectal cancer undergoing laparoscopic ($N = 46$) or open ($N = 44$) TME with EL. While a longer operative time was observed in the laparoscopic group (641 vs. 312 min, $P < 0.001$), intraoperative blood loss was significantly lower (252 vs. 815 mL, $P < 0.001$) than in the open group. Mean hospital stay was shorter after laparoscopic EL (22.9 vs. 29.1 days, $P = 0.04$); postoperative major morbidity rates were similar in the two groups (19.6% vs. 31.8%). The mean number of LPLNs harvested with laparoscopic EL was higher than with open EL (19.5 vs. 15.8, $P < 0.05$); however, this did not reflect into a significantly better overall survival at 3 years (94.7% vs. 82.9%, $P = 0.25$). A better visualization of the surgical field and lower intraoperative blood losses are considered two possible reasons for the higher number of LPLNs resected by laparoscopy.

During the last 5 years, many efforts have been done to identify the optimal patients for EL, thus avoiding overtreatment and the related postoperative major morbidity. A short-axis LPLN diameter of 8 mm or larger and a mixed signal intensity based on magnetic resonance imaging (MRI) before neoadjuvant CRT, female sex, and CRT with no induction systemic chemotherapy have been proposed as predictors of LPLN metastases.[81] On the contrary, LPLN size of 5 mm or lower at MRI after neoadjuvant CRT has been suggested as possible criterion to avoid EL.[82] However, about 10% of patients with LPLNs with a diameter of 5 mm or less have LPLN metastases[79] and enlarged LPLNs that respond to neoadjuvant CRT are associated with a poorer prognosis than LPLNs that are not enlarged at presentation.[82]

In conclusion, based on the current evidence, EL should be considered within a tailored multidisciplinary strategy in rectal cancer patients with enlarged LPLNs before neoadjuvant CRT, balancing the postoperative morbidity and the oncologic benefits. However, the results of large RCTs are needed to shed light on the unanswered questions, including the role of a laparoscopic approach and induction preoperative chemotherapy on the outcomes of this complex patient population, and as well as the opportunity to better select patients that would benefit from EL.

Conclusion

In conclusion, rectal cancer management has and will continue to evolve. Surgeons need to remain knowledgeable about these advances. Surgical techniques remain grounded on the fundamental principle of doing a proper oncologic resection. Whether performed open or minimally invasively and TaTME or not, respect for the oncologic plane and margins is paramount. Indications for watchful waiting after a complete clinical response and for extended lymphadenectomies also continues to evolve as more data is acquired, but both will likely play a future role in rectal cancer management.

References

1. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg. 1998;133(8):894–9.
2. Greenblatt DY, Rajamanickam V, Pugely AJ, Heise CP, Foley EF, Kennedy GD. Short-term outcomes after laparoscopic-assisted proctectomy for rectal cancer: results from the ACS NSQIP. J Am Coll Surg. 2011;212(5):844–54.
3. Brown SR, Mathew R, Keding A, Marshall HC, Brown JM, Jayne DG. The impact of postoperative complications on long-term quality of life after curative colorectal cancer surgery. Ann Surg. 2014;259(5):916–23.
4. Tevis SE, Kohlnhofer BM, Stringfield S, Foley EF, Harms BA, Heise CP, et al. Postoperative complications in patients with rectal cancer are associated with delays in chemotherapy that lead to worse disease-free and overall survival. Dis Colon Rectum. 2013;56(12):1339–48.
5. Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg. 2007;246(2):207–14.
6. Morris MS, Graham LA, Chu DI, Cannon JA, Hawn MT. Oral Antibiotic Bowel Preparation Significantly Reduces Surgical Site Infection Rates and Readmission Rates in Elective Colorectal Surgery. Ann Surg. 2015;261(6):1034–40.
7. Korb ML, Hawn MT, Singletary BA, Cannon JA, Heslin MJ, O'Brien DM, et al. Adoption of preoperative oral antibiotics decreases surgical site infection for elective colorectal surgery. Am Surg. 2014;80(9):e270–3.
8. Keenan JE, Speicher PJ, Thacker JK, Walter M, Kuchibhatla M, Mantyh CR. The preventive surgical site infection bundle in colorectal surgery: an effective approach to surgical site infection reduction and health care cost savings. JAMA Surg. 2014;149(10):1045–52.
9. Huibers CJ, de Roos MA, Ong KH. The effect of the introduction of the ERAS protocol in laparoscopic total mesorectal excision for rectal cancer. Int J Colorectal Dis. 2012;27(6):751–7.
10. Fleshman J, Branda M, Sargent DJ, Boller AM, George V, Abbas M, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection of Stage II or III Rectal Cancer on Pathologic Outcomes: The ACOSOG Z6051 Randomized Clinical Trial. JAMA. 2015;314(13):1346–55.
11. Stevenson AR, Solomon MJ, Lumley JW, Hewett P, Clouston AD, Gebski VJ, et al. Effect of Laparoscopic-Assisted Resection vs Open Resection on Pathological Outcomes in Rectal Cancer: The ALaCaRT Randomized Clinical Trial. JAMA. 2015;314(13):1356–63.
12. Guillou PJ, Quirke P, Thorpe H, Walker J, Jayne DG, Smith AM, et al. Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. Lancet. 2005;365(9472):1718–26.
13. Jayne DG, Guillou PJ, Thorpe H, Quirke P, Copeland J, Smith AM, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol. 2007;25(21):3061–8.
14. Jeong SY, Park JW, Nam BH, Kim S, Kang SB, Lim SB, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. Lancet Oncol. 2014;15(7):767–74.
15. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med. 2015;372(14):1324–32.
16. Law WL, Choi HK, Lee YM, Ho JW. The impact of postoperative complications on long-term outcomes following curative resection for colorectal cancer. Ann Surg Oncol. 2007;14(9):2559–66.
17. Aoyama T, Oba K, Honda M, Sadahiro S, Hamada C, Mayanagi S, et al. Impact of postoperative complications on the colorectal cancer survival and recurrence: analyses of pooled individual patients' data from three large phase III randomized trials. Cancer Med. 2017;6(7):1573–80.
18. Jayne D, Pigazzi A, Marshall H, Croft J, Corrigan N, Copeland J, et al. Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer: The ROLARR Randomized Clinical Trial. JAMA. 2017;318(16):1569–80.
19. Lawson EH, Curet MJ, Sanchez BR, Schuster R, Berguer R. Postural ergonomics during robotic and laparoscopic gastric bypass surgery: a pilot project. J Robot Surg. 2007;1(1):61–7.
20. Bege T, Lelong B, Esterni B, Turrini O, Guiramand J, Francon D, et al. The learning curve for the laparoscopic approach to conservative mesorectal excision for rectal cancer: lessons drawn from a single institution's experience. Ann Surg. 2010;251(2):249–53.
21. Guend H, Widmar M, Patel S, Nash GM, Paty PB, Guillem JG, et al. Developing a robotic colorectal cancer surgery program: understanding institutional and individual learning curves. Surg Endosc. 2017;31(7):2820–8.
22. Lacy AM, Tasende MM, Delgado S, Fernandez-Hevia M, Jimenez M, De Lacy B, et al. Transanal Total Mesorectal Excision for Rectal Cancer: Outcomes after 140 Patients. J Am Coll Surg. 2015;221(2):415–23.
23. Deijen CL, Velthuis S, Tsai A, Mavroveli S, de Lange-de Klerk ES, Sietses C, et al. COLOR III: a multicentre randomised clinical trial comparing transanal TME versus laparoscopic TME for mid and low rectal cancer. Surg Endosc. 2016;30(8):3210–5.
24. Sanghera P, Wong DW, McConkey CC, Geh JI, Hartley A. Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. Clin Oncol (R Coll Radiol). 2008;20(2):176–83.
25. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. Lancet Oncol. 2010;11(9):835–44.
26. Smith FM, Rao C, Oliva Perez R, Bujko K, Athanasiou T, Habr-Gama A, et al. Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. Dis Colon Rectum. 2015;58(2):159–71.
27. Habr-Gama A, Sao Juliao GP, Perez RO. Nonoperative management of rectal cancer: identifying the ideal patients. Hematol Oncol Clin North Am. 2015;29(1):135–51.
28. Kalady MF, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC, et al. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. Ann Surg. 2009;250(4):582–9.
29. Lefevre JH, Mineur L, Kotti S, Rullier E, Rouanet P, de Chaisemartin C, et al. Effect of Interval (7 or 11 weeks) Between

Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6). J Clin Oncol. 2016;34(31):3773–80.

30. Garcia-Aguilar J, Chow OS, Smith DD, Marcet JE, Cataldo PA, Varma MG, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol. 2015;16(8):957–66.
31. Habr-Gama A, Perez RO, Sao Juliao GP, Proscurshim I, Fernandez LM, Figueiredo MN, et al. Consolidation chemotherapy during neoadjuvant chemoradiation (CRT) for distal rectal cancer leads to sustained decrease in tumor metabolism when compared to standard CRT regimen. Radiat Oncol. 2016;11:24.
32. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: characterization of clinical and endoscopic findings for standardization. Dis Colon Rectum. 2010;53(12):1692–8.
33. Perez RO, Habr-Gama A, Pereira GV, Lynn PB, Alves PA, Proscurshim I, et al. Role of biopsies in patients with residual rectal cancer following neoadjuvant chemoradiation after downsizing: can they rule out persisting cancer?. Colorectal Dis. 2012;14(6):714–20.
34. Lambregts DM, Maas M, Bakers FC, Cappendijk VC, Lammering G, Beets GL, et al. Long-term follow-up features on rectal MRI during a wait-and-see approach after a clinical complete response in patients with rectal cancer treated with chemoradiotherapy. Dis Colon Rectum. 2011;54(12):1521–8.
35. Patel UB, Brown G, Rutten H, West N, Sebag-Montefiore D, Glynne-Jones R, et al. Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. Ann Surg Oncol. 2012;19(9):2842–52.
36. Lambregts DM, Vandecaveye V, Barbaro B, Bakers FC, Lambrecht M, Maas M, et al. Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: a multicenter study. Ann Surg Oncol. 2011;18(8):2224–31.
37. Dos Anjos DA, Perez RO, Habr-Gama A, Sao Juliao GP, Vailati BB, Fernandez LM, et al. Semiquantitative Volumetry by Sequential PET/CT May Improve Prediction of Complete Response to Neoadjuvant Chemoradiation in Patients With Distal Rectal Cancer. Dis Colon Rectum. 2016;59(9):805–12.
38. Maas M, Lambregts DM, Nelemans PJ, Heijnen LA, Martens MH, Leijtens JW, et al. Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. Ann Surg Oncol. 2015;22(12):3873–80.
39. Smith FM, Ahad A, Perez RO, Marks J, Bujko K, Heald RJ. Local Excision Techniques for Rectal Cancer After Neoadjuvant Chemoradiotherapy: What Are We Doing?. Dis Colon Rectum. 2017;60(2):228–39.
40. Perez RO, Habr-Gama A, Sao Juliao GP, Proscurshim I, Scanavini Neto A, Gama-Rodrigues J. Transanal endoscopic microsurgery for residual rectal cancer after neoadjuvant chemoradiation therapy is associated with significant immediate pain and hospital readmission rates. Dis Colon Rectum. 2011;54(5):545–51.
41. Habr-Gama A, Lynn PB, Jorge JM, Sao Juliao GP, Proscurshim I, Gama-Rodrigues J, et al. Impact of Organ-Preserving Strategies on Anorectal Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. Dis Colon Rectum. 2016;59(4):264–9.
42. Sao Juliao GP, Ortega CD, Vailati BB, Habr-Gama A, Fernandez LM, Gama-Rodrigues J, et al. Magnetic resonance imaging following neoadjuvant chemoradiation and transanal endoscopic microsurgery for rectal cancer. Colorectal Dis. 2017;19(6):O196-O203.
43. Perez RO, Habr-Gama A, Sao Juliao GP, Proscurshim I, Fernandez LM, de Azevedo RU, et al. Transanal Endoscopic Microsurgery (TEM) Following Neoadjuvant Chemoradiation for Rectal Cancer: Outcomes of Salvage Resection for Local Recurrence. Ann Surg Oncol. 2016;23(4):1143–8.
44. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Jr., Silva e Sousa AH, Jr, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240(4):711–7; discussion 7-8.
45. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2017;2(7):501–13.
46. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014;88(4):822–8.
47. Habr-Gama A, Sao Juliao GP, Gama-Rodrigues J, Vailati BB, Ortega C, Fernandez LM, et al. Baseline T Classification Predicts Early Tumor Regrowth After Nonoperative Management in Distal Rectal Cancer After Extended Neoadjuvant Chemoradiation and Initial Complete Clinical Response. Dis Colon Rectum. 2017;60(6):586–94.
48. Borstlap WAA, van Oostendorp SE, Klaver CEL, Hahnloser D, Cunningham C, Rullier E, et al. Organ preservation in rectal cancer: a synopsis of current guidelines. Colorectal Dis. 2017.
49. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet. 2018;391(10139):2537–45.
50. Smith FM, Locke D. The BMJ opinion [Internet]. BMJ2017. Available from: https://blogs.bmj.com/bmj/2017/10/06/fraser-smith-and-david-locke-when-surgeons-unwittingly-dont-obtain-informed-consent/.
51. Perez RO, Habr-Gama A, Sao Juliao GP, Vailati BB, Fernandez LM, Gama-Rodrigues J, et al. Should We Give Up The Search for a Clinically Useful Gene Signature for the Prediction of Response of Rectal Cancer to Neoadjuvant Chemoradiation?. Dis Colon Rectum. 2016;59(9):895–7.
52. Bettoni F, Masotti C, Habr-Gama A, Correa BR, Gama-Rodrigues J, Vianna MR, et al. Intratumoral Genetic Heterogeneity in Rectal Cancer: Are Single Biopsies representative of the entirety of the tumor?. Ann Surg. 2017;265(1):e4-e6.
53. Carpinetti P, Donnard E, Bettoni F, Asprino P, Koyama F, Rozanski A, et al. The use of personalized biomarkers and liquid biopsies to monitor treatment response and disease recurrence in locally advanced rectal cancer after neoadjuvant chemoradiation. Oncotarget. 2015;6(35):38360–71.
54. Marks JH, Myers EA, Zeger EL, Denittis AS, Gummadi M, Marks GJ. Long-term outcomes by a transanal approach to total mesorectal excision for rectal cancer. Surg Endosc. 2017;31(12):5248–57.
55. de Lacy FB, van Laarhoven J, Pena R, Arroyave MC, Bravo R, Cuatrecasas M, et al. Transanal total mesorectal excision: pathological results of 186 patients with mid and low rectal cancer. Surg Endosc. 2018;32(5):2442–7.
56. Lelong B, de Chaisemartin C, Meillat H, Cournier S, Boher JM, Genre D, et al. A multicentre randomised controlled trial to evaluate the efficacy, morbidity and functional outcome of endoscopic transanal proctectomy versus laparoscopic proctectomy for low-lying rectal cancer (ETAP-GRECCAR 11 TRIAL): rationale and design. BMC Cancer. 2017;17(1):253.
57. Bislenghi G, Wolthuis AM, de Buck van Overstraeten A, D'Hoore A. AirSeal system insufflator to maintain a stable pneumorectum during TAMIS. Tech Coloproctol. 2015;19(1):43–5.
58. Luketina RR, Knauer M, Kohler G, Koch OO, Strasser K, Egger M, et al. Comparison of a standard CO(2) pressure pneumoperitoneum

insufflator versus AirSeal: study protocol of a randomized controlled trial. Trials. 2014;15:239.
59. Waheed A, Miles A, Kelly J, Monson JRT, Motl JS, Albert M. Insufflation stabilization bag (ISB): a cost-effective approach for stable pneumorectum using a modified CO2 insufflation reservoir for TAMIS and taTME. Tech Coloproctol 2017;21(11):897–900.
60. Lee L, Kelly J, Nassif GJ, de Beche-Adams TC, Albert MR, Monson JRT. Defining the learning curve for transanal total mesorectal excision for rectal adenocarcinoma. Surg Endosc. 2018.
61. Lee L, de Lacy B, Gomez Ruiz M, Liberman AS, Albert MR, Monson JRT, et al. A Multicenter Matched Comparison of Transanal and Robotic Total Mesorectal Excision for Mid and Low-rectal Adenocarcinoma. Ann Surg. 2018.
62. Penna M, Hompes R, Mackenzie H, Carter F, Francis NK. First international training and assessment consensus workshop on transanal total mesorectal excision (taTME). Tech Coloproctol. 2016;20(6):343–52.
63. McLemore EC, Harnsberger CR, Broderick RC, Leland H, Sylla P, Coker AM, et al. Transanal total mesorectal excision (taTME) for rectal cancer: a training pathway. Surg Endosc. 2016;30(9):4130–5.
64. Swedish Rectal Cancer T, Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, et al. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med. 1997;336(14):980–7.
65. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. Lancet. 1993;341(8843):457–60.
66. Fujita S, Yamamoto S, Akasu T, Moriya Y. Lateral pelvic lymph node dissection for advanced lower rectal cancer. Br J Surg. 2003;90(12):1580–5.
67. Ueno M, Oya M, Azekura K, Yamaguchi T, Muto T. Incidence and prognostic significance of lateral lymph node metastasis in patients with advanced low rectal cancer. Br J Surg. 2005;92(6):756–63.
68. Sugihara K, Kobayashi H, Kato T, Mori T, Mochizuki H, Kameoka S, et al. Indication and benefit of pelvic sidewall dissection for rectal cancer. Dis Colon Rectum 2006;49(11):1663–72.
69. Mori T, Takahashi K, Yasuno M. Radical resection with autonomic nerve preservation and lymph node dissection techniques in lower rectal cancer surgery and its results: the impact of lateral lymph node dissection. Langenbecks Arch Surg. 1998;383(6):409–15.
70. Hida J, Yasutomi M, Fujimoto K, Maruyama T, Okuno K, Shindo K. Does lateral lymph node dissection improve survival in rectal carcinoma? Examination of node metastases by the clearing method. J Am Coll Surg. 1997;184(5):475–80.
71. Watanabe T, Itabashi M, Shimada Y, Tanaka S, Ito Y, Ajioka Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. Int J Clin Oncol. 2015;20(2):207–39.
72. Fujita S, Mizusawa J, Kanemitsu Y, Ito M, Kinugasa Y, Komori K, et al. Mesorectal Excision With or Without Lateral Lymph Node Dissection for Clinical Stage II/III Lower Rectal Cancer (JCOG0212): A Multicenter, Randomized Controlled, Noninferiority Trial. Ann Surg. 2017;266(2):201–7.
73. Valentini V, Aristei C, Glimelius B, Minsky BD, Beets-Tan R, Borras JM, et al. Multidisciplinary Rectal Cancer Management: 2nd European Rectal Cancer Consensus Conference (EURECA-CC2). Radiother Oncol. 2009;92(2):148–63.
74. Kusters M, Beets GL, van de Velde CJ, Beets-Tan RG, Marijnen CA, Rutten HJ, et al. A comparison between the treatment of low rectal cancer in Japan and the Netherlands, focusing on the patterns of local recurrence. Ann Surg. 2009;249(2):229–35.
75. Nagawa H, Muto T, Sunouchi K, Higuchi Y, Tsurita G, Watanabe T, et al. Randomized, controlled trial of lateral node dissection vs. nerve-preserving resection in patients with rectal cancer after preoperative radiotherapy. Dis Colon Rectum. 2001;44(9):1274–80.
76. Watanabe T, Tsurita G, Muto T, Sawada T, Sunouchi K, Higuchi Y, et al. Extended lymphadenectomy and preoperative radiotherapy for lower rectal cancers. Surgery. 2002;132(1):27–33.
77. Georgiou P, Tan E, Gouvas N, Antoniou A, Brown G, Nicholls RJ, et al. Extended lymphadenectomy versus conventional surgery for rectal cancer: a meta-analysis. Lancet Oncol. 2009;10(11):1053–62.
78. Fujita S, Akasu T, Mizusawa J, Saito N, Kinugasa Y, Kanemitsu Y, et al. Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial. Lancet Oncol. 2012;13(6):616–21.
79. Ogura A, Akiyoshi T, Nagasaki T, Konishi T, Fujimoto Y, Nagayama S, et al. Feasibility of Laparoscopic Total Mesorectal Excision with Extended Lateral Pelvic Lymph Node Dissection for Advanced Lower Rectal Cancer after Preoperative Chemoradiotherapy. World J Surg. 2017;41(3):868–75.
80. Nagayoshi K, Ueki T, Manabe T, Moriyama T, Yanai K, Oda Y, et al. Laparoscopic lateral pelvic lymph node dissection is achievable and offers advantages as a minimally invasive surgery over the open approach. Surg Endosc. 2016;30(5):1938–47.
81. Akiyoshi T, Matsueda K, Hiratsuka M, Unno T, Nagata J, Nagasaki T, et al. Indications for Lateral Pelvic Lymph Node Dissection Based on Magnetic Resonance Imaging Before and After Preoperative Chemoradiotherapy in Patients with Advanced Low-Rectal Cancer. Ann Surg Oncol. 2015;22 Suppl 3:S614–20.
82. Kim MJ, Chan Park S, Kim TH, Kim DY, Kim SY, Baek JY, et al. Is lateral pelvic node dissection necessary after preoperative chemoradiotherapy for rectal cancer patients with initially suspected lateral pelvic node?. Surgery. 2016;160(2):366–76.