New Strategies in Rectal Cancer

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INTRODUCTION

The development and implementation of newer treatment modalities have significantly increased the complexity in the management of rectal cancer,1 with surgical treatment remaining as the main pillar. Interest into the different approaches for total mesorectal excision (TME), including standard laparoscopy, robotic surgery, and transanal TME are increasing rapidly. This interest is not only based on the advantages of smaller incisions, but also on the desire to obtain a better specimen quality, which may translate into a better oncological outcome.

Several recent trials have focused on the oncological outcomes of laparoscopic rectal cancer surgery compared with the standard open approach, and results have been mixed,2–5 with some showing laparoscopy to be either equivalent or even favorable to open surgery, whereas others were unable to establish noninferiority for surgical treatment.

KEYWORDS

- Transanal TME
- Organ-preserving strategies
- Local excision
- Watch and wait

KEY POINTS

- Neoadjuvant chemoradiation may lead to significant tumor regression and to complete pathologic response in rectal cancer.
- Assessment of tumor response may identify patients who could be managed with organ-preserving strategies, including the Watch and Wait strategy and local excision.
- When organ-preserving strategies are used for rectal cancer, close surveillance may allow early detection of local recurrences and salvage alternatives.
- In case of incomplete response to chemoradiation, the best alternative for most patients will still be proper total mesorectal excision: minimally invasive or conventional open surgery.

INTRODUCTION

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laparoscopy. Most experts agree that laparoscopic rectal cancer surgery is very complex and technically demanding, and it cannot be universally applied to all patients. To overcome specific technical complexities associated with laparoscopic TME, transanal total mesorectal excision (TaTME) has emerged as a technique that enables meticulous endoscopic dissection from the bottom up, which reduces the technical constraints of the narrow pelvis.

In addition to changes in the surgical approach to rectal cancer, there have also been many advances in neoadjuvant therapy with subsequent management tailored to the tumor response. Neoadjuvant chemoradiation (nCRT) may lead to significant tumor regression, ultimately leading to complete pathologic response in up to 42% of patients. Assessment of tumor response after nCRT and before radical surgery may identify patients with complete clinical response that could be managed nonoperatively with strict follow-up (watch and wait [WW] strategy) and thus avoiding unnecessary postoperative morbidity with good long-term oncological outcomes and excellent functional results. In addition, close surveillance may allow for early detection of local recurrences and subsequent salvage surgery without a significant compromise in the oncological outcome.

This article discusses these new strategies for the management of rectal cancer.

ORGAN PRESERVATION IN RECTAL CANCER

Different organ-preserving strategies for the treatment of rectal cancer have gained popularity in recent years. Regardless of approach, proctectomy is associated with significant postoperative morbidity, including long-term urinary, sexual, and fecal continence dysfunction in addition to the requirement for temporary or definitive stomas associated with the procedure. Also, depending on age and comorbidities, postoperative mortality also may be quite significant. Therefore, in selected patients, surgical and even nonsurgical approaches that spare the rectum have been suggested. The observation that rectal cancers could develop significant tumor regression with reduction in primary tumor size (downsizing), depth of tumor penetration, and even potential nodal sterilization (downstaging) after nCRT could set the ideal stage for organ-preserving alternatives, including local excision of small and superficial residual tumors. In addition, regression of the primary tumor could result in complete disappearance of the tumor in the resected specimen (complete pathologic response [pCR]) in some patients. In a subset of these patients, complete regression of the primary tumor is clinically detected before surgical resection, referred to as a complete clinical response (cCR). It is in these patients with a cCR after nCRT that we have considered a WW strategy without immediate surgical resection. To consider these approaches, surgeons must take into consideration several aspects of the disease, patients, and treatment modalities that may be quite relevant during their clinical decision-making process.

Assessment of Tumor Response

When considering patients for the WW strategy, assessment of tumor response is crucial. However, this assessment can be challenging due to uncertainties regarding the optimal timing of the assessment, and the most accurate clinical and radiological tools for this purpose.

Of note, assessment of tumor response is also recommended for patients with a partial clinical response in which organ-preserving strategies are not being considered. Even if the plan after nCRT is a radical resection, one needs to consider that after nCRT, the surgeon may be facing a considerably different tumor. Knowing this
potentially new “anatomy” ahead of time may allow the surgeon to optimize intraoperative surgical strategy and to know in advance what challenges could be anticipated during the procedure. Therefore, reassessment of tumor response should be performed in all patients.

**Timing for the Assessment of Tumor Response**

The grade of tumor regression after nCRT appears to be a time-dependent phenomenon. The first randomized trial to consider the effect of different time intervals in the response to CRT was a French study comparing 2 versus 6 weeks from nCRT. In this study, all patients underwent radical surgery after these 2 time intervals and patients with 6-week intervals presented significantly more tumor regression after nCRT. Due to this study, a 6-week time interval between nCRT completion and performance of radical surgery has been considered the standard of care for many years. However, retrospective studies consistently reported that patients undergoing radical surgery after longer than 6 to 8 weeks from nCRT were more likely to develop pCR. One of these studies suggested that the rates of pCR after nCRT may keep rising after nCRT for as long as 12 weeks from treatment completion. However, there was a question of whether these prolonged intervals from nCRT would result in excessive tissue fibrosis in the area included in the radiation therapy field that could lead to increased technical difficulty and postoperative morbidity after radical surgery.

In 2015, Garcia-Aguilar and colleagues performed a prospective, nonrandomized study evaluating patients in nCRT regimens with progressively longer interval periods before surgery. Although one group received surgery 6 weeks after cCRT completion, the other 3 groups had extended intervals of 12, 16, and 20 weeks, with supplemental chemotherapy during the extended intervals. Even though this was not a randomized study, patients in different groups had similar baseline demographics and tumor stages. The investigators found that extended intervals were associated with significantly higher rates of pCR (6 weeks = 18%, 12 weeks = 25%, 16 weeks = 30%, and 20 weeks = 38%). In addition, the investigators found that the extended intervals did not have a deleterious impact on overall morbidity, blood loss, or the technical difficulty of the case.

Another recently published randomized study came to different conclusions. In the GRECCAR-6 trial, patients were randomized to post-CRT intervals of 7 or 11 weeks. The investigators found that pCR rates were similar with the 2 intervals, but the morbidity rates were higher in the 11-week group (higher for Clavien Dindo classes 1 and 2, similar for classes 3–5), and the quality of mesorectal excision was worse in the 11-week group, suggesting the detrimental effects of prolonged time after nCRT on fibrotic changes in the surgical and previously irradiated fields. Of note, there were several limitations to this trial, including issues with adherence to the prescribed time interval, resulting in several patients from the 7-week group having longer intervals before surgery.

The optimal interval after nCRT remains undetermined, and additional ongoing trials will definitely provide more data to allow us to understand the benefits and risks of using prolonged intervals after treatment. In fact, it may be the case that a single and fixed interval may not be appropriate for all patients. Instead, patients/tumors may respond differently as a function of time to nCRT. Ultimately, responsive tumors may require and actually benefit from prolonged intervals from nCRT, whereas unresponsive tumors may not. It is likely that responsive tumors that are being considered for organ-preserving strategies should have their assessment of response and ultimately surgical strategy decision deferred to longer than 12 weeks. On the other
hand, tumors with little response that still require radical TME may benefit from 6-week to 8-week intervals between nCRT completion and radical surgery.25

**Tools in Assessment of Tumor Response**

**Clinical and endoscopic assessment**

Clinical assessment is one of the most important tools to evaluate tumor response. Commonly, patients with tumor regression would have relief of their symptoms. Digital rectal examination (DRE) is an irreplaceable tool for the evaluation of response. The stringent criteria to consider a complete clinical response (cCR) includes the absence of any irregularity, mass, ulceration, or stenosis during the DRE. The surface has to be regular and smooth.16

Endoscopic evaluation of the area harboring the original tumor is the remaining key component of clinical assessment. It is important to look for any irregularity or superficial ulcers missed during DRE. A flat white scar and telangiectasias are common endoscopic findings among patients with a cCR (Fig. 1). Even though flexible scopes provide photographic documentation of endoscopic response, rigid proctoscopy may suffice for most patients.16

In the presence of a cCR by DRE and proctoscopy, endoscopic biopsies are not recommended. Even in the setting of incomplete clinical response, endoscopic biopsy results should be interpreted with caution. Among patients with significant response, negative predictive values of these endoscopic biopsies have been reported to be consistently low.26 Residual mucosal disease can be missed due to adjacent scarring, and residual disease within the bowel wall or mesorectum may be accompanied by a normal mucosal surface. Therefore, a negative biopsy in the setting of incomplete clinical response does not rule out microscopic residual cancer.

**Radiological assessment**

Even though historically the definition of a cCR has been based on clinical and endoscopic findings by direct assessment of the rectal wall, radiological studies have always attempted to provide additional information unavailable to the finger or the proctoscope, particularly regarding nodal or mesorectal status of the disease. Currently, however, significant developments in imaging definition and interpretation have resulted in significant increases in accuracy for the assessment of response not only within the mesorectum compartment, but also within the rectal wall.

High-resolution magnetic resonance (MR) is now routinely used for the assessment of response. The ability to discriminate between fibrosis and residual disease has

**Fig. 1.** Endoscopic view of rectal cancer before (A) and after 10 weeks from nCRT completion (B) showing a complete clinical response (cCR).
improved with advances in technology, placing the resonance as an essential tool to confirm clinical and endoscopic findings of a cCR. MR may provide an accurate radiological (mrTRG) estimate of the pathologic tumor regression grade (TRG). The utilization of this mrTRG score may identify good and poor responders with significant impact in disease-free and overall survival (Fig. 2).

Even though clinical and endoscopic assessment using stringent criteria will result in high specificity rates for the detection of a pCR, a significant number of patients with incomplete clinical response will still harbor complete pathologic response. In fact, it seems that most patients with pCR after nCRT have incomplete clinical response after 8 to 12 weeks from nCRT. Therefore, there is a potential role for MR studies to identify patients with incomplete clinical response who may ultimately harbor pCR. Currently, these patients would be referred for immediate radical surgery; however, radiological tools may be able to accurately identify these patients and avoid potentially unnecessary surgery.

Recently, a study that compared mrTRG and residual mucosal abnormalities following nCRT suggested that the mrTRG system may identify nearly 10 times more complete pathologic responses compared with clinical endoscopic findings. These findings may improve the selection of patients with pCR despite initial incomplete clinical response and that may be appropriate candidates for deferral of surgery.

Diffusion-weighted magnetic resonance imaging (DWI-MR) may add significant functional information to standard MRI. The fact that diffusion properties of water molecules may vary in areas of tissue necrosis, high cellularity (frequently observed within tumor tissues), or fibrosis may be used to help assess tumor response to nCRT (Fig. 3). Absence of restriction to diffusion of water molecules has been associated with the absence of residual cancer (complete response). On the other hand, restriction to diffusion of water molecules (seen as high signal intensity in the area of the previous tumor) may indicate the presence of residual cancer cells (incomplete response). Initial reports with DWI-MR for the assessment of response to nCRT have shown promising results with high accuracy rates and may constitute a useful tool during assessment of response.

PET/computed tomography (CT) imaging has been studied for the prediction of response to CRT. The use of molecular imaging may provide additional information
to standard structural/anatomic features to help distinguish between fibrosis or residual tumor. The use of fludeoxyglucose (FDG) allows for the estimate of tissue metabolism (standard uptake values [SUV]) within areas of interest and fused images of PET and CT may indicate precise anatomic areas of residual cancer cells, even among mucinous histologic subtypes.35 Most of the available studies have focused on SUV variation for the identification of complete responders to nCRT using variable interval periods and sequential PET/CT imaging.36-38 Accuracies, however, have been insufficient for its routine recommendation into clinical practice. A recently reported study suggested that the combination of SUV variation and volumetric reduction in tumors could predict complete response to nCRT. Using individual technical calibration for determining metabolic tumor volumes estimates, variation in total lesion glycolysis (determined by metabolic tumor volume

![Fig. 3. Image showing a residual ymrT2 cancer following nCRT (A, yellow arrow) and diffusion restriction (high signal intensity, yellow arrow) (B) with correspondent low signal intensity in the apparent diffusion coefficient map (C, yellow arrow) (suggestive of residual cancer by DWI-MR).](image-url)
and mean SUV values) was found to be the best predictor of response to nCRT using sequential PET/CT imaging at baseline and 12 weeks from nCRT completion\(^3\) (Fig. 4).

**Complete Response: Watch and Wait Strategy**

**Watch and wait strategy: follow-up**

When a nonoperative strategy for cCR in rectal cancer is considered, a relatively intensive follow-up is certainly required. Patients should be encouraged to adhere to this strict follow-up program to allow early recognition of any local or systemic recurrence and, therefore, increasing the chance of a successful salvage treatment. After initial assessment of response confirming a cCR, visits should be performed every 1 to 2 months during the first year, every 3 months during the second year, and every 6 months thereafter. DRE, proctoscopy, and carcinoembryonic antigen level determination are recommended for all visits. Timing for radiological assessment during follow-up has not yet been standardized. Routine MR for the assessment of the rectal wall, mesorectum, and pelvic nodes every 6 months for the first 2 years and yearly thereafter has been our practice.\(^4\)

**Outcomes**

Patients managed nonoperatively under the WW strategy after a cCR following neoadjuvant chemoradiation were originally reported to have similar long-term oncological outcomes to patients with complete pathologic response after radical surgery.\(^9\) Additional retrospective studies reported by others have consistently shown similar oncological outcomes between these subgroups of patients.\(^10,11,40–44\) These findings further support the idea that patients with a cCR may be spared from the morbidity and mortality of radical surgery with no oncological compromise.\(^13\) In addition, functional outcomes of patients managed nonoperatively not only appear to be better than with radical surgery, but also better than other organ-preserving strategies (transanal local excision).\(^7,11\)

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Fig. 4. PET/CT showing a baseline tumor with significant FDG uptake and precise metabolic tumor volume (green lines) delineation (A) and post-CRT images showing significant metabolic volume reduction (B) within the region of interest (green squares - ROI). (From Dos Anjos DA, Perez RO, Habr-Gama A, 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;59:805–12; with permission.)
Local recurrences after this treatment strategy are still a concern and may develop at any time during follow-up. Most local recurrences appear to develop within the first 12 months of follow-up and may represent limitations in the precise identification of microscopic residual disease among “apparent” complete clinical responders. For these reasons, these “early recurrences” developing within the initial 12 months of follow-up have been called “early regrowths” instead. Still, close and strict follow-up may allow early detection of regrowths, leading to oncological outcomes equivalent to those who have an incomplete clinical response and underwent surgery 8 to 12 weeks after CRT completion. In addition, local recurrences (late and early regrowths) are usually amenable to salvage therapies, often allowing sphincter preservation, and associated with excellent long-term local disease control.

Considering that the rate of cCR or pCR was historically fewer than 30% of patients across most of the studies, one could assume that this treatment strategy could benefit a rather limited proportion of patients with rectal cancer. However, the observation of increased rates of complete response (clinical or pathologic) using regimens with consolidation chemotherapy and with the inclusion of earlier stages of disease (cT2N0 otherwise candidates for ultra-low resections or abdominoperineal resections) may result in nearly 50% who ultimately avoid surgical resection. This has been further confirmed in a prospective trial including patients with T2 and T3 rectal cancers managed by CRT and an additional endorectal high-dose brachytherapy boost (total 65 Gy) that showed a 58% cCR rate at 2 years of follow-up without surgical resection.

Finally, in the era of evidence-based medicine, a randomized prospective trial is still lacking to definitively demonstrate the oncological equivalence of WW and radical surgery in the setting of a cCR following nCRT. Even though such a trial is not likely to be performed, a recent study using a propensity-score matched cohort analysis comparing WW and radical surgery has been designed to demonstrate noninferiority of the WW approach. Curiously however, the comparison between groups demonstrated a slight superiority of the nonoperative management of these patients in terms of survival and a clear benefit in colostomy-free survival even when accounting for the development of local recurrences.

Organ Preservation After Incomplete Response

As previously mentioned, transanal local excision with or without the use of endoscopic microsurgical platforms has been suggested to provide insufficient oncological outcomes for most patients with T1 or T2 rectal cancer. A very small subset of patients fulfilling strict favorable criteria are considered to be appropriate candidates for this organ-preserving strategy. Local recurrence rates have mirrored the risk of mesorectal nodal metastases for T1 and T2 cancer, respectively. Of note, advanced techniques, such as transanal endoscopic microsurgery (TEMS) and transanal minimally invasive surgery (TAMIS), have allowed the surgeon to selectively perform larger resections that include mesorectal tissue. However, conventional local excision is a procedure that typically removes the primary cancer with no associated mesorectal tissue, and thus oncological failures after this treatment strategy have been associated with the risk of unsuspected and unremoved metastatic mesorectal nodes. In this setting, the potential effects of nCRT on primary tumor size, depth of tumor penetration, and mesorectal nodal sterilization could result in a residual tumor amenable to local excision even in the setting of an incomplete response to nCRT.

Indeed this organ-preserving strategy may be a valid alternative in the treatment of select patients with rectal cancer after nCRT. The only randomized study comparing TEMS to laparoscopic TME in the management of cT2N0 rectal cancer after nCRT...
has suggested similar local recurrence-free survival and postoperative morbidity favoring the TEMS group.\textsuperscript{49} However, a later update of this trial suggested that patients undergoing TEMS were more likely to develop any disease recurrence.\textsuperscript{50} Another prospective single-arm study reported on long-term outcomes with local excision after nCRT for the management of cT2N0 rectal adenocarcinomas. This study reported considerably low local recurrence rates (<5%), suggesting that this organ-preserving strategy could be safe for the management of these patients after nCRT.\textsuperscript{51}

Certain issues must be considered when evaluating the 2 previously mentioned studies. First, in both studies, only select (small) cT2N0 rectal cancers were included. Particularly for the ACOSOG Z6041 study, it becomes difficult to understand whether there is a chance that “unfavorable” cT2N0 never entered the study.\textsuperscript{51} Second, local recurrences in both studies were exclusively observed among poor responders to nCRT. This means that none of the recurrences observed were among patients with complete pathologic response of the primary tumor (ypT0).

Ultimately, local excision of primary tumors that respond poorly to nCRT may prove to be insufficient. Data from 2 prospective European studies revealed that patients with residual ypT2 cancers that refused subsequent TME, and instead underwent local excision, developed considerably high rates of local recurrence.\textsuperscript{50,52} Despite an appropriate R0 resection of these residual ypT1 or ypT2 cancers, the presence of remote islands of cancer cells away from the primary residual visible ulcer/tumor can develop during the partial response to nCRT (also known as the “fragmented” pattern of tumor regression or tumor scatter). These fragments may contribute to local failures after local excision.\textsuperscript{53–55} Fragmented patterns of tumor regression are possible regardless of baseline staging features among these unresponsive tumors.\textsuperscript{53} Therefore, one could argue that the patients who can be safely managed by local excision after nCRT are those who experience complete tumor regression (ypT0). In this subset of patients with a favorable response, the oncological outcome is usually excellent after local excision.\textsuperscript{56}

To further complicate the decision process in selecting this organ-preserving strategy, one has to consider the consequences of local excision in the setting of a previously irradiated field. Suturing of 2 radiated borders of the rectum together may lead to significant difficulties in tissue healing and seems to justify the considerable rates of associated morbidity after this procedure.\textsuperscript{57,58} Wound complications, including partial separation and even complete dehiscence occur in 25% to 70% of patients after nCRT, which has several clinical consequences, including significant anal pain, requiring readmission in up to 30% of patients, and even occasional diverting stomas. Such complications have been clearly observed in a prospective trial using short-course radiation therapy followed by delayed TEMS. The observation of severe postoperative complications (including rectal-sacral fistulas) among patients led the investigators to interrupt the trial.\textsuperscript{59}

In addition, significant scarring of these separated wounds may have other clinically relevant consequences. Even though TEMS has been associated with minimal long-term detrimental functional consequences, in the setting of nCRT and frequent wound dehiscences, local resection may lead to significant anorectal dysfunction. Patients managed by nCRT followed by TEMS compared with patients with cCR managed by WW showed consistently worse functional outcomes for the former group of patients.

There is also concern that oncological outcomes may be compromised in the event that salvage TME is required after nCRT and local excision, and some studies have shown a negative impact on the quality of the mesorectal excision.\textsuperscript{50} The risk that
salvage TME will require an abdominal perineal excision instead of a restorative proctectomy is quite significant. A recently reported study on the outcomes for salvage TME for local recurrences after nCRT and TEMS suggested considerably high local recurrence rates, frequent need for abdominoperineal resections (APRs) and frequent risk for achieving an R1 resection with circumferential resection margin positivity (CRM+).

Altogether, these data may suggest that local excision should be offered with extreme caution after nCRT to patients with selected rectal cancers. Patients with suspected pCR are probably the best indication for this strategy. However, these patients will probably do better if no surgical resection is undertaken, provided that they have developed complete clinical response. A few patients with incomplete clinical response harboring ypT0 lesion or even residual adenomas (Fig. 5) within the area or border of previously invasive cancers may be a specific subset of patients for whom a WW strategy is inappropriate. In these patients, local excision with TEMS may be both diagnostic and therapeutic. Small and early baseline cancers (cT2N0) are preferred even though poor responders (ypT1-2) may still harbor a significant risk for local recurrences. Fragmented patterns of regression to nCRT may constitute a significant source for local recurrences, even in small residual ypT1-2 cancers (Fig. 6). Postoperative morbidity in the event that salvage TME is required may be quite significant. Even though good (complete) responders are preferred, worse functional and similar oncological outcomes compared with nonoperative management of such patients may further limit the use and indication of such procedure.

Ultimately, in the setting of an incomplete response to nCRT the best alternative for most patients will still be proper total mesorectal excision, regardless of the surgical access (minimally invasive or conventional TME).

Fig. 5. Microscopic view of a full-thickness fragment locally excised by TEMS harboring a residual adenoma within the area of the original invasive cancer (yellow) and the presence of acellular mucin deposits (red).
TOTAL MESORECTAL EXCISION: OPEN, LAPAROSCOPIC, AND ROBOTIC

Despite considerable postoperative morbidity, functional consequences, and even mortality, TME with an intact mesorectum, and proper radial margins (>1 mm) and distal margins (≥1 cm) provides excellent local disease control. Oncological outcomes (particularly in terms of local disease control) seem to be directly related to achieving a proper TME specimen regardless of the exact surgical approach. Historically, open TME has been considered the standard approach for this operation; however, the development of minimally invasive approaches with laparoscopic colorectal procedures led to significant improvements in short-term outcomes for colon cancer surgery with similar long-term oncological outcomes.

In theory, optimal visualization of the pelvis and standardization of key technical steps were expected to result in at least similar oncological outcomes and potentially maintaining the short-term outcomes benefits observed for colon cancer surgery. However, regarding laparoscopic TME (lap TME), the issues of nCRT, the need for autonomic nerve preservation, and the technical demands of a TME and a well-constructed low colorectal or coloanal anastomosis challenge even the most specialized surgeon. Therefore, it was only recently that randomized trials specifically addressed these issues for the management of rectal cancer. A premise to most if not all of these studies was the use of pathologic findings (quality of the mesorectum and CRM+) as a surrogate for oncological outcomes.

The COREAN trial, demonstrating similar oncological outcomes between open and laparoscopic TME, was promising in supporting routine use of the minimally invasive approach. The COLOR II trial performed in Europe also suggested similar oncological outcomes between laparoscopic and open surgery for rectal cancer. Two interesting aspects of this particular trial are worth noting. First, there was a significant difference in the CRM+ rate between the 2 arms favoring the open approach among mid-rectal cancers. On the other hand, among distal rectal cancers, the opposite was observed, with rate of CRM+ favoring the laparoscopic approach. Even though oncological

Fig. 6. Microscopic view of “fragmented” pattern of regression after nCRT with isolated foci of cancer cells separated by areas (double arrow) of fibrotic non-neoplastic tissue.
outcomes were similar between groups (except for stage III disease, in which it was actually better for the laparoscopic group), one could argue that worse pathologic outcomes for mid-rectal cancers could possibly suggest worse surgical performance with the laparoscopic approach. The worse results observed in the open group for distal cancers could be possibly related to the APR technique rather than TME surgery itself, as APRs have been historically associated with worse pathologic outcomes.67

These controversial findings were further complicated by 2 well-designed and highly publicized randomized controlled trials (RCTs) comparing open and laparoscopic surgery for TME, both of which were published in the October 2015 issue of the *Journal of the American Medical Association*. In the ACOSOG Z6051 trial, surgeons underwent previous credentialing to ensure proper surgical expertise before entering the trial.4 In this study, investigators decided to use as the primary endpoint a composite of pathologic variables including quality of the mesorectum specimen, CRM status, and distal resection margin. Originally designed to demonstrate noninferiority of laparoscopic to open TME, the study failed to demonstrate that laparoscopy was not inferior to open surgery. Possible reasons for these unexpected findings include the use of an endpoint (composite pathologic endpoint) not previously validated. In addition, the power calculations were based on a higher-than-observed composite success rate for open ("standard") TME.

Another important and similarly designed RCT was performed in Australia and Asia (ALAcaRT trial), and reported similar outcomes failing to demonstrate noninferiority of laparoscopic surgery to open surgery for the performance of TME.5 These 2 recent studies, both of which involved master surgeons with extensive experience performing laparoscopic TME, resulted in a proper amount of concern in the colorectal community that laparoscopic TME is not appropriate for all patients with locally advanced rectal cancer, and patients must be selected carefully for this technique.

Another promising improvement in minimally invasive TME involves the surgical robot. Robotic technology reports improved visualization using a stable high-definition camera and a more precise rectal dissection using articulated instruments with motion scaling. Surgeon ergonomics also may be improved, which reduces the physical demands of an already-difficult pelvic dissection. However, although these advantages were presumed to translate into improved surgical outcomes, systematic reviews and meta-analyses have failed to show significant benefits to robot TME when compared with laparoscopic TME, with the exception of a decreased rate of conversion to open surgery.68

Moreover, it has been demonstrated in the same reviews that robotic TME is associated with a prolonged operating time when compared with laparoscopic TME, with several contributing factors, including surgeon and assistant familiarity, learning curves, and extra time taken to dock the robot. Results from the single randomized study comparing robotic to laparoscopic TME surgery (ROLARR trial) remain unpublished, and the current role of robotic surgery for rectal cancer remains controversial.

**TRANSANAL TOTAL MESORECTAL EXCISION**

Regardless of the exact reasons for the unexpected negative findings for laparoscopic and robotic TME surgery, it is clear that minimally invasive TME is a challenging procedure for even the best endoscopic surgeons. Pelvic exposure during TME is especially difficult in obese men with low tumors, as the visualization is poor, and the narrow pelvis and fatty mesorectum leave little space for dissection. Perhaps the most challenging cases involve these difficult patients in combination with an anterior distal tumor, in whom there is high risk for a positive circumferential resection margin.
regardless of the chosen technique. From this challenge, arose a new technique to battle the anatomic constraints of the narrow pelvis.

Previous experience with transanal surgery for local excision and developments in microsurgical endoscopic platforms led surgeons to consider performing TME via a transanal approach (taTME). The mesorectal dissection is performed transanally from bottom to up using a variety of flexible or rigid transanal platforms. The first key step of the procedure includes closure and transection of the rectum distal to the tumor, thus ensuring a proper distal margin (one of the key surrogate markers for long-term oncological outcomes). This replaces one of the most challenging elements of the abdominal approach, in which the distal rectum is transected with linear staples, which often requires multiple staple loads, and can be associated with poor visualization and unintentional incorporation of adjacent organs, such as the vagina.

Once the rectum is fully incised in a circumferential manner, CO2 insufflation and laparoscopic instrumentation (including a high-definition camera) are used to perform TME under direct vision. Dissection proceeds cranially through the same surgical planes that are used for the abdominal approach. TaTME enthusiasts report improved identification of the proper planes using this technique in the narrow pelvis.

Although the taTME surgeon works from below, a separate surgeon typically works from above, completing the abdominal portions of the operation, including proximal vessel ligation and splenic flexure mobilization. The 2 dissections then meet, typically at the peritoneal reflection, which completes the dissection. There is still controversy about whether a single or 2-team approach results in different outcomes during the procedure.

Initial experience with case-control studies suggest that taTME allows similar (if not superior) pathologic outcomes compared with the abdominal approach, including distal margins, CRM status, and the quality of the mesorectum. In fact, some surgeons prefer taTME for difficult pelvic dissections even when an open abdominal approach is used.

Despite this promising initial experience, caution must be taken before 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. Previous experience with TME and transanal surgery with endoscopic microsurgical platforms may be useful to accelerate overcoming the learning curve and preventing complications. In fact, considering the change in anatomic landmarks during taTME when compared with abdominal TME, certain intraoperative complications may be more likely to develop when compared with abdominal TME, including injuries to the prostate or urethra, as well as damage to the iliac/obturator vessels and presacral veins. In addition, long-term functional outcomes after taTME are not yet available. In the meantime, registries provide an opportunity to compare and scrutinize individual results with the technique, and ultimately a randomized trial comparing taTME with conventional and minimally invasive TME is necessary before widespread adoption of the technique.

**SUMMARY**

Organ preservation in the management of rectal cancer has become a valid option for select patients after significant response to neoadjuvant CRT. Patients who develop complete tumor regression with no clinical, endoscopic, or radiological evidence of residual cancer may be offered no immediate surgery and enrolled in a strict surveillance program (WW) with excellent functional and acceptable oncological outcomes. Good responders to nCRT (ypT0 or ypTis), despite incomplete clinical response, may
warrant local excision as a diagnostic and therapeutic tool also with good oncological outcomes but at the cost of a slightly worse functional outcome and significant post-operative morbidity. Poor responders to nCRT (ypT1-2) are still at risk of significant local recurrence rates after local excision of the visible residual disease. Proper selection of these patients for organ-preserving strategies remains a challenge, and TME may provide considerably better oncological outcomes. Obtaining a proper TME specimen with adequate distal and radial margins may be challenging by minimally invasive techniques. In this setting, the transanal approach (taTME) is promising alternative to be investigated in future prospective trials.

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