Review

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Advances in Rectal Cancer Surgery

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Abstract

Surgical resection is the cornerstone of curative intent therapy for rectal cancer. The introduction of the concept of total mesorectal excision (TME) led to significant decreases in local recurrence. However, TME carries substantial morbidity. The advent of transanal endoscopic techniques, such as transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS), has allowed patients with early-stage disease to be managed with local excision and avoid the morbidity of TME. Advances in surgery such as laparoscopy, robotic surgery, and transanal approaches have also broadened the options for achieving TME. However, there is significant debate within the literature regarding the optimal approach and oncologic outcomes of these modalities.

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Advances in Rectal Cancer Surgery

While a multimodal and multidisciplinary approach to rectal cancer is critical for high-quality rectal cancer care, surgical resection, specifically total mesorectal excision (TME), remains the cornerstone of curative intent therapy. TME involves removal of the involved rectum along with the mesorectum, including the associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia in one "tumor package".[1,2] The boundaries of the package of tissue that is resected together are determined by dissection along embryological planes.[1] The proper plane for this dissection is an avascular and areolar tissue plane found between the mesorectal fascia and the parietal pelvic fascia, which is also commonly referred to as the "holy plane".[3] Meanwhile, the autonomic nerves are preserved to minimize urinary and sexual dysfunction.[1]

For tumors located in the mid to upper rectum, TME can be achieved via a low anterior resection (LAR) followed by a colorectal or coloanal anastomosis.[2] A distal margin of 5 cm is recommended for rectal tumors in the upper third of the rectum per the American Society of Colon and Rectal Surgeons (ASCRS) 2020 Clinical Practice Guidelines.[4] For tumors located in the mid to lower thirds of the rectum, a 2 cm distal margin is deemed adequate and allows for a low colorectal anastomosis. Finally, at least a 1 cm distal margin is acceptable for tumors located at or below the mesorectal margin. For the lowest of rectal tumors, particularly those that involve the anal sphincter or levator muscles, an abdominoperineal resection (APR) is required in order to achieve TME.[2] The APR removes the rectum, anus, mesorectum, and perianal soft tissues with the creation of a permanent colostomy.

The introduction of TME by Heald and colleagues in the 1980s was the most significant and long-standing development within the field of rectal cancer surgery.[5] The application of this technique resulted in a reduction of local recurrence rates from 30%-40% to 5%-15%, establishing the importance of surgical technique as critical for optimal rectal cancer outcomes.[6] Widespread application of TME has been shown to increase the rates of obtaining a negative circumferential resection margin (CRM), also known as the radial, lateral or mesorectal resection margin.[7] Negative CRM has been associated with decreased rates of both local recurrence and distant metastases.[6,8,9] Nagtegaal et al. found that of patients with a positive CRM, 16.4% developed a local recurrence within 2 years of follow up.[6] The rates of local recurrence were also similar (14.9%) in those with a margin between 1 and 2 mm. However, if margins were > 2 mm, local recurrence rates were significantly lower, ranging from 2.4 to 10.3% ($P = .0007$). Patients with a margin > 2mm also had a > 94% 2-year local recurrence-free survival, and patients with a negative CRM (> 1 mm) showed a significantly lower distant metastasis rate of 12.7% ($P < .0001$).

TME importantly addresses the mesorectal nodes and inferior mesenteric artery nodes, which are the most common sites of nodal metastases. However, metastases to the lateral sidewall nodes (common iliac, internal iliac, and obturator) can occur with more locally advanced tumors. To address this, the addition of routine lateral lymph node dissection (common iliac, internal iliac, external iliac, and obturator nodes) has been proposed in Japan.[10] In 2017, Fujita et al. performed a non-inferiority randomized control trial examining patients with clinical stage II or III rectal cancer who were either assigned to mesorectal excision (ME) alone or ME with lateral lymph node dissection (LLND). None of the included patients had pre-operative evidence of lateral pelvic lymph node enlargement. The 5-year overall survival and 5-year local-recurrence-free survival in the ME with LLND and ME alone groups were 92.6% and

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90.2%, and 87.7% and 82.4%, respectively. Rates of local recurrence were 7.4% in the ME with LLND group and 12.6% in the ME alone group. Based on these results, non-inferiority of ME alone when compared with ME plus LLND was not able to be established. The major weakness of this study was that these patients did not undergo any sort of chemoradiotherapy, which makes the data less applicable for rectal cancer patients in the United States.

However, when lateral lymph nodes are enlarged at diagnosis and/or after neoadjuvant therapy LLND does appear to offer benefit.[11-13] Ogura et al. performed an international, multi-center retrospective study examining 1,216 patients with cT3/4 rectal cancer up to 8 cm from the anal verge who underwent surgical resection (some with and some without LLND).[11] They specifically aimed to determine the effect of enlarged lateral lymph nodes and the performance of LLND on 5-year local recurrence. They found that patients with lateral lymph nodes (LLN) with a short axis of at least 7 mm had a significantly higher risk of lateral local recurrence (LLR) (hazard ratio, 2.060, $P = .045$) when compared with patients with LLN < 7 mm. Additionally, they found that in patients with LLN of at least 7 mm in size, chemoradiotherapy (CRT) and TME plus LLND had a lower local recurrence rate (LRR) when compared to those who underwent CRT and TME but no LLND (5.7% vs. 19.5%, respectively, $P = .042$).

This same group looked at LLR within the context of restaging MRI which was performed after the completion of CRT.[14] This study included 741 patients from the cohort of patients mentioned in the previous study. A total of 651 of those patients underwent CRT with TME and 90 underwent CRT with TME plus LLND. They found there was no LLR at 3 years in 28 patients who had lateral nodes 4 mm or less on restaging MRI. However, for patients who had LN at least 7 mm on primary MRI and greater than 4 mm on restaging MRI, 5-year LRR was 52.3%. When comparing patients who underwent CRT with TME alone to those who underwent CRT with TME plus LLND, those who also underwent LLND were had significantly lower LRR of 8.7% (hazard ratio, 6.2; 95% CI, 1.4-28.5, $P = .007$). These findings suggested that patients whose LLNs were less than 4 mm on restaging MRI may be able to safely avoid LLND. However, those with persistently enlarged notes are at much higher risk for local recurrence if they do not undergo LLND. This is important as pelvic recurrence can be devastating and often unresectable

There is some debate within the literature regarding the appropriate size cutoff for what is considered an enlarged or suspicious lateral lymph node.[12-14] When looking at the impact of enlarged LLNs on local recurrence, Kim et al. examined a prospectively maintained database of cT3/T4 rectal cancer patients in South Korea who all underwent preoperative CRT in addition to TME +/- LLND.[13] This study used a size cutoff of 5 mm for LLN. When comparing patients with LLN ≥ 5 mm who underwent TME and LLND with those who underwent TME alone, they found a lower 3-year LRR (20.13% vs. 5.39%, $P = .0013$) and high relapse-free survival (RFS) (65.83% vs. 77.11%, $P = .0436$). However, there was not a significant difference in 3-year overall survival. A 2020 review of literature by Peacock and Chang at MD Anderson concluded that LLND should be performed for patients with persistent lateral pelvic lymph nodes ≥ 5 mm or any other adverse imaging features (suspicious shape, border, signal intensity, and heterogeneity) following neoadjuvant chemoradiotherapy.[12] Currently, both the National Comprehensive Cancer Network (NCCN) and ASCRS Clinical Practice Guidelines recommend LLND in cases of clinically positive or clinically suspicious LLN without specific size criteria, but do not recommend routine LLND for all patients.[2,4]

While TME is the standard of care in rectal cancer surgery, it is associated with substantial potential morbidity. Up to 80 to 90% of patients who undergo a sphincter-sparing surgery for rectal cancer develops LAR syndrome to some degree.[15] LAR syndrome involves a spectrum of symptoms which can range from incontinence with frequency and urgency to constipation and incomplete emptying.[16] The pathophysiology of this syndrome is likely multifactorial and may be related to internal anal sphincter dysfunction, decrease in anal canal sensation, disappearance of the rectoanal inhibitory reflex, disruption in local reflexes between the anus and the neorectum and, finally, a reduction in rectal reservoir capacity and compliance. Proctectomy is also associated with genitourinary complications.[17,18] Up to 40% of patients experience issues with urinary retention in the immediate post-operative period.[18] While urinary retention generally resolves quickly, long-term urinary dysfunction can occur. However, the introduction of nerve-sparing mesorectal excision has improved rates of long-term urinary dysfunction from 26% to as low as 4%.[18] While sexual dysfunction is certainly a complication of proctectomy, there is poor reporting in the literature, making the true incidence of the complication unknown.[17] However, as we see a rise in the number of individuals under the age of 50 who are diagnosed with rectal cancer,[19] post-proctectomy sexual dysfunction is likely to become an even more significant concern.

As a result of the complications related to TME as described above, stakeholders continue to seek opportunities to minimize the morbidity of rectal cancer care without compromising oncologic outcomes. To this end, various advances in surgical care have been introduced.

Local Excision

While TME remains the gold-standard for surgical management of most rectal cancers, there are certain clinical scenarios where local excision can be considered and may be the preferred management. According to both the NCCN and ASCRS Clinical Practice Guidelines, transanal local excision, either directly or via an endoscopic approach, such as transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS), is indicated as curative-intent surgery for early-stage, low-risk T1N0 rectal cancer.[2,4] Criteria for low risk include size < 3 cm, favorable histopathology (well- to moderately-differentiated), location within 8 cm of the anal verge, encompassing < 30% of the rectal circumference, and no evidence of nodal involvement.[2,20,21] In these clinical scenarios, local excision can potentially offer curative resection while avoiding some of the morbidity and poor functional outcomes that are often associated with more radical surgery.[22] Local excision can also be considered for palliation in patients who are poor surgical candidates.

Local excision involves full-thickness excision of the tumor down to the mesorectal fat via a transanal approach with a goal of negative margins (ideally 1 cm radial/circumferential margin) and avoidance of tumor fragmentation.[22] The defect in the rectal wall should then be closed, when technically feasible. This can be done primarily or with the advancement of flaps from the surrounding rectal wall. The repair is oriented transversely to avoid stricture. It is important to differentiate local excision from endoscopic submucosal dissection (ESD).[23] ESD involves the injection of fluid into the submucosa, separating the mucosa from the muscular layer, which allows the endoscopist to incise the involved mucosa with an electric knife.[23] As this technique does not remove the full thickness of bowel wall, it is only appropriate for the treatment of advanced polyps and intramucosal adenocarcinoma. Endoscopic full-thickness excision has also been described.[24] The defect created is closed with either suture or over-the-scope clips. This technique is indicated for the same early-stage, low-risk lesions as those described above for TEM and TAMIS.

Local excision has become more technically feasible with advances in technology. Current options for local excision include a traditional open transanal excision (TAE) and transanal endoscopic techniques, including TEM and TAMIS.[23] The rates of local excision are increasing which, in part, may be attributed to wider adoption of these new surgical techniques.[25] Traditional TAE is typically limited to the distal 8 to 10 cm of the rectum.[26] Visualization is accomplished with anal dilatation and placement of a retractor. Post-operative pain is typically minimal, and complications are rare, but it may be difficult to achieve adequate resection for more proximal tumors or in larger patients. TEM was introduced in the 1980's by Buess and involves the use of a beveled rectoscope which is placed in the anus and forms an airtight seal, allowing for insufflation of the rectum and, therefore, improved visualization.[26,27] Full-thickness excision is then accomplished with the use of specialized laparoscopic instruments. This platform allows for excision of lesions in the portion of the rectum which is 5 to 15 cm proximal to the anal verge. Finally, TAMIS was developed as a hybrid between TEM and Single Incision Laparoscopic Surgery (SILS) and was originally described by Atallah.[28,23] This modality offers a 360-degree view of the rectum and allows for excision of more distal rectal tumors which are not as easily accessible via a TEM platform.[26] The initial series involved 50 patients who underwent resection of both benign and malignant lesions.[29] All lesions were able to be excised successfully without conversion to another platform, all specimens were removed with grossly negative margins and only 6% were found to have microscopically positive margins on final pathology. Two recurrences (4%) were reported at 6- and 18-month follow up and no long-term complications were noted at 20 months.

A number of studies have been performed comparing traditional transabdominal resection of early-stage rectal cancer with local excision. One randomized control trial specifically compared 50 patients with T1N0 rectal cancer who were assigned to either traditional transabdominal resection or TEM.[30] This RCT found equivalent 5-year rates of local recurrence and overall survival. Additionally, the TEM group was found to have decreased morbidity, blood loss, length of stay and operative time. A large meta-analysis which included the RCT mentioned above and 12 observational studies also compared local and radical resection for T1N0 rectal tumors.[31] While the combined local excision group, which included patients who underwent both traditional TAE and TEM, had higher rates of local recurrence (relative risk, 2.36; 95% CI, 1.64-3.39; $P < .01$), this difference was not seen when radical resection was compared with the TEM sub-group. Incidence of post-operative complications, mortality and permanent ostomy were lower in the combined local excision group when compared to radical resection.

A number of retrospective studies and meta-analyses have been performed to specifically compare TEM to traditional TAE and have consistently demonstrated the superiority of TEM over traditional TAE.[27,32,33] de Graaf et al. reported that after traditional TAE the rate of negative margins was 50% compared to 80% after TEM.[32] The rate of fragmentation was also higher in the traditional TAE group as compared to TEM (23.8% vs. 1.4%). Finally, the local recurrence rate was higher in the traditional TAE group (28.3% vs. 3.7%). A large meta-analysis further supported the oncologic superiority of TEM over traditional TAE.[33] Although, no differences were seen in post-operative complication rates, TEM was found to have higher rates of negative microscopic margins (OR, 5.281, $P < .001$), lower rates of specimen fragmentation (OR 0.096, $P < .001$), and lower rates of lesion recurrence (OR 0.248, $P < .001$) when compared with traditional TAE. While there are less data available comparing outcomes of TAMIS to TAE, it seems that the outcomes of TAMIS are largely similar to those seen with TEM.[34,35]

More recently, investigators have sought to determine if transanal approaches can be combined with radiation and/or chemotherapy to allow sphincter preservation for patients with more advanced tumors. Lezoche et al. randomized 70 patients with T2N0 rectal cancer who had previously undergone chemoradiotherapy to TEM or laparoscopic resection.[36] This study had a median follow-up of 84 months. There were two local recurrences (5.7%) in the TEM group and one (2.8%) in the laparoscopic resection group. Distant metastases were seen in one patient in each group. The probability of survival for rectal cancer was also the same for both groups (94%).

The CARTS study further evaluated the viability of local excision in concert with chemoradiotherapy for early-stage rectal cancer.[37] This non-randomized clinical trial studied patients with cT1-T3N0M0 rectal cancer who were treated with neoadjuvant chemoradiotherapy (CRT) followed by TEM in cases of good clinical response. The primary outcome was the number of ypT0-1 specimens after performing TEM. The secondary outcomes included locoregional recurrence and health-related quality of life (HRQL). After the completion of CRT, 85% of patients were deemed appropriate for and subsequently underwent TEM. Seventy-four percent of these patients were able to be treated with local excision alone. The 5-year local recurrence rate was 7.7%, with 5-year disease-free and overall survival rates of 81.6% and 82.8%, respectively. HRQL data revealed improved emotional well-being in those who were treated with local resection, though rates of low anterior resection syndrome (LARS) remained high (50% reported significant LARS). This trial concluded that in early-stage rectal cancer, approximately two-thirds of patients could be adequately treated with a combination of CRT and TEM with good long-term oncologic outcomes. It is important to note that one downside of this approach is the potential side effects of chemotherapy and radiation that the patient with the early-stage disease may have avoided had they undergone radical resection.

Minimally Invasive Proctectomy

As discussed, TME remains the gold standard for surgical management of rectal cancer. However, there are multiple approaches to TME without a clearly superior technique. Though traditionally done via an open approach, 3 minimally invasive approaches (laparoscopic, robotic, and transanal) have been developed and are used to varying extents in practice.

Laparoscopic Approach

While there are benefits to laparoscopic surgery including decreased pain, faster return of bowel function and shorter length of stay, the oncologic outcomes associated with this approach may be slightly inferior.[38] The first randomized control trial to specifically examine the oncological results of a laparoscopic approach compared to an open approach was the CLASICC trial.[39] This trial included patients in the United Kingdom with both colon and rectal cancer and the main short-term endpoints were positivity rates of circumferential and longitudinal resection margins. Rates of positive resection margins were similar for patients for both approaches. However, specifically in patients undergoing laparoscopic anterior resection for rectal cancer, a non-significant difference in circumferential resection margin (CRM) positivity was seen when compared to the open approach (12% vs. 6%, respectively). Despite the higher rates of positive CRM seen in this sub-population, 3-year follow up results demonstrated no difference in overall survival, local recurrence or quality of life scores.

Subsequently, the COREAN trial specifically compared laparoscopic to open approaches in patients in South Korea with mid to low rectal cancer after neoadjuvant chemoradiotherapy (CRT).[40] In this non-inferiority randomized control trial, no differences were seen with regard to involvement of the circumferential resection margin, macroscopic quality of the TME specimen, number of harvested lymph nodes, and perioperative morbidity. The laparoscopic surgery group had earlier return of bowel function, shorter time to resume a normal diet and less morphine usage. Additionally, three months after proctectomy or ileostomy takedown, the laparoscopic group had better physical functioning scores compared to the open group. The long-term outcome of this study, 3-year disease-free survival, was similar between groups, 72.5% (95% CI 65.0-78.6) for the open surgery group and 79.2% (72.3-84.6) for the laparoscopic surgery group).[41] This study further justified the use of laparoscopy for rectal resection.

Simultaneously with the COREAN trial, COLOR II was a large, multi-center, non-inferiority RCT which included over 1000 patients with rectal adenocarcinoma.[38] Similar to prior studies, the laparoscopic group was found to have a longer procedure time, but less blood loss, quicker return of bowel function, and shorter hospital stay. With regard to oncologic outcomes, no difference was seen in the completeness of the resection macroscopically or the rate of positive circumferential resection margin (10% for both groups). Rates of locoregional recurrence, disease-free survival, and overall survival at 3 years were also comparable for the laparoscopic vs. open group.[42]

Despite the encouraging findings of the CLASICC, COREAN and COLOR II trials, there were limitations to these studies (eg, sample size, high conversion rate) that left many still uncertain about the appropriateness of the laparoscopic approach for TME. Two subsequent RCTs were performed in the mid-2010s, ALaCaRT and ACOSOG Z6051.[43,44] Both trials were designed similarly as non-inferiority RCTs comparing laparoscopic and open resection of stage II/III (T1–3, N0–2, M0) rectal cancer, within 12 cm of the anal verge in patients who received neoadjuvant chemoradiotherapy. The primary outcome was a composite of oncological resection, assessed as negative distal margin, negative circumferential margin, and total mesorectal excision quality. All three parameters had to have been achieved to consider the surgery a success. ACOSOG Z6051 involved 35 centers in the United States and Canada and enrolled a total of 486 patients.[43] Resection was deemed successful in 81.7% of laparoscopic resections and 86.9% of open resections, which did not support non-inferiority of the laparoscopic approach based on a preset margin of error of 6%. Despite this, follow-up results of this trial looking at 2-year disease-free survival, local recurrence, and distant recurrence, found no significant difference between the two groups.[9] The ALaCaRT trial recruited a total of 475 patients in Australia and New Zealand and set a non-inferiority margin of error of 8%.[44] Successful resection was accomplished in 82% of patients in the laparoscopic group and 89% in the open group (risk difference of – 7.0% [95% CI, -12.4% to ∞]; $P = .38$ for non-inferiority). Based on the results of this trial, non-inferiority of the laparoscopic approach was also unable to be established. However, once again, no significant differences were seen in the longer-term clinical outcomes, specifically local recurrence, disease-free survival, or overall survival at 2 years.[45] Critics of these trials note that the oncologic composite score used in these trials has not been validated, and it is known how this score relates to more meaningful long-term outcomes.[46]

There have been 2 major meta-analyses performed to evaluate this question for the literature as a whole[47,48] Arezzo et al. performed a meta-analysis of 27 studies (8 RCTs and 19 non-RCTs) encompassing over 10,000 patients and specifically examined clearance of circumferential resection margin for rectal cancer in laparoscopic and open approaches.[47] Of note, the CLASICC, COREAN, and COLOR II trials were included in this meta-analysis. When the RCTs alone were examined, the laparoscopic group had a positive CRM rate of 7.9% compared with 6.9% in the open group (RR 1.0). When data from the non-RCTs were added, the rate of positive CRM for the laparoscopic group was 8.0% compared to 12.7% for the open group (RR 0.68). No significant differences between the approaches were seen with regard to the rate of R0 resections, distal margin clearance, mesorectal fascial integrity, and local recurrence at 5 years. A more recent meta-analysis evaluated 5 randomized prospective trials (including both ACOSOG and ALaCaRT) and found no differences with respect to complete mesorectal excision, number of lymph nodes harvested, distal margin difference, post-op complications or length of stay, regardless of laparoscopic or open approach.[48] However, significant differences were seen with regard to CRM involvement- 8.5% in the laparoscopic group and 5.4% in the open group ($P = .05$).

Robotic Approach

While studies of laparoscopic TME were still ongoing, robotic-assisted TME was introduced in the early 2000s[49] and was quickly disseminated into practice.[50] This approach offers specific advantages over laparoscopy including 3-D view, a stable camera platform and the use of articulated instruments which make fine dissection more feasible, particularly in a narrow pelvis.[51] NSQIP data used to compare the 2 modalities found that robotic cases typically have longer operative times but lower rates of conversion to open and shorter hospital length of stay, compared to laparoscopy.[52] The major disadvantage of robotic surgery is the increased cost compared with laparoscopic surgery.[51]

Many of the initial studies comparing the 2 modalities in rectal cancer resection were performed at single institutions.[53,54] Baik et al. performed a single institution, single surgeon, prospective, comparative, non-randomized study comparing a total of 113 patients undergoing either laparoscopic surgery or robotic surgery for rectal cancer resection.[53] While mean operative time was similar between the two groups, significant differences were appreciated with regard to conversion to open rate, serious complication rate and TME quality. The conversion rate was 0% in the robotic group compared with 10.5% in the laparoscopic group ($P = .013$). The serious complication rate was 5.4% in the robotic group and 19.3% in the laparoscopic group ($P = .025$). The mesorectal grade was more commonly complete in the robotic group (robotic: 52 complete, 4 nearly complete, 0 incomplete vs. laparoscopic: 43 complete, 12 nearly complete, and 2 incomplete, $P = .033$). Circumferential resection margin involvement was not statistically significantly different between the groups ($P = .749$).

Another single institution study matched 20 patients who underwent robotic rectal resection for rectal cancer to patients who had a laparoscopic approach based on gender, BMI and tumor location.[54] The primary outcome of the study was quality of TME, which was found to be significantly better in the robotic group (complete TME: 95 vs. 55 %; $P = .0003$, nearly complete TME 5 vs. 37 %; $P = .04$, incomplete TME 0 vs. 8 %, $P = .09$). They did note a trend for lower positive circumferential margin in the robotic group (10 vs. 25 %, $P = 0.1$), but this was not statistically significant.

The first major RCT to evaluate rectal cancer resection via a robotic approach compared to a laparoscopic approach was the ROLARR trial which was published in 2017.[55] This was an international, multicenter, randomized clinical trial which included 471 patients. The primary outcome was conversion to open, while the secondary outcomes included intraoperative complications, postoperative complications, circumferential resection margin positivity, quality of life scores, bladder and sexual dysfunction, and oncological outcomes. No differences were seen with regard to conversion to open between the two groups (8.1% in the robotic group vs. 12.2% in the laparoscopic group, $P = .16$). While circumferential resection margin positivity was slightly higher in the robotic groups (6.3% vs. 5.1%, $P = .56$), this was not found to be statistically significant. Similarly, no statistically significant differences were found with regard to the secondary outcomes. One of the major criticisms of this trial was that it only required that participating surgeons had performed a minimum of 30 minimally invasive rectal cancer resections (at least 10 of each).[56] As a result, there was significant variability in surgeon experience, particularly when it came to robotic surgical experience. As with any new surgical technique, there is an expected learning curve. Unfortunately, at this time, the literature has poorly defined what that learning curve may look like for the robotic platform, particularly robotic TME.[57]

Shortly after publication of the ROLARR trial, another RCT by Kim et al. compared laparoscopic and robotic approaches for rectal cancer resection. This study included 163 patients with T1-3NxM0 rectal cancer, and the primary outcome was the quality of the TME specimen.[58] TME quality did not differ between the two groups (80.3% complete in the robotic groups vs. 71.8% complete in the laparoscopic group, $P = .599$). There were also no differences seen between the two groups with regard to resection margins, number of harvested lymph nodes, morbidity, or return of bowel function.

A number of meta-analyses have been published more recently examining the differences in the outcomes between the robotic and laparoscopic approaches.[59-61] Huang et al. performed a large meta-analysis including 1305 patients with rectal cancer from 8 RCTs published between 2008 and 2018 (including the RCTs by Jayne and Kim discussed above).[59] Overall, the rate of conversion to open in the robotic group was lower compared to the laparoscopic group (11.89% vs. 5.72%, respectively, 95% CI 1.357-3.613, $P = .001$). Shorter operative time was noted in the laparoscopic group. No statistically significant differences were seen in length of stay or return of bowel function between the two groups. Additionally, no differences were seen with regard to short term oncologic factors, specifically circumferential margin positivity, distal resection margin positivity and number of lymph nodes harvested. Prete et al. published a meta-analysis of 5 RCTs, demonstrating similar findings with decreased rates of conversion to open in the robotic surgery group and increased operative time in the robotic group when compared to the laparoscopic group but no differences in oncologic factors.[60] Finally, the largest and most recent meta-analysis on the topic analyzed 20 studies involving a total of 5496 patients.[61] The robotic group was associated with longer operative time (odds ratio [OR] 0.48, 95% confidence interval [CI]; 0.14, 0.82), lower conversion to open surgery rate (OR 0.55, 95% CI; 0.44, 0.69), shorter LOS (OR - 0.15, 95% CI; -0.30, 0.00), faster bowel function recovery (OR - 0.38, 95% CI; -0.74, -0.02), and lower postoperative complications (OR 0.79, 95% CI; 0.65, 0.97). No differences were seen with regard to oncologic factors (number of lymph nodes extracted, distal resection margin and circumferential margin).

Transanal Approach

The most recent innovation in rectal cancer surgery came with the advent of the transanal TME (taTME) which was first described by Sylla and Lacy in 2010.[62] This “bottom up” approach was the first of its kind within the realm of rectal cancer surgery. This technique was thought to be able to address the increased conversion to open rates and lower quality oncological resections associated with a narrow male pelvis, low and bulky tumors and obese patients.[63]

One large prospective database at a single institution examined 373 patients with rectal cancer who underwent sphincter preserving TME surgery though a combined minimally-invasive transanal and abdominal approach.[64] The vast majority of patients had a distal tumor and received neoadjuvant radiotherapy (91% and 97.7%, respectively). TME specimens were complete or near complete in 96% of patients. Furthermore, 94% of specimens had a negative CRM and 98.6% had a negative distal margin. With a mean follow up of 5.5 years, the local recurrence rate was 7.4%.

Two matched case control studies have demonstrated similar oncologic outcomes when comparing taTME to a purely laparoscopic approach.[65,66] Velthuis et al. examined 25 patients with mid to distal rectal cancers who underwent taTME and matched them with similar patients who underwent laparoscopic resection.[65] They found that 96% of TME specimens in the taTME group were complete, as compared to 72% in the traditional laparoscopic group ($P < .05$). Oncologic factors, including CRM, length of specimen and distal margin, were comparable between the two groups. de'Angelis et al. performed a similar case match control study involving 32 patients with rectal adenocarcinoma in the distal rectum who underwent taTME.[66] When compared to matched patients who underwent laparoscopic resection, patients in the taTME group had significantly shorter operative time (195 vs. 225 minutes, $P = .017$) and hospital stay (7.8 vs. 9 days, $P = .018$). No differences were seen with regard to oncologic adequacy of the specimen (CRM positivity, distal resection margin, number of lymph nodes harvested or macroscopic quality of mesorectum). Disease-free survival at 2 years was not statistically significantly different between groups (90.5% for taTME group vs. 85.2% for laparoscopic group, $P = .395$).

Similarly, a retrospective cohort review was performed on patients with distal rectal cancer (< 6 cm from anal verge) who underwent transanal or laparoscopic TME (20 and 30 patients, respectively) over a 3-year period performed by a single surgeon.[67] This study found no differences between the 2 groups with regard to CRM or distal margin positivity. The investigators also noted similar recurrence rates, 5% in the taTME group and 6.6% in the laparoscopic TME group.

In more recent years, meta-analyses have been performed specifically comparing taTME to laparoscopic TME for the treatment of rectal cancer.[68,69] Hajibandeh et al. compiled 18 comparative studies which included 1000 patients who underwent taTME and 1048 patients who underwent laparoscopic TME.[68] The transanal approach was associated with significantly higher likelihood of R0 resection (OR 1.67, $P = .01$), larger number of harvested lymph nodes (MD 1.08, $P = .01$), lower rate of positive CRM (OR 0.67, $P = .04$) and lower rate of conversion to an open procedure (OR 0.17, $P < .00001$) compared with laparoscopic TME. Ma et al. similarly found lower rates of conversion to open (OR = 0.29, 95% CI = 0.11-0.81, $P = .02$), higher rate of complete mesorectal grading (OR = 1.75, 95% CI = 1.02-3.01, $P = .04$) and less involvement of positive CRM (OR = 0.39, 95% CI = 0.17-0.86, $P = .02$) in the taTME group as compared to laparoscopic TME.

While it is important to note that the current data comparing taTME to laparoscopic TME is all retrospective in nature, the literature supports the notion that rates of oncologic adequacy of the specimen from taTME are at least equivalent, if not potentially improved, compared to a traditional laparoscopic approach. However, there have also been substantial concerns about learning curve and complications for taTME. One study by Persiani et al. examined 121 consecutive taTME procedures done by a single team in order to determine the number of operations needed to decrease the mean operative time, the major complication rate and anastomotic leakage rate.[70] They determined that the learning curve to decrease operative time was 71 cases, 54 cases for major complications and 27 cases for anastomotic leakage rates. This learning curve is likely too steep for this procedure to be practical for most surgeons. The most concerning complication described related to taTME has been urethral injuries, which occur as a result of dissection of incorrect tissue planes.[71] This is thought to be related to the unique transanal perspective and surgeons' unfamiliarity with the periprostatic anatomy. Carbon dioxide (CO_2) embolism has also been described, with an estimated incidence of 0.4%.[4]

COLOR III is a currently ongoing international, multicenter, superiority, randomized trial designed to compare taTME and conventional laparoscopic TME as surgical treatment for mid and low rectal carcinomas.[72] The primary endpoint is involved CRM and the secondary endpoints include completeness of mesorectum excision, residual mesorectum, morbidity and mortality, local recurrence, disease-free and overall survival, percentage of sphincter-saving procedures, functional outcome and quality of life. The investigators on this study predict that the difference in involvement of CRM between the two treatment strategies will be in favor of TaTME, however, results are still pending. In the meantime, taTME can be selectively considered for specific patient populations, specifically larger males with low rectal tumors, as this transanal approach may offer improved visualization when compared to laparoscopic and robotic approaches.

Watch and Wait

With the increasing use of neoadjuvant chemoradiotherapy, the treatment paradigm of "watch and wait" (WW) has emerged as a means for organ preservation in patients with a complete clinical response following chemoradiotherapy.[73] One single center retrospective case series compared 113 patients with a watch and wait strategy (WW) after confirming a complete clinical response following neoadjuvant therapy with 136 patients who underwent neoadjuvant therapy followed by TME and were found to have a pathologic complete response at the time of their resection.[74] While no pelvic recurrences were identified at 5 years in the patients who underwent TME, 19% of patients in the WW group had a local recurrence discovered on routine surveillance and all were able to undergo salvage surgery (20 TME and 2 transanal excisions). This resulted in rectal preservation in 82% of patients in the WW group. Overall survival at 5 years was 73% (95% CI, 60%-89%) in the WW group and 94% (95% CI, 90%-99%) in the TME group. Disease-free survival was 75% (95% CI, 62%-90%) in the WW group and 92% (95% CI, 87%-98%) in the TME group. A higher rate of distant metastasis was observed among patients in the WW group who had local recurrence when compared to those who did not have local recurrence (36% vs. 1%, $P < .001$).

One of the largest databases of patients undergoing a WW approach after complete clinical response following neoadjuvant therapy included 880 patients from 47 centers in 15 countries.[75] Two-year local recurrence was found to be 25.3% (95% CI, 22.3%-28.6%). Five-year overall survival was 84.6% (95% CI, 80.8%-87.6%) and 5-year disease-specific survival was 93.8% (95% CI, 90.8%-95.8%). Despite the growing evidence that this approach may be safe for select patients, most experts agree that additional studies with longer follow up are needed before patients with clinical complete response after neoadjuvant therapy are able to be routinely recommended for the watch and wait approach.[2] Experts also emphasize the need for intensive surveillance for patients who have a complete clinical response and forgo surgery. We await the results of the ongoing organ preservation of rectal adenocarcinoma (OPRA) trial which will examined survival for patients treated with either induction or consolidation chemoradiotherapy, followed by watch and wait for those with a complete or near-complete clinical response.[76]

Conclusion

TME remains the gold standard for surgical management of rectal cancer.[1,2,4] However, for early-stage, low-risk T1N0 rectal cancer, advances in local excision techniques, particularly transanal endoscopic techniques like TEM and TAMIS have provided surgical options which are less morbid with good oncologic results.[30,31] There is also good evidence to suggest that local excision may be successfully utilized in conjunction with chemoradiotherapy for some patients with more advanced local tumors.[36,37] For those undergoing TME, the optimal approach remains up for debate. Multiple RCTs have been performed comparing outcomes for the variety of minimally invasive approaches vs. the open approach, however, the findings remain mixed.[4,38-43,45] What is clear is that achieving an oncologically-adequate specimen (negative CRM and distal margin) is critical for minimizing local recurrences.[6] Additionally, learning curves for all the approaches exist. As a result, it is imperative that the surgeon monitor their own outcomes to ensure that whichever approach is used, the oncologic quality of the specimen is optimized and morbidity is minimized to secure the best possible patient outcomes.

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