The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Rectal Cancer 2023 Supplement

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The American Society of Colon and Rectal Surgeons (ASCRS) is dedicated to ensuring high-quality patient care by advancing the science, prevention, and management of disorders and diseases of the colon, rectum, and anus. The Clinical Practice Guidelines (CPG) Committee is composed of society members who are chosen because they have demonstrated expertise in the specialty of colon and rectal surgery. This committee was created to lead international efforts in defining quality care for conditions related to the colon, rectum, and anus and develop CPG based on the best available evidence. Although not proscriptive, these guidelines provide information on which decisions can be made and do not dictate a specific form of treatment. These guidelines are intended for the use of all practitioners, health care workers, and patients who desire information about the management of the conditions addressed by the topics covered in these guidelines. These guidelines should not be deemed inclusive of all proper methods of care nor exclusive of methods of care reasonably directed toward obtaining the same results. The ultimate judgment regarding the propriety of any specific procedure must be made by the physician considering all the circumstances presented by the individual patient.

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STATEMENT OF THE PROBLEM

Colorectal cancer is the third most common cancer and the third most common cause of cancer-related deaths in the United States.[1] Approximately 30% of these cancers will originate in the rectum, and the American Cancer Society estimated a total of 44,850 new rectal cancer diagnoses in the United States for 2022.[2]

Adenocarcinoma of the rectum is inherently complex. Surgery for rectal cancer is technically challenging and is associated with major alterations in GI, urinary, and sexual functions and with decreased quality of life.[3–5] The treatment of rectal cancer is also rapidly evolving, with new data emerging on a regular basis.

In 2020, the ASCRS published its most recent CPG for rectal cancer.[6] This was a comprehensive assessment covering a wide spectrum of topics. Since then, there have been

several high-impact studies regarding the evaluation and treatment of rectal cancer that warrant updated recommendations and supporting statements from the ASCRS. The purpose of this CPG supplement is not to replace the 2020 CPG but to enhance these guidelines with the latest high-impact data.

Of note, there remain certain outstanding questions that were intentionally omitted from this addendum because there is insufficient evidence to construct a formal recommendation regarding certain topics. Examples include the role of circulating tumor DNA (ctDNA) in determining prognosis and the utility of adjuvant therapy,[7] immunotherapy in the treatment of mismatch repair deficient rectal cancers,[8,9] selective use of preoperative radiation therapy,[10] and selective versus routine lateral pelvic lymph node dissection for patients who have received pelvic radiation therapy.[11–13] These topics will be addressed in the comprehensive revision of our rectal cancer guidelines as data evolve.

METHODOLOGY

These guidelines are based on the past set of ASCRS Practice Parameters for the Management of Rectal Cancer published in 2020. An organized search of MEDLINE, PubMed, Embase, and the Cochrane Database of Systematic Reviews was performed of research published between January 14, 2020, and June 7, 2023. Individual literature searches were conducted for each statement within the guideline and were restricted to English language and adult patients. Search strategies were based on the concepts of upper and lower rectal cancer, neoadjuvant therapy, organ preservation, and transanal total mesorectal excision (taTME). Key word combinations using MeSH terms, subjects, and titles were used for the search, including rectal cancer, adenocarcinoma, intraperitoneal, upper rectal, neoadjuvant therapy, total neoadjuvant therapy (TNT), consolidation, induction, clinical complete response (cCR), pathologic complete response (pCR), organ preservation, watch-and-wait, endoscopic biopsy, taTME, ctDNA, lateral pelvic lymph node dissection, and immunotherapy. Directed searches using embedded references from primary articles were performed in selected circumstances, and other sources, including practice guidelines and consensus statements from relevant societies, were also reviewed.

The 3718 screened articles were evaluated for their level of evidence, favoring clinical trials, meta-analyses/systematic reviews, comparative studies, and large registry retrospective studies during single-institutional series, retrospective reviews, and peer-reviewed, observational studies. A final list of 121 sources was evaluated for methodological quality, the evidence base was analyzed, and a treatment guideline was formulated by the subcommittee for this guideline (Fig. 1).

CERTAINTY OF EVIDENCE

The final grade of recommendation and level of evidence for each statement were determined using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system.[14] The certainty of evidence reflects the extent of our confidence in the estimates of effect. Evidence from randomized controlled trials (RCTs) start as high certainty, and evidence derived from observational studies start as low certainty. For each outcome, the evidence is graded as high, moderate, low, or very low (Table 1). The evidence can be rated down for risk of bias, inconsistency, indirectness, imprecision, and publication bias. The certainty of evidence originating from observational studies can be rated up when there is a large magnitude of effect or dose–response relationship. As per GRADE methodology, recommendations are labeled as "strong" or "conditional." Current recommendations are stated in Table 2. When agreement was incomplete regarding the evidence base or treatment guideline, consensus from the committee chair, vice chair, and 2 assigned reviewers determined the outcome. Recommendations formulated by the subcommittee were reviewed by the entire CPG Committee. The submission was then approved by the ASCRS Executive Councils and peer-reviewed in *Diseases of the Colon and Rectum*. In general, each ASCRS CPG is updated approximately every 5 years. The next update on rectal cancer will be another comprehensive update of current evidence on all topics. No funding was received for preparing this guideline, and the authors have declared no competing interests related to this material. This guideline conforms to the Appraisal of Guidelines for Research and Evaluation checklist.

1. Tumors of the upper rectum do not usually benefit from neoadjuvant chemoradiotherapy (CRT) and should typically be treated with initial surgical resection. Strength of recommendation: conditional, based on moderate-quality evidence.

In a review of the literature, textbooks, and North American treatment guidelines, recommendations regarding the treatment of upper rectal cancer are conspicuously missing. The "upper rectum" refers to the most proximal component of the rectum, which lies above the anterior peritoneal reflection.[6] An international, expert-based consensus reported "upper rectal cancers" to lie entirely above the peritoneal reflection, which is usually 11 to 15 cm from the anal verge but varies based on individual patient anatomy.[15] MRI[16] and rigid or flexible endoscopy are critical in localizing tumors to the upper rectum. It is important to have a multidisciplinary discussion regarding each case to determine which tumors can be defined as "upper rectum" by the above criteria.

The main goal of neoadjuvant CRT (NACRT) is to reduce local recurrence (LR) after proctectomy. However, upper rectal cancers have been shown in

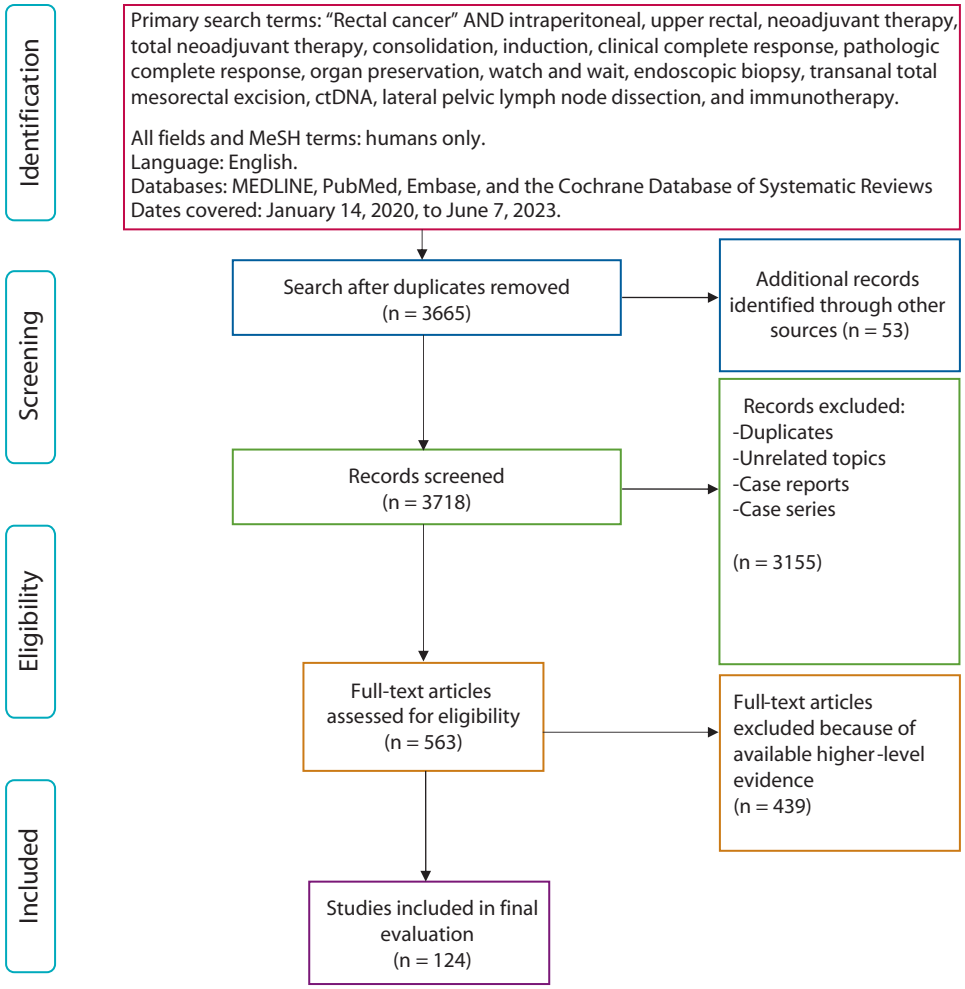

FIGURE 1. PRISMA literature search flow chart. PRISMA = Preferred Reporting Item for Systematic Reviews and Meta-Analysis.

multiple retrospective studies to have lower rates of LR compared to cancers of the middle and lower rectum.[17–19] A 2019 meta-analysis evaluated 5 studies with 3381 patients who underwent surgery for rectal cancer without neoadjuvant chemotherapy or radiation therapy. This study found that despite similar rates of T3/4 and/or node-positive cancers, upper rectal cancers were associated with a significantly lower risk of LR compared to middle and lower rectal cancers (OR 0.495; 95% CI, 0.302–0.811; $p = 0.005$).[20] A 2021 meta-analysis of 7 retrospective cohort studies including 4280 patients demonstrated that upper rectal cancers have LR rates

TABLE 1. Interpretation of strong and conditional recommendations using the GRADE approach

Evaluation	*Description*
Recommendation	
Strong	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences
Conditional	Different choices will be appropriate for individual patients consistent with their values and preferences. Use shared decision-making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences
GRADE certainty rankings	
High	The authors are confident that the true effect is similar to the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
Low	The true effect might be markedly different from the estimated effect
Very low	The true effect is probably markedly different from the estimated effect

GRADE = Grading of Recommendations, Assessments, Development, and Evaluation.

TABLE 2. Summary and strength of GRADE recommendations

	Summary	*Recommendation strength*	*GRADE quality of evidence*
1	Tumors of the upper rectum do not usually benefit from neoadjuvant chemoradiotherapy and should typically be treated with initial surgical resection	Conditional	Moderate
2	Total neoadjuvant therapy is typically recommended for stage II or III mid or low rectal adenocarcinoma	Conditional	High
3	Following neoadjuvant therapy for rectal cancer, patients should be assessed to determine the response to treatment	Strong	Low
4	The value of endoscopic biopsy to assess for the presence of residual disease is limited by the high false negative rate	Conditional	Very low
5	A watch-and-wait strategy can be offered to selected patients with a clinical complete response in experienced centers with established protocols	Conditional	Moderate
6	In addition to routine surveillance for disease recurrence, patients managed using a watch-and-wait strategy should undergo surveillance to assess for local tumor regrowth	Strong	Expert consensus
7	Compared to laparoscopic and robotic TME, transanal TME for mid and low rectal cancer has similar overall complication rates and functional outcomes	Conditional	Moderate

GRADE = Grading of Recommendations, Assessments, Development, and Evaluation; TME = total mesorectal excision.

similar to left-sided colon cancers rather than lower rectal cancers (OR 0.63; 95% CI, 0.37–1.08; $p = 0.1$).[21] These data call into question the utility of NACRT for upper rectal cancers, especially in light of the known deleterious impact of NACRT on long-term function.[22]

A long-term follow-up from the Swedish Rectal Cancer trial evaluated 243 patients with rectal cancers ≥11 cm from the anal verge and found that short-course radiation therapy (SCRT) did not reduce LR compared to upfront surgery (8% vs 12%; $p = 0.3$).[23] A long-term follow-up from the Dutch TME trial evaluated 551 patients with cancers ≥10.1 cm from the anal verge and also found that SCRT did not reduce LR compared to upfront surgery (3.7% vs 6.2%; $p = 0.122$).[24] The 2009 MRC CR07 and NCIC-CTG C016 trial performed a subgroup analysis on 207 patients with tumors 10 to 15 cm from the anal verge and demonstrated no difference in 3-year LR between those receiving NACRT versus upfront surgery (1.2% vs 6.2%; $p = 0.19$).[25]

Postoperative radiation therapy appears to be similarly ineffective in reducing LR of upper rectal cancers. A 2019 single-center retrospective review from Korea reported on 263 patients with stage II and III upper rectal cancer, and it used propensity score matching to compare outcomes between postoperative CRT and postoperative chemotherapy alone.[26] Three-year LR-free survival was similar between the 2 groups (94.1% vs 90.1%; $p = 0.70$). A 2021 single-center retrospective study from China evaluated 222 patients with stage II and III rectal cancer located entirely above the peritoneal reflection and also reported that postoperative radiation therapy had no impact on LR.[27]

The recently published PROSPECT trial did not exclusively study patients with upper rectal cancer but presented an alternative treatment paradigm that deserves more study and could be potentially extrapolated to this population of patients. The study was a multicenter, noninferiority randomized trial of 1194 patients. All patients had T2 node-positive, T3 node-negative, or T3 node-positive rectal cancer in which the surgeon deemed NACRT followed by sphincter-sparing surgery to be the correct approach. Importantly, patients with T4 tumors, lymph nodes >10 mm in short axis, or tumors within 3 mm of the mesorectal margin on MRI were excluded. Patients were randomly assigned (585 to FOLFOX [5-fluorouracil, leucovorin, and oxaliplatin] upfront versus 543 to standard long-course CRT upfront). Patients in the FOLFOX arm received 6 cycles of FOLFOX and then restaging. If the tumor shrunk by less than 20%, patients were offered CRT (9.1% of patients received this.) If the tumor decreased in size by at least 20%, patients were offered surgery. The FOLFOX strategy was shown to be noninferior to conventional CRT in disease-free survival (DFS; HR for death 0.92; $p = 0.005$ for noninferiority). DFS at 5 years was 80.8% in the FOLFOX group versus 78.6% in the CRT group (p = nonsignificant [NS]). The overall survival was 89.5% in the FOLFOX group versus 90.2% in the CRT group (p = NS). The LR rate at 5 years was 1.8% in the FOLFOX group versus 1.6% in the CRT group (p = NS).[28]

Ultimately, the decision to use preoperative radiation therapy for local control in upper rectal cancers is multidisciplinary. None of these clinical studies were designed specifically to answer this clinical question. Instead, subset analyses of patients with upper rectal cancers were conducted. Although neoadjuvant radiation therapy is not routinely needed for upper rectal cancers, certain subsets of patients, including those with T4b tumors, posteriorly threatened mesorectal fascia, or extramural vascular invasion, may possibly benefit from it, but there are subsets that are underrepresented in clinical trials.[29]

2. TNT is typically recommended for stage II or III mid or low rectal adenocarcinoma, particularly in patients hoping to maximize the chance of having a complete clinical and/or pathological response. Strength of recommendation: conditional, based on high-quality evidence.

Adjuvant chemotherapy has been shown to improve DFS for locally advanced rectal cancer, even in the setting of a pCR.[6,30,31] However, many patients never receive adjuvant therapy for many reasons, including postoperative complications. In the rigorous setting of randomized trials, adjuvant chemotherapy completion rates range from 50% to 82%.[32,33] However, cohort and database studies that report on patients outside of clinical trials often have much lower completion rates ranging from 32% to 42%, depending on age, comorbidities, surgical complications, and final pathology.[31,34,35]

To improve chemotherapy completion rates, the concept of TNT emerged. This approach has patients complete all intended radiation therapy and chemotherapy before undergoing surgery with curative intent. Multiple studies have demonstrated that patients treated with TNT are significantly more likely to complete their chemotherapy compared to c-NACRT followed by surgery and then adjuvant chemotherapy.[36] In a 2019 systematic review of 10 TNT studies including 648 patients, neoadjuvant chemotherapy completion ranged from 86% to 100%.[37] One of the intended benefits of TNT is the reduction of distant metastatic disease by ensuring the delivery of systemic chemotherapy early in the treatment process.

TNT is categorized as either "induction TNT" (systemic chemotherapy followed by radiation therapy and then consideration for surgery) or "consolidation TNT" (upfront radiation therapy followed by chemotherapy and then consideration for surgery). The radiation therapy received during TNT can also be divided into long-course radiation therapy (LCRT) with radiosensitizing chemotherapy and SCRT; either radiation therapy approach can be incorporated into induction or consolidation TNT. The term "near-TNT" refers to regimens in which neoadjuvant radiotherapy, chemotherapy, and adjuvant chemotherapy are used.

In addition to having higher rates of chemotherapy completion compared to conventional therapy, TNT is associated with increased rates of cCR and pathological complete response (pCR). Multiple studies have demonstrated improved DFS.[38–41] The differences in OS have been variable among different studies, and we attempt to highlight the OS numbers individually for each trial in the following paragraphs. Three recent meta-analyses confirmed that compared to conventional therapy, TNT was associated with higher rates of pCR, improved DFS, and improved OS.[42–44] In addition to the above-mentioned factors, another advantage of TNT is the decreased time interval to ileostomy closure that is facilitated by omitting adjuvant therapy.[45]

Tumor Response

In a recently published single-center retrospective study, 36 of 66 patients with rectal cancer (55%) who received TNT had a cCR, whereas 59 of 399 patients with rectal cancer (15%) who had a c-NACRT had a cCR ($p < 0.001$).[41] In a 2019 retrospective case series, cCR was achieved in 80 of 126 patients (63%) treated with LCRT-based TNT.[46] In this study, patients with a longer interval between completing TNT and assessing clinical response were more likely to achieve a cCR (median interval to cCR 18.7 was [±9.2] weeks and some patients did not achieve cCR until ≥32 weeks). SCRT-based TNT also results in a high rate of cCR. For example, in the prospective nonrandomized NORMAL-R study, in which 19 patients received 25 Gy in 5 fractions followed by FOLFOX ×4 to 8 cycles or CAPOX (capecitabine and oxaliplatin) ×5 cycles, 74% of patients had a cCR and 68% of patients maintained their cCR status 1 year after TNT completion.[47]

The RAPIDO trial compared SCRT-based TNT versus c-NACRT and found that the rate of pCR was 28% after TNT and 14% after c-NACRT ($p < 0.0001$).[39] In the Timing of Rectal Cancer Response to Chemoradiation (TIMING) trial, pCR increased from 18% in the c-NACRT arm to 38% in the group that received 6 cycles of oxaliplatin-based consolidation chemotherapy after long-course CRT ($p = 0.003$).[38] It is unclear whether the increased responses noted in the TIMING trial were a function of simply waiting longer for surgery versus any effects of the consolidation chemotherapy. Recent meta-analyses, including various LCRT-based TNT and near-TNT regimens, have also shown higher pooled rates of pCR after TNT/near-TNT compared to c-NACRT (19%–22% vs 13%–14%).[44,48] In a 2022 meta-analysis that included 7 studies, with 1865 patients who underwent SCRT, the pooled pCR rate for SCRT-based TNT versus c-NACRT was 23% and 13%, respectively ($p < 0.01$).[49] Although most clinical studies present pCR as an end point, it may not be the most clinically useful metric to follow because it is not correlated with organ preservation and may just reflect favorable tumor biology.[50]

TNT-Related Toxicity

In the RAPIDO and UNICANCER-PRODIGE-23 trials, there were no increases in grade 3 or more treatment-related toxicity with TNT compared to c-NACRT.[39,40] In a 2020 meta-analysis, the toxicity profile of TNT regimens was comparable with that of c-NACRT.[48] In contrast to this, in the recently published STELLAR trial, the prevalence of acute grade 3 or more toxicities was significantly higher for SCRT-based near-TNT versus c-NACRT

(26.5% vs 12.6%; $p < 0.001$).[51] In this trial, only toxicity that occurred during neoadjuvant treatment was assessed, whereas, in the other studies, toxicity related to both neoadjuvant and adjuvant therapies was considered, which may partially explain the discrepancy.

Operative Difficulty and Complications

The 2015 TIMING trial randomly assigned patients with locally advanced rectal cancer to 4 study groups with different durations of consolidation chemotherapy before surgery. All patients received long-course CRT. Group 1 did not receive consolidation chemotherapy before surgery. Group 2 received 2 cycles of mFOLFOX followed by surgery, whereas group 3 received 4 and group 4 received 6 preoperative cycles. Due to this methodology, the interval between CRT and proctectomy increased across the 4 study groups (from 6 weeks for group 1 to 20 weeks for group 4). Objective measures, such as sphincter preservation, margin status, number of lymph nodes examined, and blood loss, were similar across all 4 groups, and there were no differences in postoperative complications. Although there was a significant subjective increase in pelvic fibrosis for patients with longer intervals between LCRT and surgery (rated by operating surgeons on a scale of 1–10), there were no significant differences in the perceived technical difficulty of the cases. Notably, however, the authors did not report on the relative completeness of the mesorectal specimen between groups.[38] In the UNICANCER-PRODIGE-23 trial, postoperative complications occurred in 29% of the TNT group and 31% of the c-NACRT group ($p = 0.66$), and there were no differences in rates of anastomotic leak or abscess (10% vs 11%). There was also no difference in the completeness of the mesorectal specimen between the 2 groups.[40] In a 2022 meta-analysis of SCRT-TNT versus c-NACRT, pooled postoperative complication rates were 42% for the SCRT-TNT group and 37% for the c-NACRT group ($p = 0.06$).[49] The results of the RAPIDO short-course trial should be interpreted with caution. A recent 5-year follow-up reported locoregional failure in 12% of patients in the experimental arm versus 8% of patients in the standard treatment arm ($p = 0.07$). Although the original publication did not report on specimen quality, the 5-year follow-up data show worse surgical quality in the short-course TNT arm with breach of the mesorectum occurring in 21% versus 4% of standard treatment arm patients ($p = 0.048$).[52]

Survival

Meta-analyses and prospective trials have shown improved DFS in patients with rectal cancer treated with LCRT- or SCRT-based TNT/near-TNT regimens compared to SCRT or LCRT combined with adjuvant chemotherapy. In the TIMING trial, 5-year DFS was increased in the study groups that received any number of consolidation chemotherapy cycles (76%–86%) compared to those that received none (50%; $p = 0.004$), but there were no differences in OS.[53] In the RAPIDO trial, TNT was associated with improved 3-year DFS compared to c-NACRT (76.3% vs 69.6%; $p = 0.01$).[39] The 5-year RAPIDO results also showed a significant decrease in cumulative 5-year distant metastasis in the short-course TNT group compared to the conventional therapy group (23% vs 30.4%, $p = 0.011$). In the UNICANCER-PRODIGE-23 trial, the 3-year DFS was 76% in the near-TNT group and 69% in the c-NACRT group ($p = 0.03$).[40] In a 2021 meta-analysis of TNT versus c-NACRT and adjuvant chemotherapy, DFS was increased after TNT (71% vs 65%; $p < 0.001$), as was OS (85% vs 82%; $p = 0.006$).[44] In a 2022 meta-analysis of 7 studies, with 1865 patients, that compared SCRT-TNT and c-NACRT, DFS was found to be increased for SCRT-TNT compared to c-NACRT (RR = 1.10; 95% CI, 1.02–1.18; $p = 0.01$), but there was no difference in OS (RR = 1.03; 95% CI, 0.97–1.08; $p = 0.36$).[49] The 7-year results of the PRODIGE-23 trial were presented at the American Society of Clinical Oncology. The FOLFIRINOX (folinic acid, fluorouracil, irinotecan hydrochloride, and oxaliplatin) TNT arm of the trial showed an increase in DFS of 7.9%, in OS of 6.9%, and in metastasis-free survival of 9.9% compared to conventional long-course CRT.[54] The published results of this trial are awaited, as are the results of the JANUS trial comparing long-course TNT with consolidation FOLFOX or CAPOX versus FOLFIRINOX (https://clinicaltrials.gov/ct2/show/NCT05610163). Our subsequent guidelines will reflect these findings.

Induction Versus Consolidation TNT

The German CAO/ARO/AIO-12 RCT compared induction TNT with LCRT (n = 156) to consolidation TNT with LCRT (n = 150) followed by surgery with curative intent. This trial demonstrated modestly higher rates of pCR for consolidation versus induction TNT (25% vs 17%, OR 1.69 [95% CI, 0.96–2.99]; $p = 0.071$) and no differences in postoperative complications.[55] The recently published long-term oncologic outcomes from the trial after a median follow-up of 43 months (range, 35–60 months) revealed no differences in 3-year DFS (73% in both groups; $p = 0.82$), 3-year locoregional recurrence (6% and 5%; $p = 0.67$), and distant metastases rates (18% and 16%; $p = 0.52$) in the induction and consolidation arms, respectively.[56]

In the Organ Preservation in Rectal Adenocarcinoma (OPRA) trial, patients were similarly randomly assigned to LCRT with induction versus consolidation chemotherapy, but patients with a cCR were offered organ preservation rather than proctectomy.[57] The authors reported a 3-year DFS of 76% for both groups, but long-term organ preservation (ie, proctectomy-free survival) was increased in the consolidation group (53% vs 41%; $p = 0.01$). There were

no differences in the rate of treatment-related toxicities, LR-free survival, distant metastasis-free survival, or OS between the treatment groups.[57] This study suggested that consolidation TNT may be more appropriate if the goal of treatment includes organ preservation. The 5-year results of the OPRA trial were recently presented at the American Society of Clinical Oncology. In total, 34% of the patients assigned to a watch-and-wait approach had recurrence within 5 years. Of these, 94% of recurrences occurred within 2 years and 99% occurred within 3 years. For organ preservation, TME-free survival was significantly higher in the consolidation chemotherapy arm (54%) than in the induction chemotherapy arm (39%; $p = 0.01$). There were no differences in DFS or OS. Patients who underwent TME upfront had no difference in DFS versus those who underwent TME after having failed the watch-and-wait approach (62% vs 61% at 5 years; $p = 0.86$).[58]

3. Following neoadjuvant therapy for rectal cancer, patients should be assessed to determine the response to treatment. Strength of recommendation: strong, based on low-quality evidence.

As detailed in the 2020 guidelines, restaging after completion of neoadjuvant therapy impacts the treatment plan for a significant percentage of patients.[6] Reassessment of tumor response can assist with determining the necessary extent of surgical resection, especially in the presence of initially threatened margins. Patients without any evidence of residual tumor or lymphadenopathy are considered to have a cCR. A cCR is determined by a combination of digital examination (when within reach), endoscopy, and imaging with a rectal cancer protocol pelvic MRI. cCR has been reported to occur in up to 65% of patients who received TNT for rectal cancer.[46,57,59] In patients with a cCR, a digital rectal examination (DRE) of distal tumors should reveal a smooth, regular scar without palpable ulcer or nodularity. DRE can often detect subtle irregularities even in the presence of normal overlying mucosa.[59] Flexible endoscopic examination of a cCR should reveal a flat, white scar without residual ulcer or mass.

In patients with a cCR, MRI of the pelvis should demonstrate no evidence of residual tumor within the rectal wall and no residual lymphadenopathy.[59] Under these circumstances, T2-weighted MR images of the rectum should be dark without an intermediate signal and no suspicious lymph nodes. MR diffusion-weighted imaging should reveal no diffusion restriction in the area where the tumor was previously located.[60–66] Both the European Society of Gastrointestinal and Abdominal Radiology[67] and the North American Society of Abdominal Radiology[68] recommend both T2-weighted images and diffusion-weighted images when restaging rectal cancer after NACRT.

Most evidence suggests that the response to CRT is time dependent and that higher rates of both cCR and pCR are achieved after longer intervals after completion of neoadjuvant treatment,[46,69–73] although this has not been uniformly reported.[74] In a retrospective study of 126 patients after consolidation TNT, 49 patients (39%) achieved a cCR and had no local regrowth during the study period.[46] A median interval of 18.7 weeks was required to achieve a cCR in these 49 patients, whereas only 18 patients (37%) had a cCR within 16 weeks of completing radiation therapy. In this study, patients with earlier T stages (eg, cT2/T3a) achieved a complete clinical response significantly earlier compared with patients who had more advanced disease ($p = 0.03$).

Although the recommendation in terms of the exact timing to assess for a cCR has not been established, evaluation within 8 to 12 weeks after completing neoadjuvant therapy is recommended.[46,57]

4. The value of endoscopic biopsy to assess for the presence of residual disease is limited by the high false-negative rate. Strength of recommendation: conditional, based on very low-quality evidence.

After neoadjuvant therapy, the tumor bed is often left with a flat scar or a small residual ulcer. Although having a flat scar may support classifying patients as a cCR, only surgical excision of a scar or ulcer can determine pCR status. Meanwhile, endoscopic biopsy has not been shown to be useful in assessing for residual disease in the rectal wall, especially when there is concern for an incomplete response. In a 2012 retrospective case series, endoscopic biopsies were performed before proctectomy on 39 patients with subjective downsizing of their tumors, but still incomplete clinical responses to neoadjuvant therapy.[75] This study showed that 100% of patients with a biopsy positive for cancer were found to have residual cancer on final pathology, However, only 3 of 28 "negative" biopsies were truly negative (ie, associated with a pCR) and calculated a negative predictive value of only 11% for endoscopic biopsies in this setting. A 2021 retrospective case series evaluated 161 patients who underwent flexible endoscopy to assess their response to neoadjuvant therapy[76]; 55 patients underwent endoscopic biopsy as a component of their assessment. Although 30 of these patients (54.5%) had residual tumors noted on their final operative pathology, only 7 of 30 patients (23%) had endoscopic biopsies positive for adenocarcinoma. Based on these studies, endoscopic biopsy does not accurately predict the presence of residual disease in the neoadjuvant setting. If there is any indication that a persistent tumor is present, oncologic resection is strongly recommended.

5. A watch-and-wait strategy can be offered to selected patients with a cCR in experienced centers with established protocols. Strength of recommendation: conditional, based on moderate-quality evidence.

The earliest report describing an intentional watch-and-wait strategy for patients with a cCR was published in

1998 in a retrospective case series of 118 patients with potentially resectable low rectal cancers. After receiving 6 weeks of CRT, 36 patients (30.5%) had a cCR. Thirty of these patients with a cCR (83%) did not undergo proctectomy and were free of locoregional recurrence at a median follow-up of 36 months.[77] A subsequent publication from the same group reported a 10-year OS of 97.7% and a DFS of 84% in these patients that did not differ from the 6 patients with a cCR who had undergone proctectomy.[78] During the past 20 years, several modifications have been made to the treatment and surveillance strategies related to patients with a cCR, which have helped to further shape the current organ preservation strategies available for these patients.[46,59,78]

Several retrospective studies have evaluated the safety of watch-and-wait/organ preservation (WW/OP) strategies for patients with a cCR. A 2016 prospective cohort study evaluated 100 patients with a cCR or near-cCR who underwent WW/OP for a median follow-up of 41 months.[79,80] Fifteen patients (15%) developed local regrowth (12 luminal and 3 nodal) within 25 months of completing CRT. In this study, the 3-year OS was 96.6%, distant metastasis-free survival was 96.8%, and DFS was 80.6%. A 2019 retrospective case series reported on 197 patients with cCR who underwent WW/OP after neoadjuvant therapy and found that 55 patients (28%) experienced a local regrowth at a median follow-up of 55 months.[81] Importantly, nodal status (N0 vs N1-2) was not predictive of cCR or local regrowth after a cCR, and local regrowth rates were similar across all the different baseline clinical stages. Five-year surgery-free survival (39.7% vs 46.8%; $p = 0.2$) and distant metastases–free survival (77.5% vs 80.5%; $p = 0.49$) were similar between baseline clinical node-positive and node-negative patients. A subsequent publication involving the same cohort of patients with a mean follow-up of 64 months demonstrated a 5-year LR-free survival of 69% and 5-year OS of 82%.[82]

A retrospective 2018 study identified 880 patients with cCR from the International Watch-and-Wait Database with a median follow-up of 3.3 years.[83] Although the 2-year cumulative incidence of local regrowth in this cohort of patients was 25%, 88% of all local regrowth occurred within 2 years of completing neoadjuvant therapy and 97% recurred in the bowel wall. Of those patients with local regrowth, 78% underwent subsequent TME with curative intent. Patients without local regrowth had 5-year DFS of 97% and OS of 88%, whereas patients with local regrowth had 5-year DFS of 84% and OS of 75%.

The 2022, phase II OPRA trial evaluated the outcomes of 324 patients with stage II or III rectal adenocarcinoma randomly assigned to treatment with either induction TNT or consolidation TNT.[57] Both treatment arms received LCRT and, after TNT, patients were categorized as having a cCR, a near-complete clinical response (ncCR), or an incomplete clinical response (iCR). Of the 304 patients who underwent restaging, 225 (74%) had cCR or ncCR and were offered nonoperative management with close surveillance, and the remaining 26% of patients who had an incomplete response were offered proctectomy. After a median follow-up of 3 years, 75 of 225 patients (33.3%) experienced local regrowth and were recommended to undergo TME. The 3-year TME-free survival was 41% (95% CI, 33–50) for induction TNT and 53% (95% CI, 45–62) for consolidation TNT ($p = 0.02$). There were no differences between the 2 groups in LR-free survival, 3-year DFS, distant metastasis–free survival, or OS, suggesting that both TNT strategies were safe. However, consolidation TNT was associated with higher rates of rectal preservation. For patients with a cCR or ncCR, a watch-and-wait strategy was shown to have similar DFS compared to historical outcomes from routine TME. The 5-year results of OPRA had been described previously and continue to support consolidation chemotherapy TNT and watch-and-wait in appropriate patients. It is important to note that there is no consensus definition of ncCR across experts in the field; variability in definitions exist, and LR may be higher in patients with a ncCR versus a cCR.[84] In addition, local regrowth has been shown to be a risk factor for distant recurrence in patients in watch-and-wait protocols.[85]

In a 2018 systematic review of 17 studies including 692 patients with cCR treated with a WW/OP strategy, local regrowth was seen in 153 patients (22.1%). Of the 153 recurrences, 147 (96%) occurred within 3 years of TNT. The recurrences were luminal and/or within the mesorectum in 149 patients (97%), whereas the remaining 4 were classified as "nonregrowth pelvic recurrences" (2 in the lateral pelvic lymph nodes, 1 vaginal, and 1 perineal).[86] For the 147 patients with local regrowth who were offered treatment, salvage surgery was performed in 130 patients (88%), of whom 121 (93%) had a complete (ie, R0) resection. Fifty-seven patients developed metastatic disease (8.2%), of which 35 (60%) occurred in the absence of synchronous local regrowth. The 3-year OS for patients in the WW/OP group was 93.5% (95% CI, 90.2–96.2).

6. In addition to routine surveillance for disease recurrence, patients managed using a watch-and-wait strategy should undergo surveillance to assess for local tumor regrowth. Strength of recommendation: strong, based on expert consensus.

As stated previously, 20% to 30% of patients managed with a WW/OP protocol experience local regrowth, and early detection is associated with high rates of salvage TME.[57,86] Patients with local regrowth who undergo subsequent proctectomy have R0 resection rates and long-term survival similar to patients undergoing upfront TME in published studies.[57,86] It is important to recognize that these results were achieved in the setting of rigorous follow-up in clinical trials. Although there are no studies comparing

the merits of one surveillance regimen over another for patients with a cCR undergoing WW/OP, frequent reassessments are necessary to prevent delays in diagnosis and allow for salvage surgery when appropriate.[87–91]

Systemic disease surveillance should not differ from current guidelines for colorectal cancer after surgical resection with curative intent.[92] In terms of LR, rectal and mesorectal regrowth occurs more frequently in the first 3 years after TNT, and the intensity of WW/OP surveillance is highest during this time frame.[83,86,93] Most published surveillance strategies include the same modalities used to determine a cCR, including a DRE and endoscopy every 3 to 4 months with rectal cancer protocol MRI every 6 months for the first 2 to 3 years. After that, recommendations often include DRE and endoscopy every 6 months and MRI performed annually.[57,81,94–97]

Data regarding the use of liquid biopsy using ctDNA as both a surveillance tool and as a predictor of pCR remain inconclusive. Several meta-analyses have shown that higher levels of ctDNA either at the time of cancer diagnosis or after completing neoadjuvant therapy were associated with an increased long-term risk of both locoregional and distant recurrence.[98,99] Numerous other smaller retrospective studies also suggested that detectable or higher levels of ctDNA predict worse outcomes. However, data remain inconsistent as to whether ctDNA correlates with having a pCR. A systematic review of 21 publications including 1499 patients[100] demonstrated that ctDNA could be used to predict pCR, whereas 3 other reviews suggested that it could not.[101–103] At this time, there is not enough high-level evidence to support using ctDNA to predict pathologic response.

7. Compared to laparoscopic TME (l-TME) and robotic TME (r-TME), taTME for mid and low rectal cancer has similar overall complication rates and functional outcomes. Strength of recommendation: conditional, based on moderate-quality evidence.

There were early concerns regarding intraoperative complications specific to taTME, including CO_2 embolism and urethral injury.[104] The early Norwegian taTME experience reported LR in 10 of 110 patients (9.5%), many of which were multifocal, at a median follow-up of 11 months, which led to a national moratorium on the technique in 2018.[105] There was also a recommended "pause" from the Association of Coloproctology of Great Britain and Ireland.[106] For these reasons, taTME was characterized as controversial in the 2020 CPG.[6] More recent data, including 2 RCTs, have clarified the relative incidence of these complications and compared oncologic outcomes of taTME to open TME, r-TME, and l-TME. In addition, COLOR III,[107] ETAP-GRECCAR,[108] and ROTA[109] RCTs are ongoing and are anticipated to contribute substantially to the available high-level data on this topic in the future.

The Chinese Transanal Endoscopic Surgery Collaborative Group enrolled 1089 patients in a multicenter RCT comparing l-TME to taTME.[110] Notably, in both groups, rates of preoperative chemotherapy and/or radiotherapy were low (33% l-TME vs 39% taTME) despite many patients having stage II to III cancers. There were no conversions in the taTME group, whereas 6 patients (1.1%) in the l-TME group were converted to taTME ($p = 0.03$). There were no significant differences in the rates of intraoperative complications (6.1% for l-TME and 4.8% for taTME; $p = 0.42$) or anastomotic leak (5.3% for l-TME and 7.2% for taTME; $p = 0.21$). Among the 544 patients in the taTME group, there were 2 urethral injuries (0.4%) and 2 CO_2 emboli (0.4%). A smaller multicenter RCT of 116 patients in Spain, which used a much higher overall rate of preoperative cancer therapy (67%), compared taTME to l-TME and demonstrated similar rates of complications and anastomotic leak. They reported a significantly higher conversion rate in the l-TME group compared to taTME (20% vs 2%; $p = 0.003$). Notably, 70% of conversions in the l-TME group were conversions to taTME, and 30% were conversions to open surgery. At a median follow-up of 39 months, this trial reported LR rates of 6.1% in the l-TME group and 1.8% in the taTME group ($p = 0.3$).[111] Both of the above-mentioned trials reported similar pathologic outcomes between l-TME and taTME, including status of the distal and circumferential resection margins and completeness of the mesorectal specimen.[111] None of these procedures resulted in CO_2 embolism or urethral injury.

There are no published RCTs comparing r-TME to taTME, but a large retrospective propensity score–matched cohort study from the Netherlands compared the 2 approaches and demonstrated similar complication rates (54.6% vs 43.5%; $p = 0.251$), specimen quality (96.3% vs 98.1% complete or near-complete mesorectum, standardized mean difference 0.677), and rates of conversion to open surgery (4.6% vs 1.9%; $p = 0.518$) for r-TME and taTME, respectively.[112] Anastomotic leak rates were notably high in both arms, but there was no difference between the groups (r-TME 21.6% vs taTME 17.6%; $p = 0.62$). A 2021 systematic review and meta-analysis of 37 studies compared taTME (n = 1326) to r-TME (n = 3835) and found similar pooled conversion rates (1.0% vs 1.2%; $p = 0.91$) and pathological outcomes (circumferential resection margin positivity 3.2% vs 2.7%, $p = 0.22$; intact mesorectal specimen 84.6% vs 90.1, $p = 0.23$).[113]

With regard to long-term oncologic outcomes, a large meta-analysis of 30 trials including 5845 patients compared open TME (n = 2207), l-TME (n = 3072), r-TME (n = 388), and taTME (n = 178).[114] There were no statistically significant differences in DFS or LR rates between the 4 groups, and similar findings have been observed in smaller retrospective studies.[115,116] A 2021 study of the prospective international taTME registry reported on

2803 patients with a median follow-up of 24 months and found an LR rate of 4.8% (95% CI, 3.8%–5.8%) and a DFS rate of 77% (95% CI, 75%–79%).[117] For comparison, the ACOSOG Z6051 trial had a 2-year LR rate of 4.6% and DFS rate of 79.5% for l-TME.[33] The ALaCaRT trial had a 2-year LR of 5.4% and DFS rates of 5.4% and 80% for l-TME, respectively.[118] Although these data suggest comparable oncologic outcomes for l-TME and taTME, more data will be available in the coming years and the next comprehensive update to this guideline will reflect these data as they become available.

Nonrandomized studies comparing functional outcomes of taTME to l-TME and r-TME are limited by differences in tumor and patient characteristics between study cohorts. However, with these caveats, sexual and urinary functions across the different operative approaches seem to be comparable. Data regarding low anterior resection syndrome (LARS) are inconsistent with some studies showing higher rates of LARS after taTME and others showing similar rates of major LARS between the different operative approaches.[119–121] A large prospective national observational cohort study from the Netherlands (VANTAGE trial) aims to collect more nuanced comparative data on this topic with an anticipated enrollment of 1200 subjects.[122]

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