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SURGERY AND SURGICAL INNOVATIONS IN COLORECTAL CANCER (S HUERTA, SECTION EDITOR)

Current Surgical Strategies in the Management of Rectal Cancer

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Abstract

Purpose of Review The surgical approach to rectal cancer has become significantly more complex with the introduction of neoadjuvant therapies and organ preservation strategies. Optimal radiological imaging in association with relevant clinical findings provides critical information for final surgical management decision. The present review focuses on the surgical alternatives available in different clinical scenarios for the management of rectal cancer.

Recent Findings Most of evidence for surgical management of rectal cancer is provided by non-randomized studies. However, a few randomized clinical trials have attempted to address the optimal surgical approach for total mesorectal excision. In addition, recent randomized trials have also contributed to the understanding of the role of organ-preserving strategies among patients with excellent response to neoadjuvant treatment. Finally, one randomized Japanese study has provided oncological evidence in favor of prophylactic lateral node dissection among these patients.

Summary Radical proctectomy with total or partial mesorectal excision is the standard procedure for most patients with primary rectal cancer. Optimal approach for this procedure remains controversial. The decision between sphincter-preservation strategies and abdominal perineal resections should take into account the radiological and clinical findings. More recently, organ-preserving strategies including transanal local excisions may be used in select patients with early-stage disease or among patients undergoing neoadjuvant treatment strategies after significant primary tumor regression. Extended procedures including lateral pelvic side lymphadenectomies and exenterative procedures should be done selectively and in highly specialized centers.

Keywords Rectal cancer · Total mesorectal excision · Neoadjuvant chemoradiation · Laparoscopic surgery · Robotic surgery · Local excision · Watch and wait · Lateral lymph node dissection

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Introduction

The management of rectal cancer has become significantly more complex after introduction of neoadjuvant therapies and progressive interest in organ-preservation strategies. The previous treatment strategy used a "one size fits all" often resulted in high rates of definitive stomas as well as unacceptable local recurrence rates. The current armamentarium to the surgeon now includes multiple surgical and even non-surgical strategies for curative treatment of rectal cancer. In addition, magnetic resonance imaging (MRI) has become pivotal in the management decision process, which together with clinical findings provides objective information that aids optimal treatment options during multidisciplinary discussions.

Finally, developments in minimally invasive techniques have provided surgical solutions to overcome technical difficulties during rectal cancer surgery that have significantly

impacted surgical practice. However, even though the newly developed surgical strategies are technically sound and have clinically demonstrated equivalent (or even superior) surgical and oncological outcomes, rigorous scrutiny of these techniques in randomized controlled trials is still lacking.

Initial Tumor Assessment & Surgical Strategy

Initial patient and tumor assessment is critical in selecting the ultimate surgical strategy for individuals affected with rectal cancer. Tumor distance from the anal verge or anorectal ring, tumors' size, rectal wall (anterior, posterior or lateral), and tumor mobility may all influence surgical planning. Thus, digital rectal examination and proctoscopy are essential examinations to be performed by the operating surgeon during the initial operative assessment. In addition, MR features will be also critical for the decision process. The operative decisions include the decisions (1) between procedures with or without mesorectal excision; (2) between procedures with or without sphincter-preservation; (3) between upfront surgery or preoperative treatment; and (4) the decision for the need of additional procedures.

In contrast to the previous practice of making these decisions intraoperatively as some surgeons argued that "full mobilization of the rectum" would be needed to make decisions, clinical, endoscopic, and radiological assessment allows surgeons to make these decisions preoperatively rather than intra- or post-operatively. There are very little to no information that is currently not provided by the preoperative assessment and all efforts should be made to avoid intraoperative technical improvisations or deviations from the planned approach. Ultimately, unexpected findings should be amenable to additional treatment strategies in the postoperative period in a small percentage of patients.

Total Mesorectal Excision

Total mesorectal excision is still considered the standard operation for rectal cancer. Even though partial mesorectal excision may be performed for upper (intraperitoneal) rectal cancer, total mesorectal excision should be performed for all tumors below the peritoneal reflection [1]. (Fig. 1).

Open and Laparoscopic TME

With the development of minimally invasive procedures, namely colorectal laparoscopic (and robotic) techniques, it has been possible to obtain significant improvements in short-term outcomes with similar long-term oncological outcomes when compared to the historically open TME, which was the standard approach for this operation [2]. Only recently randomized trials have studied the differences in outcomes between the open technique and minimally invasive procedures in rectal cancer [3••, 4, 5, 6••]. Theoretically, the standardization of the key technical steps of laparoscopy and an improvement of the visualization of the pelvis could be associated to better short-term outcomes without compromising oncological results. Most, if not all, of these studies use an establishment of pathological findings [quality of the mesorectum and positive circumferential margins (CRM+)] as a surrogate for oncological outcomes. The European COLOR II trial demonstrated similar oncological outcomes between open and laparoscopic TME supporting the minimally invasive approach [5]. Furthermore, the COREAN trial also suggested similar oncological outcomes between laparoscopic and open surgery for rectal cancer surgery [4]. There are two intriguing aspects of the COLOR trial that are worth mentioning. When considering distal rectal cancers, CRM+ was more frequently observed in the open approach, favoring the laparoscopic approach. On the other hand, among mid-rectal cancers there was a significant difference in the CRM+ rate comparing both arms that favored the open approach. Oncological outcomes were similar between both arms (with the exception of stage III disease where it was better for laparoscopic approach); however, one could observe that worse pathological outcomes for mid-rectal cancers could possibly suggest worse technical performance with laparoscopy. Considering abdominal perineal resection (APR) technique has been associated with worse pathological outcomes, the frequent use of this surgical alternative might have been responsible for the worse results observed in the open group for distal rectal cancers. Recent randomized studies have been unable to put this controversy to rest. In the ACOSOG Z6051 study, a pathological endpoint that included mesorectum quality, distal resection margin, and CRM status was used as the primary endpoint. In this study, surgeons obtained accreditation before entering the study in order to standardize surgical expertise [3••]. Designed to be a non-inferiority study between laparoscopic surgery and open surgery for rectal cancer, the study failed to demonstrate non-inferiority of laparoscopy. The latter was inferior in the pathological results used as surrogate markers for oncological outcomes. These results can be attributed to the observation of pathological outcomes (used for power calculation purposes) for open ("standard") TME inferior than expected and the use of an endpoint composite not previously validated [7–9]. However, the Austro-Asian ALACART study also failed to demonstrate non-inferiority of laparoscopy to open surgery for performing TME [6••]. Despite the differences in pathological outcomes between open and laparoscopic surgery, long-term oncological outcomes were equivalent between these two surgical approaches in the ACOSOG study [10•].

Robotic TME

Robotically-assisted minimally invasive surgery was a promising improvement for rectal cancer surgery. By allowing

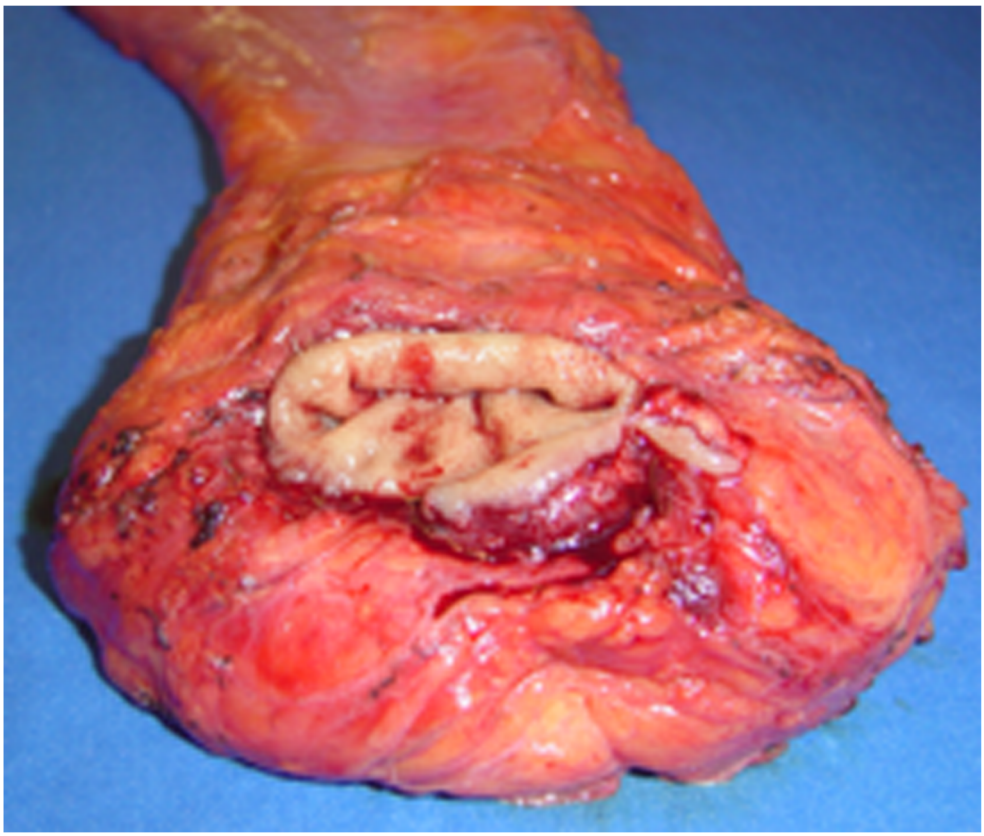

Fig. 1 Total mesorectal excision surgical specimen showing an intact mesorectum

better instrumentation and improved visualization of the rectum coupled with better surgeon-ergonomics, it promised an improvement in TME surgical outcomes. However, when meta-analyses and systematic reviews compared laparoscopy to robotically-assisted procedures a suggested decreased rate for conversion to open surgery was observed. The ROLAAR trial, which is the single randomized trial on the subject, failed to demonstrate significant differences in conversion rates when comparing both minimally invasive procedures [11••]. Lower rates than the expected conversion rates in the laparoscopy arm may explain the lack of statistical differences between both arms. However, robotic colorectal surgery is still being undertaken and further studies on this subject might elucidate more conclusive results in the future.

Transanal TME

Regardless of the exact reasons for the unexpected negative findings for laparoscopic and robotic TME surgery in terms of surgical-pathological outcomes, it has become evident that even in the setting of a controlled clinical trial with properly selected expert surgeons, laparoscopic TME is a challenging procedure with a steep learning curve. Obtaining an intact mesorectum, clear CRM and distal margins may be at risk during this approach. In an attempt to improve the obtainment of these pathological features during TME surgery that are known surrogate markers for long-term oncological outcomes, an alternative approach has been suggested.

Previous experience with transanal surgery for local excision of rectal tumors and developments in microsurgical endoscopic platforms led surgeons to consider performing total mesorectal excision transanally (taTME) [12]. The first keystep of this procedure includes closure and sectioning of the rectum distal to the tumor, thus ensuring a proper distal margin (one of the important surrogate markers for long-term oncological outcomes). This step of the procedure replaces the challenging step of the abdominal approach that requires obtaining proper distal margins by sectioning the rectum with linear endoscopic staplers, often requiring multiple staple loads and endoscopic control of the line of resection to prevent exiguous or even positive margins. With taTME, once the rectum is fully incised circumferentially, total mesorectal excision is performed under direct vision to provide an optimal TME specimen and proper CRM clearance. Dissection proceeds cranially while usually an abdominal team reaches the perineal dissection to complete protectomy, proximal vessel ligation, and splenic flexure mobilization when needed. There is still controversy whether a single or two-team approach results in different outcomes during the procedure [13].

Even though no randomized trials are yet available, initial experience with case-control studies seem to suggest similar (if not superior) outcomes as determined by pathological

markers (distal margins, CRM status and quality of the mesorectum) with the transanal approach [14]. More recently, good outcomes regarding pathological surrogate markers have been reported by international multicenter registries [15•].

However, a few words of caution are in order prior to definitive implementation of taTME into surgical practice. taTME requires proper training and, as in any other surgical procedure, there is a learning curve for the procedure [16]. Previous experience with TME and transanal surgery with endoscopic microsurgical platforms should be in place to accelerate overcoming the learning curve of the procedure such that complications are minimized [17]. In fact, considering the change in anatomical landmarks during taTME when compared to abdominal TME, a few intraoperative complications may be more likely to develop when compared to abdominal TME. Injuries to the prostate or urethra, injuries to iliac/obturator vessels and presacral veins may be more frequent with the taTME [18]. In addition, functional outcomes following taTME in comparison to the standard TME are still pending formal analysis. In the meantime, registries provide an opportunity to compare and scrutinize individual results with this technique.

The Consequences of TME

Regardless of the surgical technique, TME has several clinically relevant consequences. Unfortunately, regardless of the approach there is immediate postoperative morbidity (up to 58%) and mortality (up to 16% depending on age and comorbidities) associated with proctectomies [3••, 19]. In addition, patients may experience functional disturbances in urinary and sexual function (in up to 30% of TMEs) [20••]. Finally, even when a primary colorectal or coloanal anastomosis is possible, functional outcomes may be far from perfect [21, 22]. A proportion of patients will experience significant low anterior resection syndrome symptoms requiring additional procedures or even construction of a definitive stoma [23]. In fact, even though expert centers may report initial definitive colostomy rates $\leq 10\%$, long-term follow-up indicates that colostomy rates may be as high as 22%, as a consequence of failed anastomoses [23].

Sphincter-Preservation and Abdominal Perineal Resection

The decision between sphincter-preservation and abdominal perineal excision is currently based on clinical and radiological findings preoperatively. The ability to provide a safe ($\geq$ 1 cm) distal margin, no direct invasion of the sphincters and no tumor invasion of the intersphincteric space (as determined by MR) are minimal requirements for pursuing sphincter-preservation. A recent classification of distal rectal cancers in four subtypes has been suggested with the aim of assisting surgeons in deciding upon the optimal surgical approach. Similarly, it may allow for a standardized restaging of the tumor after treatment with a subsequent change in type of surgery, although this premise is still to be determined clinically. The classification is based on the association of preoperative MR and standardized surgery according to tumor type:

(1) Type I is a low supra-anal (tumor > 1 cm from anal ring) where an ultra-low anterior resection is appropriate.
(2) Type II juxta-anal (tumor < 1 cm from anal ring) where a partial intersphincteric resection is required.
(3) Type III intra-anal (tumor invading internal anal sphincter) treated preferably with total intersphincteric resection.
(4) Type IV transanal (tumor invading the external anal sphincter) optimally treated with abdominal perineal resection. Type IV was further divided into three subcategories according to the invasion of the EAS and levator ani muscles. Infiltration of the intersphincteric plane was considered as invasion of the external sphincter and so, a clear indication for APR. [24•]

The comparison of APR to sphincter-preservation procedures has historically showed worse oncological outcomes for APR. Even though initially considered to be intrinsically and biologically distinct entities (tumors requiring APR or sphincter-saving operation, SSO), a pathological review of the Dutch TME trial called attention to the increased rates of CRM+ and local recurrence rates among patients undergoing APR. [25, 26] Shortly, systematic reviews suggested that APR were consistently more associated with intraoperative tumor perforation and CRM+ [26]. These findings provided the setting for a review of the technical steps of the procedure, with the suggestion of an alternative approach [27]. Also known as the extralevator approach (ELAPE), technical details were reported in order to provide specimens with larger circumferential surrounding tissue and therefore minimizing the risk for CRM+ [28]. Controversy still remains whether ELAPE results in superior oncological outcomes to standard APR. Still, most studies suggest that ELAPE should be preferred in tumors $\leq$ 4 cm from the anal verge and where increased of intraoperative tumor perforation is anticipated [29•].

Beyond TME

Extension of primary rectal cancer beyond the TME plane may require surgical resection of adjacent organ or structures in order to provide R0 resection. Depending on specific anatomical structures involved, surgical resection outside of the mesorectal fascia may include a range of exenterative-type procedures. Even though most contraindications for resectability are relative (unresectable distant metastases, encasement of

external iliac vessels, predicted R2 resection, high sacral involvement–S2/S3, extension of tumor through the sciatic notch), specialized centers with expertise may still considered such cases following local multidisciplinary-team (MDT) agreement. Consensual absolute contraindications include poor performance status, bilateral sciatic nerve involvement and circumferential bone involvement [30].

Major exenterative procedures require multi-professional specialist centers and are usually associated with long operative times and length of stay. Careful selection of patients is critical in the setting of significant postoperative morbidity, limited long-term survival (30–50%) and paucity of quality of life data.

Lateral Pelvic Lymph Node Dissection

Historically, surgical clearance of lateral pelvic lymph nodes (LND) is a strategy almost exclusively restricted to eastern countries [31]. Anatomically, there is lateral drainage in the region of the medial rectal artery, which drains directly into the internal and obturator iliac vessels [32]. Prophylactic LND routinely performed in Japan, resulted in significant rates of lateral node metastases among patients with locally advanced disease (pT3 or pT4) located below the peritoneal reflection [32]. Western countries, however, neglected this procedure for several reasons. Significant anatomical complexity of the procedure, the risk of potential functional consequences (namely urinary and male sexual dysfunction), considerable intraoperative blood loss all contributed to resistance towards implementation into clinical practice.

However, an important Japanese study provided evidence in favor of this procedure for rectal cancer [33••]. A prospective clinical trial randomized patients with rectal cancer with unsuspected lateral node metastases to TME alone or TME and prophylactic bilateral LND [33••]. First, short-term outcomes revealed that the only significant morbidity associated with LND was increased intraoperative blood loss [34••]. No other complication, including male sexual dysfunction, was found to be associated with LND [35•]. These studies, however, were performed using open or minimally invasive techniques. Further case-matched studies comparing open and laparoscopic approaches demonstrated that the minimally invasive technique significantly reduced the risk for intraoperative blood loss [36•]. Finally, recent attempts to standardize the minimally invasive approach have demystified the complexity of the procedure [37]. Altogether, data suggests that LND adds minimal morbidity to TME alone (particularly when performed by minimally invasive approaches). However, evidence of the oncologic benefit of this approach was lacking until the final outcomes of the JCOG0212 trial have been recently reported showing that non-inferiority of TME alone to TME + LND was not reached. Patients undergoing TME alone presented significantly higher rates of lateral pelvic recurrence, despite the absence of suspected lateral metastatic nodes preoperatively [33••].

The problem with this study was the lack of neoadjuvant chemoradiation (CRT). One could argue that CRT could have significantly reduced the risk of lateral local recurrences among patients undergoing TME alone. In the absence of additional randomized studies, an important retrospective study has shed light on this particular matter. A review of all patients in multiple institutions (including western countries) provided data on baseline lateral node status prior to CRT and TME alone. The authors found that patients with baseline lateral nodes seen on radiological imaging ≥7 mm were at increased risk for lateral pelvic recurrence after CRT and TME alone. Based on this data, one could argue for lateral LND in patients with ≥7 mm lateral nodes at baseline despite having received neoadjuvant CRT [38•].

Organ Preservation Strategies

The main driver towards organ-preservation strategies in the management of rectal cancer was the significant clinical consequences associated with radical TME. High postoperative morbidity including sexual and urinary dysfunction as well as fecal incontinence associated with the need for temporary or definitive stomas during the procedure are quite significant after TME. In this setting, surgeons considered the possibility of offering a surgical alternative with similar oncological outcomes but less clinical consequences and stoma requirements. Full-thickness local excision of the primary tumor (without formal lymph node resection–mesorectal excision) was investigated among patients with the lowest risk of lymph node metastases (T1 and T2 tumors). Initially performed with the use of standard surgical instruments and transanal retractors, oncological outcomes were clearly inferior to TME both in T1 and T2 rectal cancers [39]. Even though one prospective trial (CALGB) did show < 10% local recurrence rates for T1 rectal cancer, rarely local excision alone was considered as a radical alternative. Instead, patients were advised to undergo completion TME or even adjuvant CRT for the optimization of local disease control [40].

More recently, an endoscopic microsurgical platform has revolutionized transanal surgery. With the use of rectal insufflation and augmented endoscopic views, this technique has resulted in significantly higher rates of R0 resections and en bloc specimens during local excision when compared to the standard approach [41]. Moreover, these platforms provide safe access to lesions up to 10–12 cm from the anal verge. However, despite the acquisition of improved quality in surgical specimens, oncological outcomes were unchanged. A multicenter experience with TEMS alone for early rectal cancer, demonstrated appropriate oncological outcomes restricted

to small, superficial and otherwise favorable pT1 rectal cancer. Patients with more advanced disease should be considered for additional adjuvant CRT or completion TME [42].

Neoadjuvant CRT for Organ-Preservation

Introduction of neoadjuvant CRT in the management of locally advanced rectal cancer led to the observation of significant tumor regression following treatment. Often tumors decrease in size (downsizing) and become less advanced (downstaging) by leaving more superficial residual cancer cells and sterilizing metastatic lymph nodes. This could in theory provide the ideal setting for a local excision: small, superficial and low risk for lymph node metastases. Initial studies reported on the outcomes of patients managed by neoadjuvant CRT followed by local excision using the TEMs platforms after significant tumor response. As CRT has evolved and become the standard of care, the assessment of tumor response has become a central clinical issue. Only patients with significant tumor response, often named as near-complete responses, were considered for organ-preserving local excision. Patients were required to harbor small residual lesions (≤3 cm), restricted to the bowel wall (ycT1–2) and no evidence of lymph node metastases (ycN0). Local excision in this setting, however, resulted in local recurrence rates ≥15%, particularly when residual cancer cells were found in the muscularis propria of the rectum (ypT2) [43–45]. A possible explanation for these unfavorable outcomes could have been and undetected baseline advanced disease. Many of these patients could have been cT3 and cN+ at baseline and have significantly affected local recurrences rates after local excision [46]. Notably, local recurrences after primary CRT and local excisions were frequently associated with CRM+ and the requirement for an APR. [47] An additional drawback of this approach included the increased risk for wound dehiscence after primary closure of excisional defects. [48]

An alternative approach was then suggested with the use of neoadjuvant CRT followed by local excision in baseline cT2 N0 rectal cancers. First, a clinical trial of stage I rectal cancer managed by CRT randomized TME and local excision (using TEM) showed similar oncological outcomes in both arms [49]. Moreover, treatment-related morbidity was significantly better in the local excision arm. A second single-arm prospective trial also managed consecutive patients with cT2 N0 by CRT followed by local excision. Local recurrence rates were considerably low (≤4%) after long-term follow-up [50•]. Finally, an important randomized study compared TME to local excision among small cT2-T3 N0 rectal cancers after neoadjuvant CRT and a good response (defined as ≤2 cm residual disease). Patients undergoing local excision had similar outcomes to TME. Worse functional outcomes were only observed after local excision followed by completion TME among patients with unfavorable pathology in the local excision specimen [20••]. Currently, local excision is considered an alternative organ-preservation strategy for highly selected patients with baseline early-stage disease (T2 or small T3 N0) undergoing neoadjuvant CRT and significant tumor response (ypT0–1 and highly selected ypT2).

Assessment of Complete Clinical Response

Assessment of response to neoadjuvant (n) treatment should be undertaken in all individuals who have received nCRT even in those individuals who are planned for radical surgery. In the latter, the evaluation of the response may allow better planning of the surgery to be performed as well as the technical challenges to be met. However, there are many uncertainties regarding the timing of the assessment and considerations on the tools currently available.

Assessment of tumor response is basically a repetition of primary tumor assessment and should include clinical examination, endoscopy, and MRI. Here, clinical and radiological assessment may indicate the absence of residual cancer. Findings consistent with complete clinical response (cCR) include the presence of a white flat scarring area and telangiectasias, frequently associated with a subtle loss of pliability of the rectal wall [51]. Ulcerations or stenoses should be considered as signs of incomplete response to treatment. Post-treatment endoscopic biopsies should be interpreted with great care. Negative biopsies are associated with a high negative predictive value (NPV) and therefore should not be considered as diagnostic of cCR [52]. Often residual cancers will have false negative endoscopic biopsies. In addition to clinical and endoscopic assessment, radiological assessment may offer additional information regarding tumor response to CRT. MRI and PET/CT may provide objective information identifying patients likely to harbor complete response [53, 54].

Even though assessment of tumor response appears to be time-dependent, prospective randomized studies have failed to demonstrate advantages in tumor response between short and long intervals for all patients [55••]. Patients with significant tumor response may benefit from longer intervals whereas patients with poor response may be best managed by immediate radical surgery [56].

Watch and Wait

Patients with cCR have been also considered for organ-preservation strategies with acceptable oncological outcomes. In addition to local excision, no immediate surgery has been considered an alternative by strict clinical and radiological surveillance of patients until development of local tumor regrowth. Oncological outcomes have been reported to be similar to radical surgery after complete pathological response with a lower risk for definitive stomas, lower treatment-related morbidity and mortality [57•]. Even though local

regrowth rates appear to be in the range of 22–25% after 3 years of intensive follow-up, definitive salvage resection is successful in 90% of these cases providing good oncological outcomes [58••, 59••]. Features associated with increased chances of complete tumor regression and successful organ-preservation include baseline stage, dose of radiation and amount of concomitant chemotherapy [58••, 60]. Patients with early-stage disease, undergoing higher doses of radiation therapy (> 50.4 Gy) and receiving consolidation chemotherapy are more likely to develop cCR and avoid radical surgery [61•, 62••].

Significant initial skepticism with nonoperative management derived from the lack of robust and prospective data with this approach. Also, the lack of a clear definition and standardization of findings consistent with complete clinical response was a significant limitation in the interpretation of initial reported data. Finally, there was little evidence to substantiate complete clinical response as an appropriate surrogate marker for a complete pathological response [63]. Since then, a significant amount of data has been reported to further substantiate this approach in very selected patients [57•, 58••, 59••]. Even though the approach is considered within international guidelines for selected patients and institutions, overall the recommendation is that it should be restricted to the setting of clinical trials or for patients unfit for standard radical surgery [64].

Conclusion

The management of rectal cancer is complex and many variables can influence its final surgical decision. Patients with rectal tumors above the peritoneal reflection usually require upfront surgical resection with straight partial mesorectal excision and primary anastomosis. Patients with extraperitonial tumors are always considered for upfront total mesorectal excision when there is no need for APR or ultra-low coloanal anastomosis and there is no increased risk of local recurrence (mrCRM+, mrN2). If APR or coloanal anastomosis is anticipated or there is a high-risk for local recurrence, neoadjuvant CRT should be the preferred initial alternative. Patients should routinely undergo reassessment of tumor response after CRT at 6–8 weeks. Patients with excellent clinical response may be reassessed again prior to definitive management at 12–14 weeks. Patients with poor response at 6–8 weeks should be managed by TME (lateral node lymphadenectomy if baseline lateral nodes ≥ 7 mm). Reassessment at 12 weeks from CRT showing complete clinical response should consider the alternative of strict surveillance (Watch & Wait). Near-complete responders at 12 weeks should be considered candidates for local excision when APR or coloanal is anticipated and there is evidence for minimal residual disease.

Compliance With Ethical Standards

Conflict of Interest José Moreira de Azevedo declares that he has no conflict of interest.

Bruna Borba Vailati has received compensation from Johnson & Johnson and Medtronic for Service as a consultant.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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