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Advances in the management of rectal cancer

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Introduction

In 2018, 43,030 patients were diagnosed with rectal cancer in the United States. Significant advances in the multidisciplinary management of rectal cancer along with improvements in screening have led to a 52% drop in mortality rate for patients with colorectal cancer from 1970 to 2015.[1] An exception to this is patients younger than 55 years, for whom both the incidence of colorectal cancer and associated mortality rates are slowly but steadily increasing.[2] Overall, colorectal cancer remains the second leading cause of cancer-related death in this country.[1]

Surgical resection is considered definitive treatment for patients diagnosed with low-risk early-stage rectal cancer. In contrast, patients with locally advanced rectal cancer, defined as stage 2 (T3-4, N0) or stage 3 (T any, N+), additionally benefit from multimodality treatment with radiation, chemotherapy, or both. Patients who are identified as having metastatic disease at the time of diagnosis may still be eligible for curative resection depending upon the extent and pattern of spread of the cancer and the response to preoperative chemotherapy.[3]

In this monograph, we review the staging of rectal cancer then discuss the evidence supporting specific recent advances in treatment. Finally, we describe the National Accreditation Program for Rectal Cancer (NAPRC), which aims to improve the quality of rectal cancer care by establishing centers of excellence.

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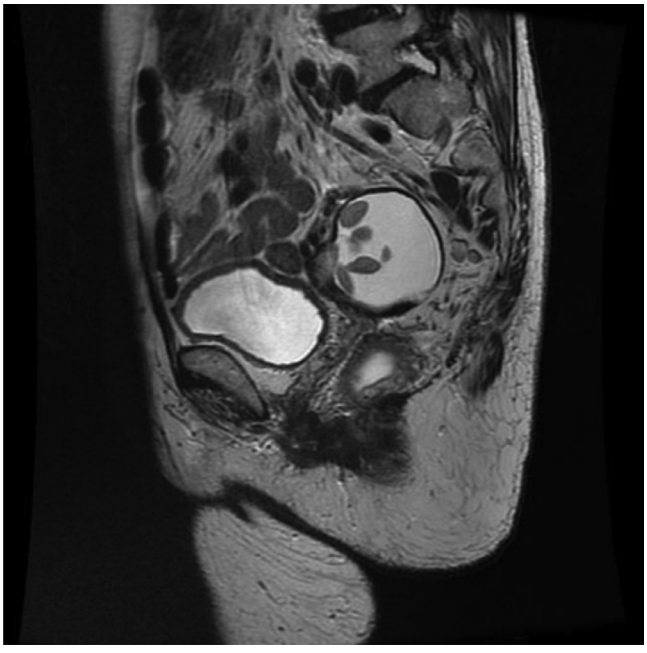

Fig. 1. Rectal cancer protocol MRI. This sagittal image demonstrates the abnormal lymph nodes that can be identified with MRI within the mesorectum.

Staging

Because the treatment strategy for rectal cancer varies considerably depending upon the stage at diagnosis, it is critical that patients are accurately staged prior to beginning treatment. The standard staging evaluation is defined by the National Comprehensive Cancer Network (NCCN) and also supported by the American Society of Colon and Rectal Surgeons practice parameters for management of rectal cancer.[3,4] Along with routine laboratory tests (eg, complete blood count, chemistry panel), it is recommended that the carcinoembryonic antigen (CEA) level be assessed to establish a baseline that can be followed post-treatment for active surveillance. CT scans of the chest and abdomen asses for systemic metastatic disease, which most commonly occurs in the liver or lungs. The chest radiograph alone is not considered sufficient to accurately identify pulmonary metastases.

Staging of rectal cancer differs from colon cancer in that it is important to assess for locally advanced disease, which is an indication for treatment with chemotherapy and/or radiation prior to surgical intervention. Magnetic resonance imaging (MRI) of the pelvis with specific rectal cancer protocol is the current standard of care to assess for local tumor advancement and lymph node involvement. Although the details of the protocol may vary between institutions, they typically include an oblique sequence (along with the axial, coronal, and sagittal sequences included with a standard MRI of the pelvis). The oblique sequence allows for more accurate measuring of distance to the mesorectum and to the top of the anal canal, since the rectum is not a transverse structure (Figs 1 and 2).

Endorectal ultrasound (EUS) or transrectal ultrasound (TRUS) were the standard imaging modalities for local staging of rectal cancer prior to more widespread adoption of MRI, and still play a complementary role. MRI is unable to distinguish between T1 and T2 tumors, and therefore, EUS may be helpful in guiding decision-making regarding local excision vs radical surgery since it is better able to visualize the layers of the rectal wall (Fig 3).

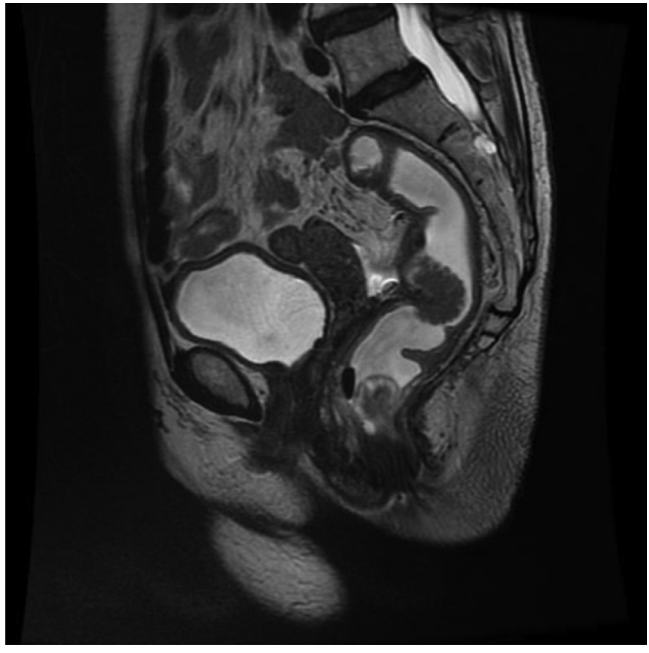

Fig. 2. Rectal cancer protocol MRI. This sagittal image demonstrates the ability of MRI to visualize the relationship of the tumor to the peritoneal reflection and the anal sphincter complex.

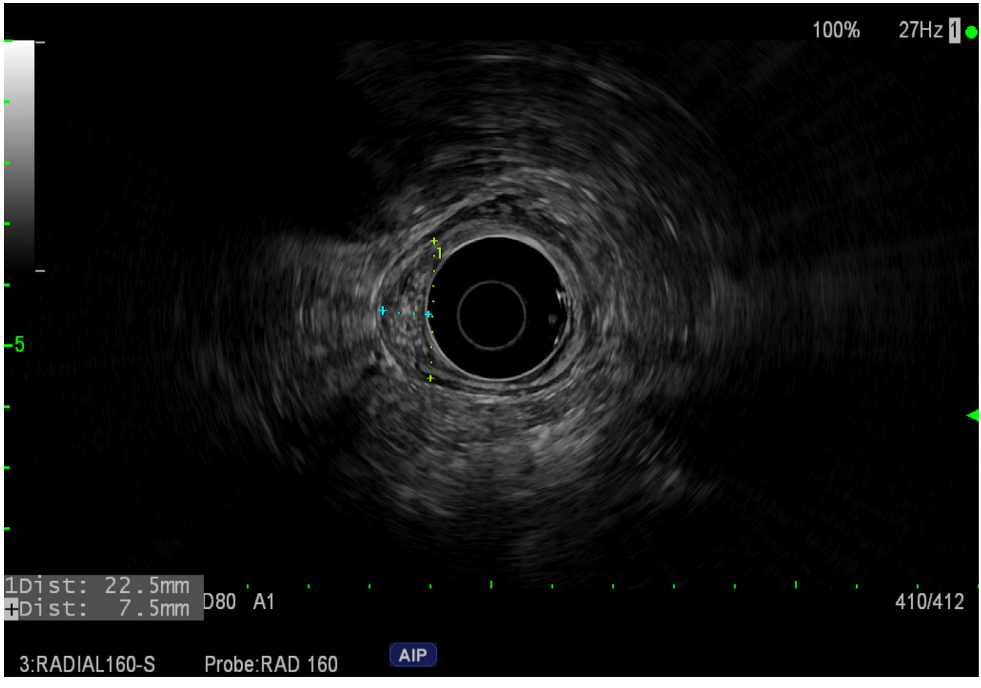

Fig. 3. Endorectal ultrasound. This ultrasound image demonstrates a T1 tumor. The plus marks indicate the edges of the tumor, and one can see no invasion of the muscularis propria.

Local excision of rectal cancer

Local excision of early-stage rectal cancer is an attractive treatment option because it is significantly less invasive than radical oncologic resection and maintains intestinal continuity without the changes in bowel function associated with low anterior resection. Because local excision involves full thickness excision of the tumor and wall of the rectum but specifically does not include oncologic lymphadenectomy, complete pathologic staging cannot be performed. As a result, local excision is associated with higher risk of local recurrence compared to radical surgical resection.[5-9] Salvage surgery with curative intent for local recurrence of rectal cancer in the pelvis after local excision is not always possible. Even when salvage surgery is feasible, there is evidence that it does not provide equivalent results to initial radical surgical resection.[10] Studies have demonstrated that neither adjuvant radiotherapy nor salvage surgery is reliable in preventing or controlling local recurrence.[11] Patient selection, risk stratification, and close postoperative surveillance are key factors in the appropriate utilization of local excision for the treatment of rectal cancer.

When a rectal cancer is diagnosed, pathology review and complete staging (as outlined above) are critical first steps to determining if a patient is a reasonable candidate for local excision. Distant disease is ruled out with CT scan evaluation. MRI of the pelvis with specific rectal cancer protocol has become the standard for local regional staging of rectal cancer and is generally considered superior to EUS for identifying lymph node involvement at most centers. However, MRI is limited in that it is unable to distinguish T1 from T2. Furthermore, MRI has been shown to actually overstage the depth of invasion in some instances. EUS may thus be better for staging early lesions as it is better able to visualize the layers of the rectal wall and depth of invasion, which is particularly important when considering a patient for local excision.[12] Of note, pelvic MRI and EUS are both specialized imaging modalities that require expertise in image capture and analysis.

Local excision is considered an appropriate treatment option for patients with an acceptably low risk of occult lymph node metastases. As such, guidelines only recommend local excision for patients with rectal cancers staged as T1N0 and without any adverse pathologic features. The overall risk of lymph node metastases for a T1 rectal cancer ranges from 3% to 15%.[5,13-16] Risk stratification within this range can be determined based on specific pathologic features of the cancer.[13-15,17] The presence of lymphovascular invasion is associated with higher odds of lymph node metastases, with reported odds ratios ranging from 2.6 to 11.[13,14,17-19] Poorly differentiated histology and high level of tumor budding (10+ per high-powered field) similarly portend increased odds of lymph node metastases (odds ratios 2.3-3.2 and 5.8, respectively).[13,17-19] Finally, the more distal in the rectum, the higher the risk of nodal metastases, with tumors located in the lower third of the rectum having a 6-fold increased odds of lymph node involvement compared to tumors located in the upper third of the rectum.[14] The higher risk of nodal metastases associated with these adverse pathologic features puts patients at a higher than acceptable risk of recurrence if they undergo local excision alone. Patients with adverse pathologic features should therefore be considered for formal oncologic resection with proctectomy and lymphadenectomy with total mesorectal excision (TME) in order to achieve complete pathologic staging and determine the need for adjuvant chemotherapy.[6,13] The balance between oncologic and functional outcomes between local excision and radical resection may be particularly difficult for patients when radical resection includes the potential for a permanent colostomy.

Management of malignant polyps is also dependent on the depth of invasion through the wall of the rectum. The extent of invasion predicts the risk of occult lymph node involvement and thus the risk of local recurrence after local excision alone. There are 2 histologic classification schemes that are commonly used to describe malignant polyps: the Haggitt classification (for cancers within pedunculated polyps) and the Kikuchi/SM classification (for cancers within sessile polyps). Haggitt levels 1-4 describe the depth of invasion of adenocarcinoma within a pedunculated polyp: level 1 lesions are located in the head of the polyp, level 2 lesions have adenocarcinoma extending into the neck of the polyp, level 3 lesions invade into the stalk of the polyp, and level 4 lesions have invasion beyond the stalk into the proper wall of the intestine,

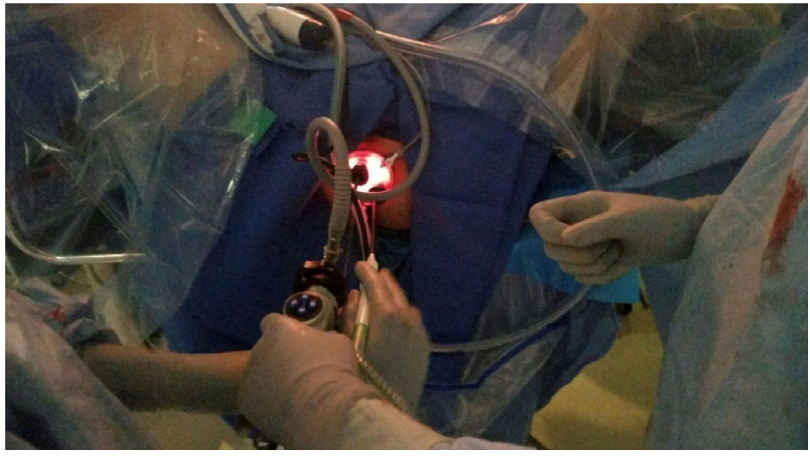

Fig. 4. TAMIS. This image demonstrates the setup for a Transanal minimally invasive surgery (TAMIS) excision of a rectal mass.

but still limited to the submucosa. For sessile polyps, the Kikuchi/SM level describes the depth of invasion through the submucosa: SM1 is invasion limited to the upper one-third of the submucosa, SM2 lesions involve the middle third of the submucosa, and SM3 lesions involve the lower (deepest) third of the submucosa. Haggitt levels 1-3 and Kikuchi/Sm level 1 are associated with a relatively low risk of lymph node metastases (approximately 1%-3%), whereas Haggitt level 4 and Kikuchi/Sm levels 2-3 are associated with a higher risk of lymph node metastases (8%-27%).[14,15] In general, oncologic resection with proctectomy and TME is therefore recommended for patients with malignant polyps classified as Haggitt 4 or SM3 who are acceptable operative candidates.[14,15] One caveat to using these classification schemes is that a pathologist will often be unable to determine the exact SM level after endoscopic biopsy alone, due to limitations in depth of sampling. Full-thickness local excision is often required to determine definitive SM level.

When evaluating patient candidacy for local excision of rectal cancer, the clinician must also consider anatomy. Transanal local excision has traditionally been performed with an open technique, which limits the reach of the surgeon, typically to approximately 8 cm or less from the anal verge. Further limitations may depend on the patient's body habitus or in which quadrant the lesion is located (ie, anterior vs posterior). Newer techniques such as transanal endoscopic microsurgery (TEM) and transanal minimally invasive surgery (TAMIS) have revolutionized local excision for rectal cancer (Fig 4). Using a minimally invasive approach, these techniques utilize pneumorectum and proctoscopy to resect rectal tumors. The procedures allow for more proximal reach, up to the rectosigmoid junction (>15 cm from the anal verge). These techniques are also able to provide better visualization and ability to resect specimens without fragmentation, which has been an issue with traditional transanal excision.[5,20] More recently, the use of a robotic platform to perform minimally invasive local excision has been described.[21] With these advanced platforms, full thickness excision is possible, but a specialized surgeon skillset is required. Tumors comprising more than 40% of the circumference of the rectum are still challenging to approach with local excision.

Even favorable-risk patients after local excision of a T1 rectal cancer have risk of both local and distant failure. These risks have been variably reported. In a systematic review and meta-analysis of local resection vs radical proctectomy for T1N0M0 tumors, Kidane and colleagues reported higher risk of local recurrence for patients undergoing local excision compared to oncologic proctectomy (relative risk 2.36, 95% confidence interval [CI] 1.64-3.39). Patients undergoing local excision also had a higher risk of 5-year mortality (relative risk 1.46, 95% CI 1.19-1.77). Notably, this survival difference was not identified when analyzing the subgroup of patients who

underwent local excision with a TEM approach. Short-term outcomes, however, were more favorable for patients undergoing local excision alone, with lower major perioperative morbidity (relative risk 0.20, 95% CI 0.10-0.41), and mortality (relative risk 0.31, 95% CI 0.14-0.71) when compared to patients undergoing oncologic proctectomy. In addition, the need for a permanent stoma was significantly lower in the local excision cohort (relative risk 0.17, 95% CI 0.09-0.30).[22] These data warrant frank discussions with patients about the potential oncologic disadvantages of local excision. They also highlight the need for rigorous oncologic surveillance after local excision. Surveillance protocols in the absence of oncologic resection recommend proctoscopy and EUS or pelvic MRI with rectal cancer protocol every 3-6 months for the first 2 years after surgery, and then every 6 months for 5 years.[23] These surveillance protocols can be burdensome and costly for patients and thus should be included in the preoperative decision-making discussion for local excision vs oncologic resection, especially if close follow-up would be difficult or unreliable for the patient.

In general, T2 rectal cancer is not recommended for local excision, unless the patient is not considered an appropriate surgical candidate for radical oncologic resection due to clinical factors including functional status or comorbidities, as the risk of occult lymph node metastases in this group is 19%-26%.[13,16,24] Recently, researchers have explored if adding multimodality treatment would reduce the risk of local recurrence for patients undergoing local excision of T2 tumors. The ACOSOG Z6041 trial treated 79 patients with cT2N0 rectal cancer with neoadjuvant chemoradiotherapy followed by local excision. Median follow-up was 56 months. This trial demonstrated a low local recurrence rate (4%) and a 6% distant recurrence rate. However, this was at the cost of a high incidence of local and systemic toxicities, with 29% of patients having gastrointestinal adverse events.[25] The GRECCAR 2 trial similarly treated patients with T2 or T3 rectal cancer with neoadjuvant chemoradiotherapy. If the patient had a clinically favorable response, they were then randomized to local excision (N = 74) or proctectomy with TME (N = 71). Oncologic resection was performed following local excision for patients found to have ypT2-3 tumors. In this study, although local recurrence and survival were similar in the 2 groups, 35% of patients in the local excision group required subsequent proctectomy. Among these patients, 46% experienced major operative morbidity (Dindo III-V) and 25% required permanent colostomy, compared to only 9% of those randomized to initial oncologic resection.[26] Finally, most recently, the CARTS study included 55 patients with cT1-3N0 rectal cancer who were all treated with neoadjuvant chemoradiation followed by TEM. The 5-year local recurrence and overall survival rates were favorable (7.7% and 82.8%, respectively); however, the study was underpowered to compare to a cohort of patients that underwent proctectomy. In addition, low anterior resection syndrome (defined by incontinence, frequency, clustering, and urgency with defecation) was present and major for 50% of patients and minor in 28%, despite organ preservation. These poor functional outcomes should give surgeons pause.[27] With the limited available data, local excision for T2 rectal cancer, even in the setting of chemotherapy and radiation, is currently only recommended for those patients that are not candidates for an oncologic resection or in the setting of a clinical trial.

In summary, local excision for rectal cancer is an attractive treatment modality for low-risk T1 rectal cancers without adverse pathologic features. To safely forgo oncologic resection, patient selection is crucial, and rigorous postoperative surveillance is needed. Although chemoradiation followed by local excision for T2 tumors provides acceptable oncologic outcomes, it comes at the risk of unacceptable functional toxicity and thus is currently only recommended in the setting of a clinical trial, or in patients who have a prohibitive operative risk.

Minimally invasive surgery for rectal cancer

Surgical resection is a key element in the treatment of rectal cancer. Local recurrence rates after proctectomy for rectal cancer have improved over the last 20 years due to greater adoption of a standardized technique for TME, which requires sharp dissection and removal of the mesorectum with the rectum, keeping the fascia propria of the mesorectum intact. The

mesorectal dissection can be graded as complete, near-complete, or incomplete based upon pathologic evaluation of the intactness or the fascia propria. This mesorectal grading schema is valuable for assessing prognosis as the completeness of the mesorectal excision is a predictor of local tumor recurrence in the pelvis. Furthermore, use of sharp dissection to perform a standardized TME improves the chances of achieving a negative circumferential resection margin (CRM), which is strongly associated with lower risk of local recurrence and improved long-term survival.[28] As a result, the completeness of the mesorectal excision is often used to measure the quality of rectal cancer surgery.

Multiple surgical approaches to rectal cancer are currently available, including open, laparoscopic, and robotic. Regardless of the approach, the oncologic principles of rectal cancer surgery do not change. Minimally invasive rectal cancer surgery is one of the most complex and pervasive operations in colorectal surgery. The advantages of laparoscopic surgery include less blood loss, less postoperative pain, earlier return of bowel function, shorter hospital stay, and reduced cost of care. Disadvantages include technical challenges associated with advanced laparoscopy in the confined space of the pelvis, longer operative times, and a longer learning curve to accomplish advanced laparoscopic techniques.[29]

Several clinical trials have examined the safety and oncologic outcomes of laparoscopy. One such trial was the Medical Research Council (MRC) Conventional vs laparoscopically assisted resection in colorectal cancer (CLASSIC).[30] This study randomized 381 patients with rectal cancer to laparoscopic vs open surgery in a 2-to-1 fashion and was designed to evaluate both short-term and long-term outcomes. The study found a conversion rate of 30% in the laparoscopic group, as well as a higher rate of positive CRM compared to the open group, although this did not reach statistical significance (12% vs. 6%; p=0.19). These two findings are thought to be the result of a lack of experience with advanced laparoscopic techniques amongst the surgeons in the study at that time (1996-2002). In this study, the mean hospital stay was 2 days shorter for patients who underwent a laparoscopic approach versus open approach. However, patients that required conversion to an open procedure had higher rates of surgery-related complications and death compared to patients who underwent an open or successful laparoscopic procedure. When 10-year overall survival was examined, it was similar between the laparoscopic and open groups. Based on these findings, the study concluded that the long-term results support use of laparoscopic surgery for patients with rectal cancer.

A similar study, called the Colorectal Cancer Laparoscopic or Open Resection II trial,[47,29] was later conducted from 2004 to 2010 and was designed as a noninferiority phase 3 trial. Patients with rectal cancer were again randomized in a 2-to-1 fashion to laparoscopic vs open rectal resection. There were 1103 patients in this study, with two-thirds of the patients having received neoadjuvant chemoradiotherapy. The primary outcome was locoregional recurrence at 3 years. With laparoscopy, the study authors noted decreased blood loss, longer operative times, earlier return of bowel function, shorter hospital day (by 1 day), no difference in morbidity or mortality and, no difference in anastomotic leak. In terms of oncologic outcomes, there was no difference in CRM or distal margin status, lymph node yield, disease-free survival, or overall survival. The study authors performed a subgroup analysis of patients with a low rectal cancer and found that compared to open, patients undergoing a laparoscopic approach had a decreased rate of positive CRM (9% vs 22%) and a decrease in locoregional recurrence (4.4% vs 11.7%). Therefore, the authors concluded that laparoscopic surgery in patients with rectal cancer without invasion of adjacent tissues is associated with improved patient recovery and is oncologically safe.

In contrast, 2 more recent studies reported results contrary to the above results in regard to the use of laparoscopy for rectal cancer surgery. The first is the Australian Laparoscopic Cancer of the Rectum trial,[31] a randomized, phase 3, noninferiority trial conducted in Australia and New Zealand.[32] This trial was conducted in 2010-2014 and included 475 patients with T1-T3 rectal cancer. One half of the patients enrolled in the study received neoadjuvant chemoradiotherapy. The primary endpoints were oncologic factors (intact TME, negative CRM [$\geq$1 mm], and a negative distal margin [$\geq$1 mm]). The above criteria were met in 82% of the laparoscopic patients and 89% of open rectal cancer resection patients. Noninferiority was not established. The second trial was the ACOSOG Z6051 trial.[33] This was a multicenter, randomized, noninferiority trial

conducted from 2008-2013. The 486 patients in this study had stage II or III rectal cancer and were randomized to laparoscopic vs open surgery after neoadjuvant chemoradiotherapy in a 1-to-1 fashion. The primary outcomes were negative CRM, negative distal margin, and completeness of the TME. Meeting all 3 of these primary endpoints was considered a successful operation. Noninferiority was not supported in this study as 81.7% of patients undergoing a laparoscopic approach received a successful operation, vs 86.9% of patients who underwent an open approach. In addition, operative times were longer for patients in the laparoscopic group compared to the open group, but lengths of postoperative stay were similar.

Both the ALaCaRT and ACOSOG clinical trials have recently published updated results. For the ALaCaRT trial, there was no difference in 2-year recurrence, disease-free survival, or overall survival between the open and laparoscopic groups.[31] For the ACOSOG Z6051, there was also no difference between the laparoscopic vs open groups at 2-year follow-up for disease-free survival and local recurrence.[34] A recently published systematic review and meta-analysis focused on the pathologic outcomes (CRM involvement and completeness of the mesorectal excision) of laparoscopic vs open rectal cancer surgery.[35] This study included 14 randomized control trials (2989 rectal cancer patients) from 1995 to 2016. The rate of positive CRM was 7.9% in the laparoscopic group and 6.1% in the open group ($P = 0.26$). The incomplete mesorectal excision rate was 13.2% in the laparoscopic group, and 10.4% in the open group ($P = 0.02$). There was no difference in distal resection margin involvement, mean distance to radial margin, or mean number of lymph nodes harvested. These findings question the oncologic safety of laparoscopy for the treatment of rectal cancer. However, neither of the large randomized controlled trials has demonstrated that these adverse pathologic findings result in meaningful long-term differences in disease-free survival or overall survival.

There are several potential advantages for the use of robotic technology in rectal cancer surgery. Such advantages include the ability to see tissue in 3D, increased dexterity with the articulating arms, ambidextrous capability, and a shorter learning curve compared to laparoscopy. The disadvantages with this technology, however, are its expense, more limitations on operating in multiple quadrants without collisions, the need to undock and then re-dock (longer operating times), and lack of tactile feedback. There is one trial that examined the use of the robot in rectal cancer, the Robotic vs Laparoscopic Resection for Rectal Cancer (ROLARR trial).[36] This was a multi-institutional study with 237 robotic cases compared to 234 laparoscopic cases. The study was designed as a superiority trial with intraoperative conversion to open surgery as the primary endpoint, and CRM positivity and 3-year local recurrence rates as secondary endpoints. The overall rate of conversion was 10.1%, with 12.2% in the laparoscopic group and 8.1% in the robotic group, which was not statistically significant. There was also no statistically significant advantage of the robot over laparoscopy in terms of lymph node yield, CRM positivity, quality of TME, or 30-day postoperative morbidity. Therefore, no oncologic or clinical advantage was found with the use of this technology compared to laparoscopic surgery.

Transanal TME

Visualizing and accessing the distal rectum to perform a high-quality resection with TME for rectal cancer can be technically challenging given the fixed, narrow confines of the pelvis. As mentioned in prior sections above, achieving a complete TME with negative distal and CRMs provides the best chance for optimal long-term oncologic outcomes for patients with rectal cancer. Part of the difficulty of obtaining an intact TME for distal rectal cancers is that the mesorectum begins to taper and thin toward the anus. The angulation and rigidity of the bony pelvis additionally make the visualization necessary to perform a complete TME challenging, regardless of approach.[29] As a result, oncologic outcomes for patients with low rectal cancers are inferior compared to tumors with a more proximal location.[37] To address these technical difficulties, some have postulated that there may be a benefit to performing the distal transection transanally, as the distal margin of the tumor can be clearly identified with this approach. Additionally, performing part, if not all, of the mesorectal excision transanally would minimize

the technical challenges described above. This technique, sometimes called the "bottom up" approach, was first described in 2009 and is termed transanal TME (taTME).

TaTME is typically done with the patient in the lithotomy position and can be accomplished by a single team or by 2-team approach, with one team performing the taTME from below while the second team simultaneously enters the abdomen to begin the rectal dissection from above. Advantages of the 2-team approach include shorter operative times, improved visualization, and better traction. The approach to the abdomen can be open, laparoscopic, or robotic. The TME can be started from above or can be completed completely transanally. For the transanal portion of the procedure, the rectum is irrigated, and a purse-string suture placed distal to the tumor to occlude the rectum. A transanal access platform, typically a TAMIS port, is placed and pneumorectum is established. Under endoscopic visualization, the rectum is transected circumferentially, and the dissection then continued proximally in the TME plane. The extraction can then be performed transanally, along with hand sewn vs stapled anastomosis.

The greatest advantages of this technique are achieved in patients with locally advanced cancers occurring in the distal third of the rectum. For these patients, the planned site of transection is clearly visible, even in the obese, narrow, male pelvis. Performing a taTME approach for mid-rectal tumors is more challenging as the purse-string must be placed distal to the tumor using TAMIS or TEM technique. Additionally, it is difficult to perform a partial or tailored TME using a transanal approach. However, taTME may be helpful if the surgeon is not able to progress from an abdominal approach due to difficult pelvic anatomy. For upper rectal cancers, taTME is not indicated. Finally, there are patient factors that make the taTME approach to the "difficult" pelvis a more favored technique, such as the android, male pelvis, visceral obesity, and most radiation changes.

Although taTME does effectively address real issues with access to the distal rectum, this technique does come with its own technical challenges and learning curve. For example, most surgeons are not familiar with this visual perspective, thus resulting in risk of misperception about anatomical location, which can lead to major complications. The risk of ureteral injury is close to 10% in addition to injury of the urethral sphincter, which can lead to urinary dysfunction and incontinence.[38] Another risk with this approach is development of a local abscess due to bacterial contamination from transection of the rectum transanally followed by establishment of pneumorectum. In one case series, one-third of taTME patients were found to have positive blood cultures and 17% developed a presacral abscess.[39] Although $C0_2$ insufflation can aide in dissection, it can also expose planes laterally and posteriorly outside the planned operative field, which can result in nerve or venous damage.[40] Because of these risks, it is important that individuals performing this procedure do so after formal training.

In terms of the oncologic outcomes from this technique, we are currently limited to case series and one international registry. A systematic review demonstrated similar technical success with taTME compared to laparoscopic TME, with acceptable oncologic and perioperative outcomes.[41] The authors also found no significant difference in risk of anastomotic leak between the 2 approaches. Another systematic review demonstrated advantages of taTME with regards to CRM involvement, operative time, blood loss, conversion, hospital say, postoperative complications, and readmission.[42] A report from the taTME International Registry reported postoperative morbidity of 32.6%, anastomotic leak rate of 6.7%, and mortality rate of 2.6%.[38] There is one multicenter phase II study that is currently accruing patients and will compare TaTME with laparoscopic TME. This 5-year study, which is funded by ASCRS and SAGES, plans to enroll 100 patients in order to determine the safety and efficacy of taTME in terms of the quality of surgical resection as well as perioperative, oncologic, and functional outcomes.

Given the technical challenges associated with this new technique and the potential for serious complications such as ureteral and urethral injuries, there has been a strong push for design and implementation of national programs that can provide formal training opportunities for surgeons and increase the safety of the procedure. However, a review from a major institution that provides this training to surgeons noted that structured training is useful, but the risk of iatrogenic injury after training remains high, suggesting that continued modification of training programs and monitoring of outcomes is needed.[43]

Total neoadjuvant therapy for locoregionally advanced rectal cancer

Significant advances in the multidisciplinary management of locally advanced rectal cancer have occurred over the last several decades. Since the 1990s, the standard treatment paradigm for local advanced rectal cancer, which includes stage 2 (T3/T4, N0) and stage 3 (T any, N+) disease, has included neoadjuvant chemoradiation, followed by surgical resection, and finally adjuvant chemotherapy (for node positive disease).[3,4,44] This approach, along with improvements in surgical technique, has resulted in substantially lower rates of local failure from pelvic recurrence (5%-10% at 5 years). However, systemic recurrence remains a significant risk, with up to 30% of patients developing distant metastatic disease.[45] Thus, to address unidentified micrometastatic disease present at the time of diagnosis sooner in the treatment plan, it has been proposed to move systemic chemotherapy to the neoadjuvant setting. The total neoadjuvant therapy (TNT) approach, in which all chemotherapy and radiation are performed up front and surgical resection is performed as the final step in treatment, is currently recommended as a treatment option for LARC by the NCCN.[3]

The benefits of performing chemoradiation for LARC in the neoadjuvant setting are well established. In 1990, a National Institute for Health (NIH) consensus conference recommended postoperative adjuvant radiation for patients with LARC.[46] Though radiation did not appear to provide a survival benefit, there was significant evidence supporting decreased local recurrence in the pelvis, which is associated with significant morbidity that is difficult to effectively treat or palliate. Moving radiation to the preoperative/neoadjuvant setting was proposed as potentially being more dose-effective due to better tumor oxygenation prior to surgical intervention. The Swedish Rectal Cancer Trial, the results of which were published in 1997, randomized patients to short-course radiation (5 Gy on each of 5 days) followed by surgical resection vs surgery alone and demonstrated significantly decreased 5-year recurrence rates for patients who received preoperative radiation (27% vs 11%, $P< 0.001$).[47] However, the study was criticized for not standardizing surgical technique, which is surmised to be the reason for relatively high recurrence rates in each treatment arm. The Dutch trial addressed this using the same study design but required a standardized surgical approach with TME. Notably, local recurrence rates were lower in both arms of the study, with reported results still demonstrating a significant benefit for patients who received neoadjuvant radiation: 2.4% vs 8.2% at 2 years and 5% vs 11% at 10 years.[48] The German trial directly compared the effectiveness and toxicity of long-course radiation (50.4 Gy in 28 fractions) given pre- vs postoperatively and demonstrated a clear benefit for neoadjuvant therapy. At 5 years, local recurrence rates were 6% vs 13% ($P= 0.006$). In addition, the risks of both short-term and long-term toxicities were lower for patients who received preoperative radiation (short-term 27% vs 40%, $P= 0.001$; long-term 14% vs 24%, $P= 0.01$).[49]

Adjuvant chemotherapy is recommended for LARC based upon pretreatment clinical staging, although the evidence base supporting this recommendation is not strong and is largely extrapolated from evidence supporting the use of adjuvant chemotherapy in colon cancer.[50,51] Treatment involves 4 months of FOLFOX (5-Fluorouracil, Leucovorin, and Oxaliplatin) or CapeOx (Capecitabine and Oxaliplatin), which should be started within 8 weeks after surgery to receive maximum benefit. Unfortunately, due to the side-effect profiles of these regimens, less than one half of eligible patients complete the full intended course of chemotherapy without a missed dose or dose reduction. Additionally, various trials show that 25%-50% of patients with LARC receive no chemotherapy at all after surgery due to postoperative complications, frailty and debilitation, or patient refusal.[52,53] This persistent poor compliance led to the proposal to move chemotherapy to the neoadjuvant preoperative setting, with the goals of both increasing the percentage of patients who complete intended treatment and additionally addressing unidentified micrometastatic disease present at the time of diagnosis sooner in the treatment plan. The TNT approach also facilitates the growing study of nonoperative management for patients with LARC who have a clinical complete response to treatment.

Several institutions have published their early experience with TNT.[54-57] The NCCN considered these findings strong enough to endorse TNT as an acceptable strategy for treating LARC.[3] Reported benefits include a greater percentage of patients completing chemotherapy compared

to historical controls, shorter time with a diverting loop ileostomy, and the ability to assess treatment response after surgical resection. Several strategies for TNT are currently being studied, without consensus on the best approach. Induction chemotherapy refers to chemotherapy that is given before chemoradiation, while chemotherapy given after chemoradiation is called consolidation chemotherapy.

A prospective trial conducted in Spain randomized patients with LARC undergoing neoadjuvant chemoradiation and surgery to additionally receive induction CapeOx either in the preoperative (before chemoradiation and surgery) or the postoperative setting. Although the study authors reported no significant difference in rates of pathologic complete response, patients in the TNT arm did report significantly less treatment-related toxicities (19% vs 54%, $P< 0.001$). In addition, a substantially larger percentage of patients in the induction chemotherapy TNT cohort were able to complete intended chemotherapy, compared to patients in the traditional treatment arm (91% vs 51%, $P< 0.001$).[57,58] Several smaller prospective studies evaluating this treatment paradigm have demonstrated similarly high compliance rates for patients undergoing TNT with induction chemotherapy.

A retrospective cohort analysis from Memorial Sloan Kettering Cancer Center compared 811 patients treated with either TNT (induction fluorouracil- and oxaliplatin-based chemotherapy followed by chemoradiation, n = 308) or the traditional approach (preoperative chemoradiation and planned postoperative chemotherapy, n = 320) and found that patients undergoing TNT were more likely to receive planned chemotherapy treatment without missed doses or dose reductions. Additionally, complete response rates were greater in the TNT group, with 36% of patients achieving pathologic complete response if they underwent surgery or a sustained clinical response if they did not, compared to 21% in the traditional treatment arm. Nonoperative therapy was chosen by 73 patients (24%) in the TNT cohort, and among these patients, 67 (92%) had a sustained complete clinical response (CCR) for greater than 12 months. Of the 235 patients in the TNT cohort who underwent surgery, 43 (18%) had a pathologic complete response.[59] Although these results are encouraging, long-term follow-up data on survival are not yet available for this cohort.

Other studies have defined TNT as chemoradiation followed by consolidation chemotherapy and then surgical resection. A multicenter, phase II nonrandomized trial enrolled patients with LARC in 4 sequential study groups to evaluate this treatment strategy. After undergoing long-course chemoradiation, patients either underwent surgery or received 2, 4, or 6 cycles of modified FOLFOX (mFOLFOX). The investigators postulated that performing chemoradiation first, followed by consolidation chemotherapy, would allow greater time for tumor regression and increase the percentage of patients who would achieve a pathologic complete response. In addition, delivering chemotherapy while waiting for the tumor response to radiation may decrease the risk of progressing to systemic disease. Of note, 80% of patients completed planned chemotherapy without a missed dose or dose reduction. The authors report that patients treated with 6 cycles of mFOLFOX had significantly greater odds of achieving a pathologic complete response compared to patients who went straight to surgery 6-8 weeks after completing chemoradiation (odds ratio 3.5, $P= 0.011$). Of the 65 patients who received 6 cycles of mFOLFOX preoperatively, 25 (38%) had a pathologic complete response, compared to 11 of the 60 patients who went straight to surgery (18%). Importantly, adverse events, including pelvic abscess, anastomotic leak, and overall complications, did not differ between the study groups. The authors note that this ordering of therapy may thus increase the percentage of patients who are potentially eligible for a nonoperative approach while not increasing the risk of complications for patients who do go on to surgical resection.[60] This group has since published its long-term results that demonstrated that the addition of mFOLFOX after chemoradiotherapy and prior to surgical excision increased compliance with systemic therapy and improved disease-free survival. The authors note that this ordering of therapy may thus increase the percentage of patients who are potentially eligible for a nonoperative approach while not increasing the risk of complications for patients who do go on to surgical resection.[61] As with induction chemotherapy, several smaller prospective studies utilizing a consolidation chemotherapy TNT approach have demonstrated similarly high chemotherapy completion rates.

A third approach to TNT was evaluated by the Polish Colorectal Study Group, who randomized patients to short-course radiation followed by consolidation chemotherapy and surgery vs long-course chemoradiation with consolidation chemotherapy followed by surgery. Patients in the TNT arm demonstrated improved survival at 3 years.[62] The RAPIDO trial (NCT01558921), which was recently completed, is also evaluating this approach. The authors hypothesize that short-course radiation will prevent local progression of disease while the patient undergoes consolidation chemotherapy to treat systemic micrometastatic disease.

There are several ongoing studies that incorporate TNT in the study design. For example, patients with LARC enrolled in the multiarm phase II clinical trial NRG-GI002 NCT02921256 receive induction FOFOX before being randomized to standard chemoradiation vs radiation combined with different sensitizers. Additionally, NCT02008656 is a multi-institutional phase II clinical trial that randomizes patients with LARC to receive FOLFOX/CapeOx either before or after long-course chemoradiation (induction vs consolidation chemotherapy). Patients with a significant clinical response after completing treatment will be offered nonoperative management, while those without a significant clinical response will undergo surgical resection. The primary endpoint will be 3-year recurrence-free survival. Finally, the Alliance PROSPECT trial (NCT01515787) is evaluating whether patients with LARC who have a significant radiologic response after induction chemotherapy can safely skip radiation prior to surgical resection.

The literature describing TNT is rapidly growing. The results of the ongoing clinical trials described above will certainly help refine the current definitions of TNT and quantify the relative risks and benefits. The greatest perceived risks are overtreatment due to imprecise clinical staging and the potential for disease progression in patients who do not respond to neoadjuvant treatment. However, advances in imaging technology will hopefully continue to improve our ability to accurately identify, treat, and monitor patients with LARC. The benefits of improved compliance with chemotherapy are well accepted, as is the likelihood of a shortened period of time with an ostomy—an important quality of life factor for patients. Finally, increased adoption of TNT will also likely facilitate greater selection of patients who may be eligible for a nonoperative approach.

The watch-and-wait strategy for locally advanced rectal cancer

The treatment of locally advanced mid to distal rectal cancers has evolved substantially over the last 3 decades. Prior to the 1990s, radical resection alone with low anterior or abdominoperineal resection was the mainstay of treatment. Recognition of the fairly high local and systemic recurrence rates with surgery alone, as well as the functional loss associated with these operations, led to significant interest in finding effective adjunctive therapy to improve functional and oncologic outcomes for patients with LARC. A number of multi-institutional trials conducted in the 1990s confirmed that the addition of chemoradiation to radical resection could improve at least locoregional control of these tumors. Most North American trials[63,64] used chemoradiation in the adjuvant setting, and European trials[47,65] used the therapy in the neoadjuvant setting. Although both neoadjuvant and adjuvant approaches proved to be superior to surgery alone, there was no worldwide consensus that favored one strategy over the other. The German Rectal Cancer Trial, published in *New England Journal of Medicine* in 2004, convincingly demonstrated that the neoadjuvant approach for chemoradiation was superior to a postoperative adjuvant regimen for both locoregional control and ultimate GI tract continuity preservation rates.[49] Based primarily on that trial, in most places throughout the world starting in the early 2000s, neoadjuvant chemoradiation therapy followed by radical resection became the standard treatment for LARC.

As this approach became more universally applied, reports started to surface identifying patients who had undergone neoadjuvant chemoradiation who appeared to have had a CCR. As has been true for other cancers that were treated with neoadjuvant therapy and demonstrated dramatic clinical responses (such as squamous cell carcinoma of the anus), legitimate questions began to arise regarding the necessity of proceeding with major and morbid radical surgery in patients who showed no measurable disease following neoadjuvant chemoradiation.

One of the largest early studies suggesting a nonoperative or "watch-and-wait" approach for patients with a CCR was reported by Habr-Gama and colleagues from Brazil, published in *Annals of Surgery* in 2004.[66] The authors reported on 71 patients who had received neoadjuvant chemoradiation therapy for distal rectal cancers and sustained a CCR; rather than undergoing major resection, the patients were simply followed. With a mean follow-up of 57 months, there were only 2 (2.8%) endoluminal recurrences, both of which were salvaged with additional therapy, no extra luminal pelvic failures, and 3 (4.2%) distant failures, for an overall cancer recurrence rate of 7%. These oncologic outcomes compared favorably to a control group of 22 patients who had radical resection and a complete pathologic response, a group with a 13.6% rate of systemic failure.

In the 15 years since Habr-Gama's landmark paper, many groups have cautiously investigated and applied a watch-and-wait strategy for selected patients with rectal cancer who have evidence of a CCR following neoadjuvant therapy. Although these experiences have substantially increased our knowledge about watch-and-wait, there remain a number of unanswered questions and uncertainties regarding how this approach should fit into our overall treatment paradigm for patients with locoregionally advanced mid to distal rectal cancer. Below, we review several issues surrounding the watch-and-wait strategy that are critical to our present understanding of this approach and highlight the limitations to overcome before watch-and-wait can be universally accepted as part of a standard recommended treatment algorithm for patients with rectal cancer.

Rates of CCR

A CCR is a prerequisite for considering a watch-and-wait approach. To evaluate the validity of this approach, then, it is important to understand clearly the expected rate of CCR following neoadjuvant treatment. Dattani and colleagues[67] recently published a meta-analysis of 17 publications that describe outcomes for watch-and-wait programs at centers throughout the world. The analysis included 13 unique patient populations and 693 patients and represented the most comprehensive results regarding watch-and-wait to date. The average CCR following neoadjuvant therapy for the entire cohort was 22.3%, although the range across the 13 groups was 2.8%-78.4%. Only 3 of the 13 studies reported complete response rates greater than 20% (49.2%,[68] 67.1%,[69] and 78.4%[70]), 2 of which were from the Habr-Gama group in Brazil. Of the remaining 10 studies, 9 reported CCRs ranging from 11.3% to 19.2%.

What are the potential contributors to the wide range of reported CCR? First, these primarily retrospective studies each have a unique mechanism for defining CCR. Criteria in varying combinations have included digital rectal examination findings, gross endoscopic regression (with or without biopsy), transanal excision, CT scan, EUS, and pelvic MRI. The lack of a standardized approach to defining CCR could easily account for some of the variation in rates seen. Furthermore, the timing of the evaluation of tumor response after neoadjuvant therapy was variable, ranging from 3 to 24 weeks. Ample evidence suggests that tumor response to neoadjuvant therapy will continue to evolve for weeks after treatment is completed, so that evaluation too early may lead to an underestimation of the rate of CCR. Habr-Gama and colleagues[71] reported that in one series, the average time from neoadjuvant therapy completion to achievement of a CCR was 18.7 weeks; only 38% of patients who eventually achieved a CCR did so by 10-16 weeks after neoadjuvant therapy.

Although the majority of the studies documented pretreatment clinical staging in terms of T and N assessment, many studies include a certain percentage of T2 patients. It is difficult to sort out how many of these T2 patients were node negative, making them stage I patients; in most centers, these patients would not be candidates for multimodality therapy. Variable rates of inclusion of these "non-locoregionally advanced" cancers may also have affected the rates of CCR across the studies.

In review of these studies, another potential confounder for the prediction of CCR rates was the lack of standardization of the neoadjuvant therapy given. Although the majority of patients

received long-course external beam radiotherapy, consisting of between 50 and 54 Gy with concurrent oral or IV 5-FU, radiotherapy doses did vary from 45 Gy to as high as 66 Gy (including one study that used a 5 Gy boost of endocavitary radiation[70]). Furthermore, 70 patients in one study received 3 additional cycles of consolidation chemotherapy following their radiation treatment.[69] Finally, the recent interest in intensifying neoadjuvant therapy regimens, including those consisting of total neoadjuvant chemotherapy, may potentially significantly alter the rates of CCR to neoadjuvant treatment, adding to our uncertainty regarding this important aspect of a watch-and-wait approach.

Despite these limitations, based on the present available literature, it would be reasonable to conclude that patients with locoregionally advanced mid to distal rectal cancers undergoing standard long-course neoadjuvant chemoradiation therapy should experience a 15%-20% chance of a CCR. Further improvement in our ability to accurately identify these patients radiologically after treatment, and the evolution in the type and extent of neoadjuvant treatments, may substantially alter these rates in the future.

Oncologic outcomes following CCR and watch-and-wait

Dattani's meta-analysis offers the most current data regarding oncologic outcome in selected patients identified with a CCR undergoing a watch-and-wait strategy. In the 13 cohorts he reviewed, local failure occurred in 153/692 (22.1%) of patients. The range of local failure across the studies was 5.7%-86.4%, although 10 of 13 studies reported a local recurrence rate between 12.4% and 38%. Variability in local recurrence rates, again, may be due to heterogeneity in these retrospective studies, including the differences in definitions of CCR, follow-up regimens, initial primary staging, and length of follow-up. The author does note that 96.1% of detected local recurrences were noted within 3 years, with 65.3% detected within the first year, and 88.4 % within 2 years. The rate of metastatic disease in this patient cohort was 57/693 (8.2%). Of these cases, 34 (59.6%) were isolated metastasis without pelvic failure. When added to local failures, it appears that the overall rate of cancer recurrence was 187/692 (27%). Of these metastases, 93.5% were detected within 5 years. The mean follow-up for these studies as a whole was 46.2 months, but the range was 28-72 months. Approximately one-third of patients (211/692, 31%) had follow-up less than 3 years, and only 4 studies had follow-up for 5 or more years, accounting for 147/693 (21.2%) of all patients.

Given the relatively low rates of metastatic recurrence, these studies presented high rates of salvage surgery. The vast majority of patients with isolated locoregional recurrence underwent salvage surgery (130/153 (85%), with 121/153 (79.1%) accomplishing an R0 resection. Sphincter salvage was achieved in 59/130 (45.3%) of patients undergoing surgery for recurrent disease. Finally, although some studies did not report long-term overall survival or disease-free survival, based on the studies documenting these data, patients experienced an overall 3-year survival rate of 93.5% and a 3-year disease-free survival rate of 89.2%.

Despite limitations, the existing data suggest that watch-and-wait may be a reasonable option for selected patients with locoregionally advanced mid to distal rectal cancers who demonstrate a CCR. The data predict CCR rates somewhere between 15% and 20% and with standard neoadjuvant chemoradiation protocols, and with at least 3 years of follow-up, local failure rates of approximately 20%-30%. Most of these cases may be amenable to radical salvage surgery with high rates of R0 resection. Furthermore, systemic failure is uncommon. The mean rate of metastatic disease reported in Dattani's literature review is 8%.

Significant and substantial deficiencies in our present knowledge of the watch-and-wait approach prevent it from being considered "standard of care" for rectal cancer patients. The present literature consists almost entirely of single institutional, retrospective studies with no standardization of techniques for initial cancer staging, criteria for patient inclusion, definitions of CCR, details of neoadjuvant therapy, protocols for follow-up, and length of follow-up. Standardization and clarification of best practices in each of these areas is needed. The total length of follow-up in these studies remains too short to draw definitive conclusions regarding long-term oncologic

outcomes. Perhaps one of the biggest challenges is the fundamental question of how watch-and-wait compares with a radical resection, the present standard of care. Scientifically, this question should be answered by a large, multi-institutional trial that randomizes patients with CCR to either radical surgery or watch-and-wait—a trial that would be almost impossible to conduct, secondary to the challenges of patient accrual to such a study. These challenges were experienced by Nahas and colleagues,[72] who attempted to start such a trial in 2011 (NCT02052921). After 2 years, only 6 patients had been accrued and randomized, and the trial was closed. Finally, the present environment of evolving neoadjuvant regimens, including the concept of TNT, may have a substantial influence on CCR rates and oncologic outcomes in these patients, making our present existing data obsolete.

Given these uncertainties, what treatments are actually being provided to rectal cancer patients today? Three provider surveys have been published in the last year to attempt to answer this question. In the first, Schwartzberg and colleagues[73] sent an anonymous survey to members of the American, European, Australian, New Zealand, and Brazilian colorectal surgery societies regarding providers' perspectives on watch-and-wait. Approximately two-thirds of responses (287/452, 63.4%) came from members of the American Society of Colon and Rectal Surgery (ASCRS), although the response rate was only 13.7%. Among ASCRS respondents, 41% reported they "believed in the philosophy of watch and wait," compared to 71% of the international responders. Yahya and colleagues[74] surveyed US radiation oncologists, with 106/220 responses (48% response rate) and reported that 59% of respondents "felt comfortable" discussing a watch-and-wait approach with patients demonstrating a CCR. Finally, Crawford and colleagues[75] surveyed surgeons across Canada regarding watch-and-wait. With a response rate of 38.4%, the authors found that less than 5% would use a watch-and-wait approach for all patients, and 40% would never use it. Although limited by the challenges of all survey studies, these data suggest that watch-and-wait is being practiced around the world, but with varying frequency, perhaps related to practice type and geographic location.

In summary, multiple retrospective single-institutional studies indicate that a watch-and-wait strategy for some patients achieving a CCR after neoadjuvant treatment for their rectal cancers may be a reasonable choice compared to radical resection. A more standardized approach to pretreatment clinical staging, the definition of CCR, the logistics of neoadjuvant therapy, follow-up protocols, and longer oncologic follow-up will help better define the indications and expectations of this therapy. Multi-institutional, multinational efforts such as the International Watch and Wait Database[76] and the Oncologic Outcomes after Clinical Complete Response in Patients with Rectal Cancer Project[77,78] may help to improve the future quality of data collected in current observational trials. Furthermore, clinicaltrials.gov lists 5 separate additional prospective observational trials that are presently accruing patients. In the likely absence of future randomized trials comparing watch-and-wait to radical resection, these standardized, prospective, observational trials may help providers more clearly identify the appropriate role of watch-and-wait within the "standard of care" for rectal cancer patients in the future.

Extended lymphadenectomy

Approximately 40% of rectal cancer lymph node metastases occur along the mesorectal nodal chain that runs along the inferior mesenteric artery. This is due to the lymphatic drainage pattern of the upper and middle rectum, which travels in a retrograde fashion along the perirectal vessels originating from the inferior mesenteric artery, conveniently located within the mesorectal fascia. Since 1982, Heald's description of the TME has transformed the standard surgical approach to rectal cancer and has dramatically decreased the rate of local recurrence, as well as the morbidity associated with injuries to the pelvic autonomic nerve plexuses.[28]

With the addition of neoadjuvant chemoradiotherapy combined with TME, local recurrence rates can be brought down to less than 10%. However, it is also estimated that approximately 11%-24% of nodal metastases in rectal cancer are found in the lateral pelvic sidewall, which is outside the standard resection margins for proctectomy with TME.[79] A retrospective study in

Japan reported that the incidence of lateral pelvic lymph nodes (LPLN) in patients with T3/T4 rectal cancers was 18%. This is primarily due to the drainage pattern of the mid- to low rectum, which can either spread upward along the superior rectal vessels or laterally along the middle rectal vessels and then to the internal iliacs.[80] Extended lymphadenectomy, particularly in the context of mid- to low rectal cancers, refers to the dissection and removal of LPLN: the common iliac, internal iliac, external iliac, and obturator nodes that travel along these named arteries. Management of LPLN has been a topic of ongoing debate since the late 1970s, when surgeons in Japan began to routinely perform LPLN dissections for locally advanced rectal cancers below the peritoneal reflection. In recent guidelines put forth by the Japanese Society for Cancer of the Colon and Rectum (JSCCR), rectal cancer that occurs above the peritoneal reflection is treated by TME and adjuvant chemotherapy for node-positive disease, whereas for rectal cancer located below the peritoneal reflection, TME and LPLN dissection is the standard of care.[81]

Similar to trends toward more aggressive lymph node clearance in other GI cancers, centers in Asia tend to regard LPLN as a locoregional disease and routinely remove the nodes as part of their standard surgical approach.[81] In contrast, centers in the United States and Europe do not routinely perform LPLN dissections for rectal cancers, even in advanced disease, primarily because pelvic lymph node metastases outside the mesorectal fascia are generally considered a manifestation of more systemic disease and therefore treated with adjuvant chemotherapy. Locally advanced disease, including positive nodes within the mesorectal fascia and/or threatened CRM, are treated with neoadjuvant chemoradiotherapy followed by TME. In Western countries, LPLN dissection is rarely performed because it is thought to have little effect on outcomes. The morbidity and complications associated with LPLN dissection also contribute to the lack of interest in including this as part of the standard treatment algorithm for rectal cancer. A meta-analysis comparing extended lymphadenectomy vs standard TME for rectal cancer evaluated 20 studies, comprising 5502 patients between the years 1965 and 2009. Although perioperative mortality and morbidity were similar between the 2 groups, operative times and intraoperative blood loss were both increased in the extended lymphadenectomy group. Male sexual dysfunction and urinary impairment were also more prevalent in the extended lymphadenectomy group. Another meta-analysis demonstrated increased male sexual and urinary dysfunction (OR 3.70, 95% CI 1.66-8.23; $P = 0.0012$) in the extended lymphadenectomy group compared to standard resection with TME.[82] No significant differences were found in the 5-year survival, 5-year disease-free survival, and local or distant recurrence rates between these 2 groups.[82]

A retrospective multicenter study evaluated 1272 patients who underwent surgery for rectal cancer, 784 (62%) of whom underwent LPLN dissection. Independent prognostic risk factors for LPLN metastasis included female gender, tumors located below the peritoneal reflection, poorly differentiated adenocarcinoma, and the presence of lymphovascular invasion. Comparing patients with and without LPLN dissection, this study found no significant differences in rates of local recurrence (10.5% vs 7.4%) or 5-year overall survival (75.8% vs 79.5%).[80]

A recently published JCOG0212 trial in Japan compared TME with and without routine LPLN dissection in 701 patients with clinical stage II/III low rectal cancer. Included were those who did not have evidence of LPLN involvement on preoperative CT or MRI. In this multicenter, randomized controlled, noninferiority trial, the rate of local recurrence with LPLN dissection was lower than for those without routine dissection. This finding suggests that without neoadjuvant radiation, the addition of routine LPLN dissection to TME can be effective in reducing local recurrence.[83]

Currently, the decision to include LPLN dissection as part of the treatment algorithm for rectal cancer appears to be regionally dependent, without a clear international consensus. A majority of Western countries, including those in North America and Europe, do not consider LPLN as locoregional disease and instead treat it as distant metastases using neoadjuvant chemoradiation and/or chemotherapy in conjunction with proctectomy with TME. In contrast, in many Eastern countries, particularly Japan, rectal cancer below the peritoneal reflection is routinely treated with TME along with LPLN dissection, while neoadjuvant chemoradiation is less often utilized.[84] It is clear that both treatment strategies offer patients much-improved rates of local recurrence and overall survival compared to patients treated with proctectomy with TME alone. What re-

mains unclear are the guidelines and criteria for patient selection. In line with the current move toward patient-centered care and a more personalized approach to treatment planning, the selective inclusion of LPLN dissection for a specific subset of patients with rectal cancer may prove to be a powerful tool in the surgeon's armamentarium.

National Accreditation Program for Rectal Cancer (NAPRC)

As demonstrated by the topics covered in this monograph, there have been several significant advances in the management of patients with rectal cancer in recent years, which together make the care of these patients complex. Advances include better imaging modalities for tumor localization and staging, standardized pathologic assessment of TME and adverse tumor features, improvements in the role of radiation and chemotherapy, and increased surgical options with a greater focus on technique for adequate resection. Management that follows evidence-based guidelines summarizing these advances is associated with decreased rates of recurrence and improved survival. However, in the United States, outcomes for patients diagnosed with rectal cancer vary considerably depending upon the institution where the patient is treated, with up to one half of patients with rectal cancer not receiving guideline-recommended staging and treatment. As a result, significant disparities exist for important outcomes such as postoperative morbidity and mortality, sphincter preservation with bowel continuity vs permanent ostomy, local recurrence, and long-term survival.[85-88]

To address this variation in outcomes and broadly improve the quality of rectal cancer care, the American College of Surgeons Commission on Cancer recently established the NAPRC. This program, which began enrollment in 2017, built upon the work of the Optimizing the Surgical Treatment of Rectal Cancer (OSTRiCh) Consortium, which is a voluntary group of healthcare institutions led by surgeons who are interested in working together to improve access to high-quality rectal cancer care across the country. Other collaborators in the development of the NAPRC include the ASCRS, the Society of Surgical Oncology, the Society of Surgery for the Alimentary Tract, the Society of American Gastrointestinal and Endoscopic Surgeons, the American College of Radiology, and the College of American Pathologists. Design of the program is modeled after rectal cancer accreditation programs in Europe that have successfully decreased cancer recurrence rates and improved survival by standardizing care,[89] as well as the National Accreditation Program for Breast Centers in the United States. Central elements of accreditation include strict requirements for multidisciplinary cancer conferences (including regular attendance by a set group of specialists with rectal cancer expertise), development of a standards manual of evidence-based protocols, and external audit of compliance with protocols. Additionally, the program requires comprehensive written documentation and communication of treatment planning and treatment outcomes as well as integration of continuous quality improvement through the rapid quality reporting system and accountability and quality improvement measures.

The goal of the NAPRC is to ensure that patients with rectal cancer receive optimal patient-centered, guideline-recommended, multidisciplinary care. The October 2017 edition of the NAPRC manual outlines 22 standards required for accreditation, which are categorized as related to program management (7 standards), clinical services (13 standards), and quality improvement (2 standards). Meeting these standards is expected to improve rectal cancer outcomes as they were created using evidence-based guidelines. The NAPRC reviews quality indicators (guidelines for staging, appropriate neoadjuvant and adjuvant therapy, surgical quality indicators [(lymph node yield, margins, quality of TME, perioperative morbidity)], and oncologic outcomes [(local recurrence and survival))]. Only centers that hold Committee on Cancer (CoC) accreditation and have an established rectal cancer program that complies with the 22 standards for at least 12 months are eligible for accreditation.

Rectal cancer multidisciplinary team conferences are a central element of accreditation. The program requires official designation of members of the team, including representation from surgery, radiology, pathology, medical oncology, and radiation oncology, and requires that these members meet on a regular basis (at least twice per calendar month) to discuss patients

throughout their evaluation and treatment. Each member of the multidisciplinary team must attend at least 50% of the multidisciplinary conferences. The surgery, radiology, and pathology physician representatives are also required to complete education modules that have been endorsed by the NAPRC.

Accreditation by the NAPRC additionally requires designation of a rectal cancer program director and program coordinator, and outlines the specific requirements and responsibilities associated with each of these roles. The program director chairs the multidisciplinary team and is the liaison between the team and the facility's CoC committee. The director is also responsible for internal audits and reporting results from the National Cancer Database (NCDB) to the team at least 4 times per year. The program coordinator coordinates the activities of the multidisciplinary team, including communication between specialties, communicating to referring physicians, primary care physicians, and patients, coordinating patient visits, and oversight of data collection.

The required clinical services standards are focused on receipt of appropriate imaging and laboratory studies for staging prior to beginning treatment (CT PET/CT of chest, abdomen and pelvis; MRI of the pelvis with rectal cancer protocol; and CEA level) and use of standardized synoptic templates for MRI results, operative reports, and pathology reports that include specific required elements. In addition, there is a standard specifying that all patients, especially those diagnosed at outside facilities, should have their pathology reviewed at the treating institution to confirm adenocarcinoma. All patients diagnosed with rectal cancer should be discussed at multidisciplinary team conference prior to initiation of therapy and a recommendation summary completed and provided to primary care physician and the referring provider. The standard regarding definitive treatment planning states that patients should initiate therapy within 60 days from initial clinical evaluation. Regarding surgical resection of rectal cancer, the standard requires that 80% of procedures are performed by a surgeon who is a designated member of the rectal cancer multidisciplinary team. After surgery, pathology reports must be completed within 2 weeks and contain all of the required College of American Pathologists (CAP) data elements. Sixty percent of surgical specimens must be photographed with anterior/posterior/lateral views that should then be reviewed and regularly discussed in conference with the members of the Rectal Cancer Multidisciplinary Team within 4 weeks of definitive surgical therapy. Each year a treatment summary must be completed on at least 50% of patients. Finally, chemotherapy must be initiated for at least 50% of patients for whom it was recommended within 8 weeks of surgical resection.

In order to ensure continuous quality improvement, the NAPRC requires active participation in the Rapid Quality Reporting System (RQRS) by submitting data on set performance measures for all patients treated for rectal cancer. Each year the program is required to meet accountability measures, as defined by the NAPRC. If the program is not meeting or exceeding the expected estimated performance rate for accountability or quality measures, then a corrective plan must be developed and implemented. Following the application for accreditation, a site visit is performed to confirm compliance with these standards and appropriate clinical outcomes.

When OSTRiCh was initially established in 2011, it included only 18 centers. As of April 2017, there were more than 350 institutions involved. A recent survey of participating centers (with a 42% response rate) aimed at assessing readiness for accreditation by the NAPRC identified significant variability between institutions in the multidisciplinary management of rectal cancer and projected poor compliance with NAPRC standards.[90] The authors note that this reveals a considerable opportunity for improving the care of patients with rectal cancer across the country. Currently, there are 11 institutions that have achieved accreditation by the NAPRC, with more currently undergoing evaluation.

Leaders involved with development of the NAPRC acknowledge that many hospitals will find accreditation excessively resource intensive, especially low-volume centers.[91] Currently, the majority of patients with rectal cancer are treated in low-volume hospitals. Regionalization of all rectal cancer care to high-volume accredited Centers of Excellence, as was done in some European countries, is unlikely to be successful in isolation here in the United States. As treatment often requires multiple visits over the span of many months, treatment at accredited re-

gional hospitals may be a burden for many patients and is thus an inadequate solution given geographic and socioeconomic barriers to travel and patient preferences to receive care closer to home.[92] In addition, there is evidence to suggest that many older patients are not willing to travel great distances to a regional center, even for a lower operative mortality risk.[93] Thus, there is a critical need to develop alternative strategies that are complementary to accreditation to improve care across a wider range of institutions and ensure that disparities in care delivery are not exacerbated.

With increasing awareness of the variabilities in rectal cancer care across the country and guidelines set forth to standardize and improve care, it is expected that most major cancer treatment centers will strive to reduce this variability. By setting standards, mandating a multidisciplinary approach and carefully monitoring the quality of care (surgical, medical, radiology, pathology), the result will be that of a much more tailored approach to each patient's care along with improved outcomes.

Conclusion

The ever-expanding treatment options for patients with rectal cancer and complexity of decision-making underline the importance of managing patients with rectal cancer within the context of an experienced, multidisciplinary team.

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