Management of Locally Advanced Rectal Cancer: ASCO Guideline

Aaron J. Scott, MD[1]; Erin B. Kennedy, MHSc[2]; Jordan Berlin, MD[3]; Gina Brown, MBBS, MD[4]; Myriam Chalabi, MD, PhD[5]; May T. Cho, MD[6]; Mike Cusnir, MD[7]; Jennifer Dorth, MD[8]; Manju George, DVM, PhD[9]; Lisa A. Kachnic, MD[10]; Hagen F. Kennecke, MD[11]; Jonathan M. Loree, MD[12]; Van K. Morris, MD[13]; Rodrigo Oliva Perez, MD, PhD[14]; J. Joshua Smith, MD, PhD[15]; Matthew R. Strickland, MD[16]; and Sepideh Gholami, MD, MAS[17]

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

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PURPOSE To provide evidence-based guidance for clinicians who treat patients with locally advanced rectal cancer.

METHODS A systematic review of the literature published from 2013 to 2023 was conducted to identify relevant systematic reviews, phase II and III randomized controlled trials (RCTs), and observational studies where applicable.

RESULTS Twelve RCTs, two systematic reviews, and one nonrandomized study met the inclusion criteria for this systematic review. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RECOMMENDATIONS Following assessment with magnetic resonance imaging, for patients with microsatellite stable or proficient mismatch repair locally advanced rectal cancer, total neoadjuvant therapy (TNT; ie chemoradiation [CRT] and chemotherapy) should be offered as initial treatment for patients with tumors located in the lower rectum and/or patients who are at higher risk for local and/or distant metastases. Patients without higher-risk factors may discuss chemotherapy with selective CRT depending on extent of response, TNT, or neoadjuvant long-course CRT or short-course radiation. For patients who are candidates for TNT, the preferred timing for chemotherapy is after radiation, and neoadjuvant long-course CRT is preferred over short-course radiation therapy (RT), however short-course RT may also be a viable treatment option depending on circumstances. Nonoperative management may be discussed as an alternative to total mesorectal excision for patients who have a clinical complete response to neoadjuvant therapy. For patients whose tumors are microsatellite instability-high or mismatch repair deficient, immunotherapy is recommended.

Additional information is available at http://www.asco.org/gastrointestinal-cancer-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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Evidence-Based Medicine
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View Online Article

TARGET POPULATION AND AUDIENCE

Target Population

The target population for this guideline is patients with locally advanced rectal cancer and caregivers as defined in the guideline questions.

Target Audience

This guideline is intended for medical oncologists, surgical oncologists, radiation oncologists, gastrointestinal radiologists, pathologists, gastroenterologists, and other members of the multidisciplinary team who treat patients with locally advanced rectal cancer.

INTRODUCTION

Colon and rectal cancers are the fourth most common form of cancer in the United States.[1] Rectal cancer accounts for approximately one third of colorectal cancers. In 2023 in the United States, there were approximately 46,050 new cases of rectal cancer. Globally, there were 720,000 new cases of rectal cancer and 339,022 deaths in 2020.[2] Broadly defined, locally advanced rectal cancer includes patients with tumors that have grown through the muscularis propria and into the outermost layers of the rectum (T3), or through the wall of the rectum, may be attached to other organs or structures (T4), and/or are node-positive. Long-course postoperative radiation with a radiosensitizing fluoropyrimidine (chemoradiation [CRT]) was the standard of care for stage II and III patients before 2004.[3] After the publication of a key randomized trial in 2004, preoperative CRT was established over postoperative CRT as the standard of care because it resulted in better local control and reduced toxicity.[4] An alternative standard of care was preoperative short-course radiation.[5] With these treatment paradigms, distant metastases remained a concern, and therefore, postoperative (ie, adjuvant) chemotherapy was also included in the treatment sequence,[6] but adherence was low with this intervention, and overall survival (OS) was not improved.[7] More recently, total neoadjuvant therapy (TNT), which includes neoadjuvant chemotherapy and either short-course radiation or long-course CRT, has been proposed as a way to improve adherence, decrease the occurrence of distant metastases, and ultimately improve OS. TNT and other recent developments in the treatment of locally advanced rectal cancer are included in this guideline, including omission of radiation therapy (RT) in certain scenarios and a possible nonoperative strategy for patients whose tumors have a clinical complete response (cCR) to initial treatment. In addition, the guideline provides recommendations on immunotherapy for patients with tumors that are microsatellite instability-high (MSI-H) or mismatch repair–deficient (dMMR). Recommendations that incorporate the risk of recurrence for patient subpopulations and tumor location are provided.

GUIDELINE QUESTIONS

This clinical practice guideline addresses the following clinical questions:

1. For patients with locally advanced rectal cancer, what is the effect on OS, disease-free survival (DFS), adverse events (AEs), and quality of life of TNT, that is, neoadjuvant chemotherapy and CRT versus standard neoadjuvant CRT? Patient subgroups of interest include
   a. Those with characteristics identified using high-resolution magnetic resonance imaging (MRI), including distance of the invasive border of the primary tumor to the mesorectal fascia (MRF) and predicted circumferential resection (radial) margin (CRM) involvement (ie, ≤1 mm from MRF indicating potential CRM involvement),[8] extramural vascular invasion (EMVI), tumor deposits, tumor stage, and nodal stage.
   b. Location of tumor; useful and clinically relevant features for tumor location are provided by MRI, such as peritoneal reflection (ie, upper limit for extraperitoneal tumors *v* intraperitoneal tumors) and anorectal ring (ie, distal limit for tumors requiring abdominoperineal resection [APR] or ultra-low anterior resections).[9] Using these anatomical features, upper rectal cancer includes intraperitoneal tumors, mid rectal cancers include tumors above the anorectal ring, and distal (low) tumors have a lower edge of tumor at the level anorectal ring.[10]
   c. For the purpose and within the scope of this guideline, the Expert Panel noted that T3 rectal cancers have a heterogeneous prognosis; cancers in this group with an MRI-assessed extramural depth of invasion (spread beyond the muscularis propria) of ≤5 mm have a risk of local recurrence of <5%, compared to >20% for patients with tumor invasion >5 mm, and respective rates of 5-year OS ranging between >80% versus 40%.[11,12] The majority of ASCO Guideline Expert Panel members agreed that clinicians should interpret cancers with an extramural depth of invasion of ≤5 mm as lower-risk T3 disease. The Expert Panel agreed that this statement does not apply to low rectal cancer because of the higher risk of recurrence associated with this tumor location; patients with a low tumor within 5 mm of the total mesorectal excision (TME) plane (eg, bordering the intersphincteric space) or MRF should be considered higher risk. There is a need for guidance for early-stage rectal cancer, and ASCO plans to address this population in a separate clinical practice guideline.
2. For patients with lower risk locally advanced rectal cancer, is CRT or chemotherapy with FOLFOX and selective CRT recommended?
3. In the context of TNT, should chemotherapy be delivered before (induction) or after (consolidation) CRT?
4. In the neoadjuvant setting, is short-course or long-course radiation recommended for patients with locally advanced rectal cancer?
5. Is nonoperative management (NOM) recommended for patients who have a cCR following initial therapy?

6. For MSI-high or dMMR rectal cancers, is immunotherapy recommended as an initial approach, compared to TNT or another treatment strategy?

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only). The panel met by teleconference, and members were asked to provide ongoing input on the quality and assessment of the evidence and generation of recommendations, draft content, and review and approve drafts during the entire development of the guideline. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the guideline before review and approval by the ASCO Evidence-Based Medicine Committee (EBMC). All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review of evidence identified through online searches of PubMed from January 2013 to October 2023 and of phase II or III randomized controlled trials (RCTs) and systematic reviews. For clinical question six, prospective nonrandomized studies published since January 2022 were eligible. Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. Ratings for type and strength of the recommendation and evidence quality are provided with each recommendation. The quality of evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[13,14] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel (refer to Appendix Table A2).

Data Analysis

Hazard ratios (HRs) were extracted where available for time-to-event data; for other dichotomous outcomes, relative risk (RR) or odds ratios (ORs) were extracted where available or calculated using reported events and population totals in the treatment and control groups, using Review Manager 5.3 (RevMan 5.3). Where more than one study was available, data were pooled in meta-analyses using a random-effects model and the generic inverse variance function in RevMan 5.3. Where HRs were combined in a meta-analysis, log of the HR and its standard error were calculated and entered in RevMan 5.3. Meta-analyses were not based on individual patient data; forest plots can be found in the Data Supplement (online only). Heterogeneity was assessed using the I^2 statistic and informally categorized according to the Cochrane Handbook as low: ≤40%, moderate: 30%-60%, substantial: 50%-90%, or considerable: 75%-100%.[13]

Guideline Review and Approval

Draft recommendations were released to the public for open comment from January 17 through January 31, 2024. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with written comments received. The five respondents who completed the open comment survey either agreed or agreed with slight modifications to the recommendations, and two of the respondents disagreed with one of the recommendations. Two clinical experts who were external to the Expert Panel also reviewed the document and provided feedback. In addition, the ASCO Gastrointestinal Cancer Guideline Advisory group was invited to comment on a complete draft of the guideline. Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. In addition, a guideline implementability review was conducted. On the basis of this review, revisions were made to the draft to clarify recommended actions for clinical practice.

All changes were incorporated into the final manuscript before ASCO EBMC review and approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Guideline Updating

The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 1,545 studies were identified in the literature search. After applying the eligibility criteria, 17 full

publications and one abstract from 12 RCTs, and two systematic reviews were included, which formed the evidentiary basis for the guideline recommendations for patients with locally advanced rectal cancer.[5,7,15-32] One study that informed the recommendation for immunotherapy in patients with MSI-H or dMMR locally advanced rectal cancer was included.[33]

Evidence Quality Assessment

The quality of evidence for each outcome of interest, including risk of bias, consistency of results, directness of evidence, precision, publication bias, and magnitude of effect, was assessed by one reviewer and reviewed by the Expert Panel cochairs and members. Results of these quality assessments are included in Table footnotes. Refer to Appendix Table A2 for definitions for the quality of the evidence and strength of recommendations and the Methodology Manual for more information on the ASCO guideline development methodology.

RECOMMENDATIONS

All recommendations are available in Table 1 (see also Fig 1).

INITIAL ASSESSMENT

Literature Review and Clinical Interpretation

Rectal MRI staging is recommended because prospective data have shown that using high-resolution MRI to preoperatively assess the extent of extramural spread and its relationship to the predicted TME plane allows for selection of appropriate patients for neoadjuvant therapy.[40,41] An incomplete surgical resection, defined by an involved CRM, is associated with higher rates of recurrence and poor prognosis. Established prognostic factors that can be accurately assessed by high-resolution MRI include EMVI, tumor deposits (which are currently classified as N1c by TNM), and extramural depth of tumor invasion.[42-44] The presence of EMVI or extranodal tumor deposits is associated with a four-fold increased risk of distant recurrence and is also associated with local recurrence and mortality, and in one study, the combination of tumor deposits and EMVI identified on MRI were the only factors to retain a significant association with distant recurrence on a multivariate analysis, which included tumor size, lymph node status, and resection margin status.[45] Treatment decisions may be guided by the results of preoperative MRI if expertise is available to conduct and interpret high-resolution MRI, the results are discussed in a multidisciplinary setting, and quality of TME is consistently high.[8]

NEOADJUVANT THERAPY

Clinical Question 1

Are outcomes improved with combined TNT (neoadjuvant chemotherapy and CRT) versus standard neoadjuvant CRT for patients with locally advanced rectal cancer?

Clinical Question 2

For patients with lower risk locally advanced rectal cancer, is CRT or chemotherapy with neoadjuvant fluorouracil, leucovorin, and oxaliplatin (FOLFOX) and selective CRT recommended?

Literature Review and Analysis

Four phase III RCTs of TNT met the inclusion criteria for the comparison of TNT versus standard neoadjuvant CRT, including RAPIDO (N = 912),[28] POLISH II (N = 510),[21] PRODIGE-23 (N = 461),[23] and STELLAR (N = 599).[30] Three of these trials used short-course RT plus consolidation fluoropyrimidine and oxaliplatin-based chemotherapy in the intervention group, while in the PRODIGE-23 trial, preoperative treatment consisted of induction oxaliplatin, irinotecan, leucovorin, and fluorouracil (FOLFIRINOX), followed by CRT. Most patients in these trials had tumors located in the middle to lower rectum (Table 2). In a meta-analysis, pathologic complete response (pCR; OR, 1.74 [95% CI, 1.45 to 2.10]) and OS (HR, 0.78 [95% CI, 0.62 to 0.97]) but not DFS (HR, 0.86 [95% CI, 0.71 to 1.04]) were significantly improved with TNT, compared to standard CRT. The primary end point of the RAPIDO trial was disease-related treatment failure at 3 years, including distant metastases, which was significantly improved with TNT versus CRT (RR, 0.79 [95% CI, 0.63 to 1.00]; $P = .0480$; Table 3). Grade 3 to 4 treatment-related AEs were significantly higher in the TNT group, although the heterogeneity in this analysis was high, with results for the POLISH II and PRODIGE-23 trials showing no difference in this outcome. The rate of acute toxicity was higher in the CRT group versus TNT in the POLISH II study, which may be explained by the shorter duration of neoadjuvant chemotherapy delivered in the TNT arm.

In the RAPIDO trial, there was no significant difference in health-related quality of life (HRQOL), bowel function, or late toxicity in patients who did not experience a disease-related treatment failure.[26] This trial also reported that the longer-term rate of grade 3 or greater AEs was not significantly different between TNT and CRT groups at 3, 6, 12, and 36 months post-treatment, respectively, while the rate of neurotoxicity was significantly higher in the groups that received neoadjuvant or adjuvant chemotherapy, compared to the standard CRT group. Low anterior resection syndrome (LARS), which is influenced by neoadjuvant therapy and surgery, was 59% in the TNT group and 75% in the CRT group ($P = .02$, not statistically significant) among the 58.3% of patients without a stoma who responded to the LARS questionnaire.

Three studies met the inclusion criteria for the comparison of neoadjuvant chemotherapy versus neoadjuvant CRT (Table 4).[7,17,25] The PROSPECT phase II/III RCT of FOLFOX compared to CRT recruited 1,194 patients who were cT2 N1, cT3 N0 or N1, and candidates for sphincter-sparing surgery at baseline with mostly mid-to-high tumor location (85%)

TABLE 1. Summary of All Recommendations

Clinical Question	Recommendation
General Note. The following recommendations (strong or conditional) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible. Treatment recommendations for locally advanced rectal cancer are summarized in Figure 1.	
Assessment	1.1. Patients with locally advanced rectal cancer should be assessed for MSI or MMR status prior to commencement of treatment (good practice statement).
	1.2. Patients with locally advanced rectal cancer should undergo high-resolution pelvic MRI with dedicated rectal sequence prior to treatment to assess for risk factors for recurrence and to provide information for surgical planning. (good practice statement).
	1.3. The use of a standardized synoptic MRI report is recommended that includes relation of the primary tumor to the anal verge, sphincter complex, pelvic nodes, and MRF and includes assessment of EMVI, tumor deposits, and lymph nodes (good practice statement).
Are outcomes improved with combined neoadjuvant chemotherapy and radiation therapy, ie, TNT *v* standard neoadjuvant chemoradiation (CRT) for patients with microsatellite stable and/or proficient mismatch repair locally advanced rectal cancer?	2.1. TNT should be offered as initial treatment for patients with low rectum locally advanced rectal cancer and/or patients who are at higher risk for local and/or distant metastases, including patients with one or more of the following risk factors: T4, EMVI, and/or tumor deposits identified on MRI, threatened MRF, or threatened intersphincteric plane (evidence quality: moderate to high; strength of recommendation: strong).
	Qualifying statements for Recommendation 2.1: Clinical lymph node staging has limited accuracy.[34] Therefore, the Expert Panel recommends against making treatment decisions based solely on radiographic nodal assessment. While this patient population is defined by validated prognostic factors, RCT data are not available for specific prognostic subpopulations, therefore, clinicians and patients should discuss the potential benefits and risks of harm associated with various treatment options relative to patients' individual clinical and MRI prognostic features,[35] as well as their values and preferences.
For patients with lower risk locally advanced rectal cancer, is CRT or chemotherapy with FOLFOX and selective CRT recommended?	2.2. Patients with locally advanced middle or upper rectal cancer and a tumor depth of extramural invasion of >5 mm who meet the criteria for the PROSPECT phase II/III trial,[25] ie, T3 N0 to N1 candidates for sphincter-sparing surgery without a threatened MRF, may be offered neoadjuvant fluoropyrimidine and oxaliplatin–based chemotherapy. Selective addition of CRT may be offered following neoadjuvant chemotherapy to patients whose tumors decrease in area by <20% (evidence quality: moderate to high; strength of recommendation: conditional).
	Note for Recommendation 2.2: Recommendations for patients with a tumor depth of extramural invasion of ≤5 mm and no other risk factors will be addressed in an ASCO guideline on earlier-stage rectal cancer.
	Qualifying statements for Recommendation 2.2: Other options for patients with lower risk of recurrence include neoadjuvant long-course CRT or short-course radiation (RT). A discussion of the benefits and harms of neoadjuvant chemotherapy alone compared to neoadjuvant long-course CRT is included within the full text of the guideline. TNT may also be an option for some patients in this group, depending on the goals of treatment, eg, complete response and potentially NOM. Choice of treatment should be made with consideration to toxicity profile, likelihood of identifying a complete response following neoadjuvant therapy, duration of treatment, and feasibility.
In the context of TNT, should chemotherapy be delivered before (induction) or after (consolidation) radiation?	3.1. For patients who are candidates for TNT, the recommended timing for chemotherapy is after radiation (evidence quality: moderate; strength of recommendation: conditional).
	Qualifying Statements for Recommendation 3.1: In the OPRA phase II RCT, patients treated with chemotherapy after CRT had a higher rate of TME-free survival at 3 years, but no difference in disease-free survival compared to patients treated with chemotherapy before CRT.[20] TNT with triplet chemotherapy before CRT may be discussed for patients at greater risk of distant metastases. Consideration of the higher rates of adverse events that may occur with triplet *v* doublet chemotherapy should be made for patients with comorbidities or older age, eg, in the PRODIGE 23 trial, eligibility to the trial was limited to patients under 76 years of age to improve the safety of FOLFIRINOX chemotherapy.[23] Delivery of chemotherapy prior to CRT is an additional recommended option for TNT candidates, particularly in settings where the initiation of radiation therapy may be slower than the initiation of chemotherapy.
In the neoadjuvant setting, is short-course radiation or long-course chemoradiation recommended for patients with locally advanced rectal cancer?	4.1. If radiation is included in the treatment plan, neoadjuvant long-course CRT is preferred over short-course RT for patients with locally advanced rectal cancer (evidence quality: moderate; strength of recommendation: conditional).
	Note for Recommendation 4.1: This recommendation is based on longer-term results of the RAPIDO phase III RCT showing a significantly higher rate of 5-year locoregional failure with TNT with short-course RT (10%), compared to standard CRT (6%), while the reduction in the rate of disease-related treatment failure and distant metastases with TNT compared to CRT was maintained at 5 years post-treatment.[27]
	Qualifying statements for Recommendation 4.1: Short-course RT may also be a viable treatment option. The choice of long-course CRT or short-course RT is patient circumstance–driven, and long-course CRT may be more appropriate for patients with higher-risk features similar to those required for inclusion in the RAPIDO trial or for patients considering a goal of NOM. Research on duration of RT is currently ongoing, including the CAO/ARO/AIO-18.1 phase III trial, in which intermediate- and high-risk patients with locally advanced rectal cancer are randomly assigned to short-course RT as in the RAPIDO trial or long-course CRT, both followed by chemotherapy and surgery or NOM for patients with a cCR.[36]

(continued on following page)

TABLE 1. Summary of All Recommendations (continued)

Clinical Question	Recommendation
Is NOM recommended for patients who have a clinical complete response following initial therapy?	5.1. NOM may be discussed as an alternative to TME for patients who have a cCR following neoadjuvant therapy (Evidence quality: Moderate; Strength of recommendation: Conditional).
	Note for Recommendation 5.1: Studies of NOM in this review included patients who underwent neoadjuvant therapy that included radiation; no studies of NOM after neoadjuvant chemotherapy alone were included in this review.
	Qualifying statements for Recommendation 5.1: Decision making should include a discussion of the potential for improved functional outcomes, surgical risk, surveillance requirements, and reduced risk of a permanent ostomy if NOM is offered. A preference for this approach may be greater among those patients who require an APR or a coloanal anastomosis. The benefits of organ preservation among those with distal tumors include avoiding a TME with ultra-low anastomosis, and a location that is more amenable to close surveillance for regrowth, compared to more proximal tumors. In the OPRA trial, the surveillance protocol included DRE and flexible sigmoidoscopy every 4 months for the first 2 years from the time of assessment of response, continuing every 6 months for the following 3 years. Rectal MRI was to be performed every 6 months for the first 2 years and yearly for the following 3 years.[20] Guidance on the imaging component of response assessment and in follow-up of NOM is beyond the scope of this guideline. First assessment of complete response for the purpose of determining eligibility for NOM should be made at 8 ± 4 weeks following the completion of any TNT regimen A definition of cCR is provided. Note that this definition has been slightly modified from the original to indicate that when using cCR to inform eligibility for NOM, there should be no ulcer present (p.808)[37]: DRE and rectoscopy: No palpable tumor material present, no residual tumor material, and no erythematous ulcer or scar. MRI: substantial downsizing with no observable residual tumor material, or residual fibrosis only (with limited signal on diffusion-weighted imaging), sometimes associated with residual wall thickening owing to edema, no suspicious lymph nodes. Endoscopic biopsy: Not mandatory or required to define cCR, biopsy should not be performed and is not recommended, especially if the DRE, rectoscopy, and MRI criteria for cCR are all fulfilled.
For MSI-High or dMMR rectal cancers, is immunotherapy recommended as an initial approach, compared to TNT or another treatment strategy?	6.1. Immunotherapy is recommended for tumors that are MSI-H or dMMR (evidence quality: low; strength of recommendation: strong).
	Qualifying statement for Recommendation 6.1: The treatment options outlined in Recommendations 2.1 to 4.1 are recommended for patients with tumors that are MSI-H or dMMR and have contraindications to immunotherapy. dMMR tumors have been shown to be sensitive to CRT.[38] Historically, fluorouracil-based chemotherapy has been less effective in patients with dMMR.[39]

NOTE. The strength of the recommendation is defined as follows, Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional/Weak: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Abbreviations: APR, abdominoperineal resection; cCR, clinical complete response; CT, computed tomography; CRT, chemoradiation; DRE, digital rectal examination; dMMR, mismatch repair–deficient; EMVI, extramural vascular invasion; FOLFIRINOX, oxaliplatin, irinotecan, leucovorin, and fluorouracil; FOLFOX, neoadjuvant fluorouracil, leucovorin, and oxaliplatin; MMR, mismatch repair; MRF, mesorectal fascia; MRI, magnetic resonance imaging; MSI, microsatellite instability; MSI-H, microsatellite instability-high; NOM, nonoperative management; RCT, randomized controlled trial; RT, radiation therapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

and excluded patients with T4 tumors, N2, tumor visible within 3 mm of the radial margin, and/or tumors requiring APR. The CONVERT phase III trial of neoadjuvant CAPOX compared to neoadjuvant CRT included 663 patients with previously untreated cT2N+ or cT3-4a locally advanced rectal cancer with uninvolved MRF. The FOWARC phase III trial of neoadjuvant FOLFOX compared to neoadjuvant fluoropyrimidine-based CRT with or without oxaliplatin included 495 patients with T3 to T4N0 or T1 to T4 N1-2; one third of included patients had MRF involvement.[17]

In the PROSPECT phase II/III RCT, patients were randomly assigned to neoadjuvant FOLFOX with selective CRT depending on tumor response or CRT alone.[25] Adjuvant chemotherapy was received by 74.8% and 77.9% of patients in the FOLFOX + selective CRT and CRT groups, respectively. DFS per-protocol, which was the primary outcome, was noninferior for FOLFOX plus selective CRT compared to CRT (HR, 0.92 [90.2% CI, 0.74 to 1.14]). In the FOLFOX group, 9.1% received selective CRT, because of either insufficient response (6.5%) or failure to complete chemotherapy. Rates of local recurrence at 5 years were <2% and not significantly different between treatment and control groups. Likewise, pCR rate (21.4%, FOLFOX group *v* 24%, CRT group) did not differ significantly. In the FOLFOX group, the most frequent grade 3 or higher toxic effects of neoadjuvant therapy were neutropenia, pain, and hypertension, reported by 20.3%, 3.1%, and 2.9% of patients, respectively. In the CRT group, the most frequent grade 3 or higher toxic effects were lymphopenia, diarrhea, and hypertension, in 8.3%, 6.4%, and 1.7% of the patients, respectively. Neuropathy during neoadjuvant treatment was more often reported by clinicians

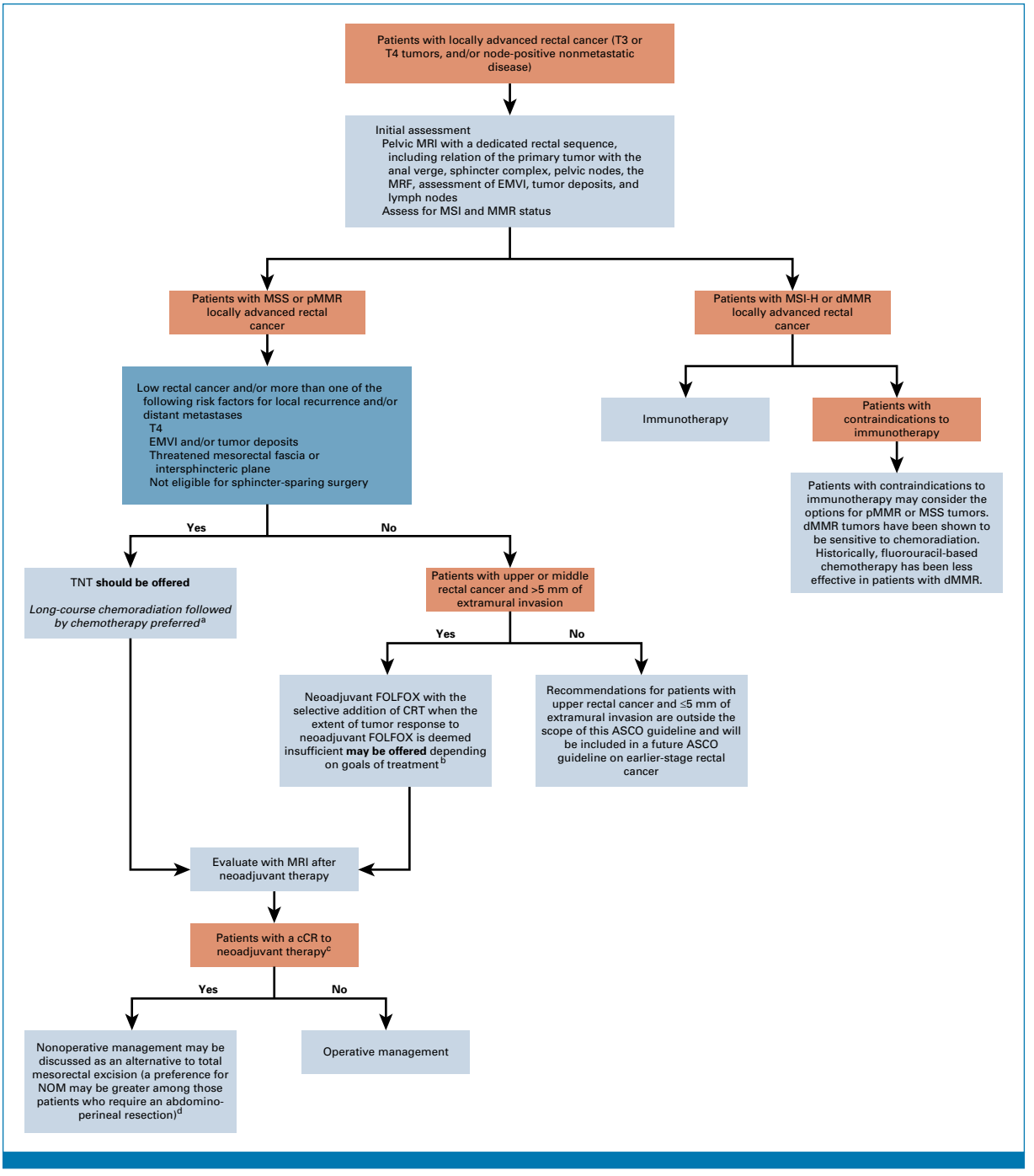

FIG 1. Treatment of locally advanced rectal cancer. [a]TNT with chemotherapy *before* RT is an additional recommended option. [b]Additional options for patients with lower risk of recurrence, depending on patient circumstances, include neoadjuvant short- or long-course radiation therapy (the latter with radiosensitizing chemotherapy), or TNT. [c]Definition of cCR: DRE and rectoscopy: no palpable tumor material present, no residual tumor material, and no erythematous ulcer or scar; and MRI: substantial downsizing with no observable residual tumor material, or residual fibrosis only (with limited signal on diffusion weighted imaging), sometimes associated with residual wall thickening owing to oedema, no suspicious lymph nodes. Endoscopic biopsy: not mandatory to define cCR, biopsy should not be performed, especially if the DRE, rectoscopy, and MRI criteria for cCR are all fulfilled. (Definition adapted from the study by Fokas et al[37]). [d]On the basis of a discussion of improved functional outcomes, surgical risk, likelihood of identifying a complete response after neoadjuvant therapy, surveillance requirements, and reduced risk of a permanent ostomy if NOM is offered. cCR, clinical complete response; CRT, chemoradiation; dMMR, mismatch repair–deficient; DRE, digital rectal examination; EMVI, extramural vascular invasion; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; MMR, mismatch repair; MRF, mesorectal fascia; MRI, magnetic resonance imaging; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NOM, nonoperative management; pMMR, proficient mismatch repair; RT, radiation therapy; TNT, total neoadjuvant therapy.

TABLE 2. Study and Patient Characteristics of Included Phase III Trials of TNT

Study (location)	Treatment Arm (No. of cycles)	No.	Completed Adjuvant Chemotherapy	Primary Outcome	Tumor Distance From Anal Verge	Patient Population
PRODIGE-23 (France)[23,32]	Standard: CAPECRT → surgery → adjuvant mFOLFOX6 or cape *v* TNT: FOLFIRINOX (6 cycles) → CAPECRT → surgery → adjuvant mFOLFOX6 or cape	230 231	69 69	3-year DFS	10.1-15 cm: 13% 5.1-10 cm: 50% ≤5 cm: 37%	cT2: 1% cT3a-b: 45% ≥cT3c-d: 54% cN1/cN2: 90%
RAPIDO (Europe and United States)[26-28]	Standard: CAPECRT → surgery → with or without FOLFOX4 (12 cycles) or CAPOX (8 cycles) *v* TNT: SCRT (5 × 5 Gy) → FOLFOX4 (9 cycles) or CAPOX (6 cycles) → surgery	450 462	26 0	3-year DRTF	≥10 cm: 33% 5-10 cm: 37% <5 cm: 24%, unknown: 7%	High risk: cT4a or cT4b or EMVI+, cN2, MRF+ or enlarged lateral lymph nodes
POLISH II (Poland)[21,22]	Standard: 5FUCRT or FOLFOXCRT → surgery *v* TNT: SCRT → FOLFOX4 (3 cycles) → surgery	254 261	39 39	R0 resection rate	>10-15 cm: 4% 5-10 cm: 40% ≤5 cm: 56%	Primary or locally recurrent cT4 or palpable fixed cT3
STELLAR (China)[30]	Standard: CAPECRT→ NOM or surgery → CAPOX (6 cycles) (required) *v* TNT: SCRT → CAPOX (4 cycles) → NOM or surgery → CAPOX (2 cycles) (required)	297 302	58 59	3-year DFS	>10 cm: 0.3% 5.1-10 cm: 50.4% ≤5 cm: 49.2%	cT2: 2.7% cT3: 83% ≥ cT3c-d: 47% cT4: 14% MRI N stage cN1/cN2: 85% MRF involvement: 56% EMVI: 53% in the TNT group and 42% in the CRT group

Abbreviations: 5FUCRT, CRT with radiosensitizing fluoropyrimidine; CAPECRT, capecitabine long-course chemoradiation therapy; cape, capecitabine; CAPOX, capecitabine and oxaliplatin; CRM, circumferential resection margin; CRT, chemoradiation; DFS, disease-free survival; DRTF, disease-related treatment failure (first locoregional recurrence, distant metastasis, new primary tumor, or death because of treatment); EMVI, extramural vascular invasion; FOLFIRINOX, fluorouracil, leucovorin, oxaliplatin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; FU/OXCRT, fluorouracil and oxaliplatin long-course chemoradiation therapy; MRF, mesorectal fascia; MRI, magnetic resonance imaging; NOM, nonoperative management; SCRT, short-course radiation therapy; TNT, total neoadjuvant therapy.

TABLE 3. TNT Versus Neoadjuvant CRT in Patients With Locally Advanced Rectal Cancer

Outcome Timeframe	Study Results	Absolute Effect Estimates		Evidence Quality (heterogeneity)	Plain Language Summary
		Neoadjuvant CRT	TNT		
pCR after surgery	RR, 1.74 (95% CI, 1.45 to 2.10) 2,192 participants in 4 studies[21,23,28,30]	143[28] pCRs per 1,000	224 pCRs per 1,000 Difference: 95 more per 1,000 (95% CI, 58 more to 142 more)	Moderate (I^2 = 53%)[a]	TNT improves pCR compared with neoadjuvant CRT
5-year OS	HR, 0.78 (95% CI, 0.62 to 0.97) 1,972 participants in 3 studies[23,27,30]	198[27] deaths per 1,000	158 deaths per 1,000 Difference: 40 fewer per 1,000 (95% CI, 70 fewer to 5 fewer)	Moderate (I^2 = 19%)[b]	TNT improves OS, compared with neoadjuvant CRT
3-year DFS	HR, 0.86 (95% CI, 0.71 to 1.04) 976 participants in 2 studies[21,23]	310[23] recurrences or deaths per 1,000	273 recurrences or deaths per 1,000 Difference: 37 fewer per 1,000 (95% CI, 78 fewer to 10 fewer)	Moderate (I^2 = 57%)[a,c]	TNT did not significantly improve DFS, compared with neoadjuvant CRT
5-year DRTF	HR, 0.79 (95% CI, 0.63 to 1.00) 912 participants in 1 study[27]	340 DRTFs per 1,000	280 DRTFs per 1,000 Difference: 60 fewer per 1,000 (95% CI, 110 fewer to 0 fewer)	Moderate	At 5 years, TNT may improve the rate of DRTF, compared with neoadjuvant CRT
LRF (median follow-up: 5.6 years)	RR, 1.45 (95% CI, 0.97 to 2.17) 906 patients in 1 study[27]	81 failures per 1,000	117 failures per 1,000 Difference: 36 fewer per 1,000 (95% CI, 2 fewer to 95 more)	Moderate	After a median follow-up of 5.6 years in the RAPIDO trial (short-course RT), there was no significant difference in locoregional failure, but a numerically higher number of failures occurred in the TNT group, compared with the neoadjuvant CRT group
Late grade 3 to 4 complications (≥1 month after surgery)	RR, 1.43 (95% CI, 0.76 to 2.69) 515 participants in 1 study[22]	59 complications per 1,000	84 complications per 1,000 Difference: 25 fewer per 1,000 (95% CI, 14 fewer to 100 more)	High	TNT did not significantly increase or decrease the rate of late complications
Grade 3 or 4 AEs during preoperative therapy	RR, 1.56 (95% CI, 1.18 to 2.07) 2,460 participants in 4 studies[21,23,28,30]	230 events per 1,000	359 events per 1,000 Difference: 129 more per 1,000 (95% CI, 41 more to 246 more)	Moderate (I^2 = 78%)[d]	TNT increases grade 3 or 4 AEs, compared with standard neoadjuvant CRT[e]
Grade 1 to 2 neurotoxicity, 6 months	RR, 1.52 (95% CI, 1.19 to 1.95) 706 participants in 1 study[26]	220 events per 1,000	334 events per 1,000 Difference: 114 more per 1,000 (95% CI, 42 more to 209 more)	High	TNT worsens grade 1 to 2 neurotoxicity at 6 months, compared with neoadjuvant CRT. Grade 1 to 2 neurotoxicity was also significantly worse in the TNT group at 12 months

Abbreviations: AE, adverse event; CRT, chemoradiation; DFS, disease-free survival; DRTF, disease-related treatment failure (the first occurrence of locoregional failure, distant metastasis, a new primary colorectal tumor, or treatment-related death); HR, hazard ratio; LRF, locoregional failure: lack of response to neoadjuvant treatment resulting in unresectable tumor or R2 resection (early LRF), or locoregional recurrence (LR) (R0 or R1 resection followed by LR); OS, overall survival; RR, relative risk; TNT, total neoadjuvant therapy.

[a]Moderate heterogeneity.

[b]More data are needed to determine the longer-term effect on OS.

[c]There was a significant DFS benefit in the TNT arm of the PRODIGE-23 study at 3 years.

[d]Substantial heterogeneity.

[e]The RAPIDO trial included grade 5 AEs; in that trial, postoperative grade 3 to 4 AEs were experienced by 33.6% of patients in the CRT group who received adjuvant chemotherapy.

TABLE 4. Studies of Chemotherapy Versus CRT for Patients With Locally Advanced Rectal Cancer

Study (year)	Tx Arms (No. of cycles)	No.	Years of Accrual	Primary Outcome	Patient Population
PROSPECT Phase II/III (United States, Canada, Switzerland)[24,25]	mFOLFOX6 (6 cycles [12 weeks]) → selective CRT if tumor regression <20% cm^2 → TME → adjuvant chemotherapy (74.8%; median 6 cycles) *v* 50.4 Gy 3D conformal RT or IMRT in 28 fractions with sensitizing fluoropyrimidine (CRT) → TME → adjuvant chemotherapy (77.9%, median 8 cycles)	585 (PP) 543 (PP)	June 2012 to December 2018	DFS per protocol	cT2 N1 (9%), cT3N0 (38.2%), or cT3N1 (52.9%) and tumors that were amenable to sphincter-sparing surgery at baseline Location: Mid (64%), low (15%), high (21%) Excluded: T4 tumors, four or more pelvic lymph nodes with a short axis larger than 1.0 cm (N2), tumor visible within 3 mm of the radial margin, distal tumors requiring APR
CONVERT Phase III (China)[7]	CAPOX (4 cycles [12 weeks]) → CRT as in the CRT group if progression → surgery → adjuvant chemotherapy (4 cycles); for R1 or R2 resection → CRT *v* 50 Gy in 25 fractions IMRT with radiosensitizing cape to GTV (45 Gy in 25 fractions to CTV) → surgery → adjuvant chemotherapy (6 cycles); for R1 or R2 resection → CRT [nonoperative strategy permitted for candidates for APR with cCR in either study arm]	331 332	June 2014 to December 2020	3-year locoregional failure-free survival	cT2N+ or cT3-4a N any uninvolved MRF up to 12 cm from anal verge Excluded: tumors adjacent to the MRF
FOWARC Phase III (China)[17]	mFOLFOX6 (4 to 6 cycles) → TME → adjuvant mFOLFOX6 (6 to 8 cycles; RT added before or after surgery at physicians' discretion, % unknown) *v* mFOLFOX6 (5 cycles) plus concurrent RT (46.0 to 50.4 Gy) → TME → adjuvant mFOLFOX6 (7 cycles) *v* FU (5 cycles) + concurrent RT (46.0 to 50.4 Gy) → TME → adjuvant chemotherapy (7 cycles)	165 165 165	June 2010 to February 2015	3-year DFS	T3 to T4N0 or T1 to T4 N1-2 (positive node defined as 1.0 cm or larger in diameter), positive margins not excluded

Abbreviations: APR, abdominoperineal resection; cape, capecitabine; CAPOX, capecitabine and oxaliplatin; cCR, clinical complete response; CRT, chemoradiation; CTV, clinical target volume; DFS, disease-free survival; FU, fluorouracil; GTV, gross tumor volume; Gy, Gray; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; IMRT, intensity-modulated radiation therapy; MRF, mesorectal fascia; MRI, magnetic resonance imaging; R1, microscopic residual disease in the resected specimen; R2, macroscopic residual disease in the resected specific; RT, radiation therapy; PP, per-protocol (main analysis conducted in the per-protocol population); TME, total mesorectal excision; TNT, total neoadjuvant therapy; Tx; treatment.

and more severe in the FOLFOX group than in the CRT group. One year after surgery, rate of AEs in the FOLFOX group and the CRT group had converged.[24] HRQOL data were collected for 61.8% of patients, and 83.3% of patients provided responses to the National Cancer Institute's Patient-Reported Outcomes version of the Common Criteria for Adverse Events. There was no significant difference in overall HRQOL for patients with FOLFOX versus CRT, however, there was a significantly improved change from baseline in the FOLFOX group for sensation of incomplete bladder emptying and bowel function at 1-2 weeks before surgery and male and female sexual function at 12 and 24 months postsurgery, respectively.[24]

In the CONVERT trial, initial results showed no significant difference in outcomes for R0 resection rate, pCR, or grade 3 to 4 AEs between the neoadjuvant chemotherapy and neoadjuvant CRT groups.[7] In addition, the sphincter preservation rate (94.9% for chemotherapy *v* 94.3% for CRT) and postoperative complications did not differ significantly (18.8% *v* 25.7% for chemotherapy *v* CRT). Results for the primary outcome, local-regional failure-free survival, are awaited. The pCR and grade 3 to 4 AE rates were consistent for PROSPECT and CONVERT with an initially higher rate of grade 3 to 4 AEs with neoadjuvant chemotherapy versus CRT (Table 5). In CONVERT, the most common grade 3 to 4 toxicities, which were leukopenia, thrombocytopenia, and anemia, did not differ between groups. cCR was recorded for two patients in the CAPOX group and five patients in the neoadjuvant CRT group in the CONVERT trial.

The FOWARC phase III trial of neoadjuvant FOLFOX compared to neoadjuvant FOLFOX + CRT included 330 patients with T3 to T4N0 or T1 to T4N1-2, and 33% of patients had MRF involvement.[17] As in the other included studies of chemotherapy versus CRT, DFS, and local recurrence were not significantly different. Unlike the results in CONVERT and PROSPECT, there was a significantly higher pCR rate in the CRT group, compared to chemotherapy (RR, 0.24 [95% CI, 0.13 to 0.45]; Data Supplement, Table S1). Longer-term follow-up is needed for assessment of OS. The full results of this study are presented in the Data Supplement.

Clinical Interpretation

Risk of locoregional recurrence is approximately 5%-9% following preoperative CRT,[28] however distant metastases occur in approximately 30% of patients,[23] and OS is not improved with the addition of RT to TME. Historically, adherence to adjuvant chemotherapy, intended to reduce the rate of distant metastases, has been low. Neoadjuvant chemotherapy was proposed to improve adherence, thus controlling micrometastases more effectively.[28] This ASCO meta-analysis showed an improvement in OS with TNT versus CRT when results from three phase III RCTs were combined, however, the POLISH II trial provided longer-term follow-up of OS and found no significant difference 8 years post-treatment.[21] A recent update of the PRODIGE-23 trial with 7-year data found that there was a statistically significant difference in OS of 4.3 months (95% CI, 0.4 to 8.4 months) favoring FOLFIRINOX + CRT versus CRT in a restricted mean survival time analysis.[32] Five-year follow-up data from RAPIDO showed no significant difference in cumulative OS. Disease-related treatment failure, the primary study outcome in RAPIDO, was improved (HR, 0.79 [95% CI, 0.63 to 1.00]), however, OS did not differ significantly (TNT: 89.1% *v* CRT: 88.9%, HR, 0.91 [95% CI, 0.70 to 1.19]).[27] Based on a significant improvement in pCR and OS rate, TNT is recommended for patients at high risk of recurrence, in order to improve both local control and reduce the risk of distant metastases. For patients with mid to upper rectal cancer and an absence of high risk factors, TNT may be considered, and neoadjuvant chemotherapy with selective CRT or neoadjuvant short-course RT or long-course CRT are also recommended treatment options, depending on patient circumstances and goals of treatment. Chemotherapy alone may be offered for these lower-risk patients to avoid the longer-term toxicity associated with RT, although there are no data showing that neoadjuvant chemotherapy is superior to standard TME and adjuvant chemotherapy. In the study that included patients with an involved MRF, pCR was significantly more likely for the group treated with CRT, versus chemotherapy. CRM positivity may be one factor used to guide selection of patients for RT.[47] RT may also be appropriate for patients who have not responded to chemotherapy, have threatened margins after chemotherapy, and/or have metastatic lateral lymph nodes.[17] Other considerations include the toxicity profile of chemotherapy alone versus CRT, duration of treatment, availability of RT, and goals of treatment. The toxicity profile of chemotherapy alone versus CRT is discussed further subsequently.

In the PROSPECT trial, rates of DFS, OS, and local recurrence were similar in the treatment and control groups, thus AEs and quality of life become increasingly important factors that may affect choice of treatment.[24,25] Severe AEs during neoadjuvant treatment, including anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, fatigue, mucositis, nausea, neuropathy, and vomiting, were significantly more frequent with FOLFOX versus CRT with radiosensitizing fluoropyrimidine (5FUCRT), while severe diarrhea was significantly more common with 5FUCRT versus FOLFOX. Among the 47% of participants who answered patient-reported outcomes questionnaires at 12 months postsurgery, severe neuropathy was significantly higher in the 5FUCRT group than the FOLFOX group (8% *v* 3%), compared to 5% versus 19% presurgery and 3% versus 5% at 18 months postsurgery, respectively. Neuropathy postsurgery may have been impacted by the administration of adjuvant oxaliplatin-containing chemotherapy to 78% (median eight cycles) and 75% (median six cycles) of patients in the 5FUCRT and FOLFOX groups, respectively. Data reported previously suggest that the rate of long-term grade 3 to 4 neuropathy following oxaliplatin-containing chemotherapy is approximately 9% after a median of 4.2 years of follow-up.[48] There were no other significant differences between groups in AEs at 12 months

TABLE 5. Neoadjuvant FOLFOX With Selective Use of CRT Versus Neoadjuvant CRT (uninvolved margins)[7,25]

Outcome Timeframe	Study Results	Absolute Effect Estimates		Evidence Quality (heterogeneity)	Plain Language Summary
		Neoadjuvant CRT	Neoadjuvant FOLFOX or CAPOX		
DFS (primary outcome) 5-year	HR, 0.92 (90.2% CI, 0.74 to 1.14) 1,128 participants in 1 study[25]	214 recurrences or deaths per 1,000	199 recurrences or deaths per 1,000	Moderate[a]	Neoadjuvant chemotherapy with selective CRT has little or no effect on DFS, compared with neoadjuvant CRT
		Difference: 15 fewer per 1,000 (90.2% CI, 51 fewer to 26 more)			
5-year OS	HR, 1.04 (95% CI, 0.74 to 1.44) 1,128 participants in 1 study[25]	98 deaths per 1,000	105 deaths per 1,000	Moderate[a]	Neoadjuvant chemotherapy with selective CRT has little or no effect on OS, compared with neoadjuvant CRT
		Difference: 4 more per 1,000 (95% CI, 25 fewer to 40 more)			
pCR	RR, 0.88 (95% CI, 0.72 to 1.07) 1,572 participants in 2 studies[7,25]	243 responses per 1,000	214 responses per 1,000	Moderate[a] (I^2 = 0%)	Neoadjuvant chemotherapy with selective CRT has little or no effect on pCR, compared with neoadjuvant CRT
		Difference: 29 fewer per 1,000 (95% CI, 68 fewer to 17 more)			
5-year local recurrence	HR, 1.18 (95% CI, 0.44 to 3.16) 1,128 participants in 1 study[25]	16 recurrences per 1,000	18 recurrences per 1,000	Moderate	Neoadjuvant chemotherapy with selective CRT has little or no effect on local recurrence, compared with neoadjuvant CRT
		Difference: 3 fewer per 1,000 (95% CI, 9 fewer to 34 more)			
Grade ≥3 (severe) AEs during neoadjuvant therapy	RR, 1.75 (95% CI, 1.48 to 2.08) 1,717 participants in 2 studies[7,25]	178 events per 1,000	312 events per 1,000	Moderate[b] (I^2 = 0%)	Acute grade 3 or greater AEs were more common in the chemotherapy group *v* CRT[c]
		Difference: 134 more per 1,000 (95% CI, 85 more to 192 more)			
Male sexual function in the past 30 days 12 months postsurgery	Measured by International Index of Erectile Function Scale: 0-75 Higher score better 186 participants in 1 study[24]	27.65 (mean at 12 months)	38.63 (mean at 12 months)	Moderate	Males in both groups had a significant reduction in sexual function in the past 30 days at 12 months postsurgery compared with baseline. The reduction in the CRT group was on average 10.44 points more than the FOLFOX group
		Mean change from baseline: 10.44 lower in the CRT group (95% CI, 4.44 lower to 16.43 lower)			
Female sexual function in the past 30 days 12 months postsurgery	Measured by Female Sexual Function Index Scale: 0-36 Higher score better 94 participants in 1 study[24]	11.97 (mean at 12 months)	17.10 (mean at 12 months)	Moderate	On average, female patients in the CRT group had a 7.54 point greater reduction in sexual functioning at 12 months after surgery than female patients in the FOLFOX group, compared with baseline
		Mean change from baseline: 7.54 lower in the CRT group (95% CI, 2.74 lower to 12.34 lower)			
HRQOL 12 months postsurgery	Measured by: EuroQoL EQ-5D-5L Index Scale 0 (death)-1 (best health state), MID = 0.07 280 patients in 1 study [24]	0.83 (mean)	0.84 (mean)	Moderate	In the PROSPECT trial, there was no significant difference in overall HRQOL at 12 months postsurgery for patients who received FOLFOX *v* CRT[46]
		Difference: 0.01 higher (MD) (95% CI, 0.02 lower to 0.05 higher)			

Abbreviations: AE, adverse event; CAPOX, capecitabine and oxaliplatin; CRT, chemoradiation; DFS, disease-free survival; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; HR, hazard ratio; HRQOL, health-related quality of life; MID, minimally important difference; nCRT, neoadjuvant chemoradiation; nCT, neoadjuvant chemotherapy; OS, overall survival; pCR, pathologic complete response; RR, relative risk.

[a]Unblinded, per-protocol analysis.

[b]Treatment duration in the FOLFOX group of the PROSPECT trial was at least 12 weeks versus 5.5 weeks for the CRT group.

[c]Patient-reported rates of severe anxiety, appetite loss, constipation, depression, dysphagia, dyspnea, fatigue, mucositis, nausea, neuropathy, and vomiting during treatment were significantly higher in the FOLFOX group versus the CRT group. The patient-reported rate of severe diarrhea was significantly higher in the CRT group versus the FOLFOX group during treatment.

postsurgery. At 18 months, patients in the CRT arm reported higher rates of mild to moderate fatigue and/or neuropathy.

Approximately 25% of per-protocol patients reported on bladder function, bowel function, sexual function, and overall HRQOL at baseline. In the subset who reported on mean change from baseline, male and female sexual function was significantly worse for patients with 5FUCRT versus FOLFOX at 12 months ($P < .01$); by 24 months postsurgery, the mean change from baseline was converging in two groups, although still significantly different ($P < .05$). HRQOL did not differ between groups at any time point. Younger women with locally advanced rectal cancer who meet the PROSPECT trial inclusion criteria and who have concerns about fertility preservation may be more likely to opt for chemotherapy alone and omission of RT from neoadjuvant treatment. Surgical outcomes are also important to patients, including the occurrence of permanent ostomies.[49] In the CONVERT trial, the rate of preventive ileostomy was 52.2% with neoadjuvant fluoropyrimidine chemotherapy versus 63.6% in the neoadjuvant CRT group ($P = .008$); the rate of sphincter preservation was similar (94.9% *v* 94.3%, respectively), and the rate of post-operative complications including anastomotic leakage and abscess was 18.8% (CAPOX) versus 25.7% (CRT; $P = .05$).[7] In the PROSPECT trial, ostomies were reportedly temporary, and a full publication on surgical outcomes for patients in that trial is forthcoming.[50]

These differences in timing and profile of AEs and patient-reported outcomes with FOLFOX versus CRT can ultimately be used to guide choice of treatment for this specific patient population and assist with discriminating between two treatment options that have similar oncologic results.

TIMING OF CHEMOTHERAPY

Clinical Question 3

In the context of TNT, should chemotherapy be delivered before (induction) or after (consolidation) radiation?

Literature Review and Analysis

Studies included in the analysis of timing of chemotherapy within TNT were the 306-person CAO/ARO/AIO-12 phase II RCT and the 324-person OPRA phase II RCT (Table 6). In the CAO/ARO/AIO-12 RCT, both the induction chemotherapy and consolidation chemotherapy groups were compared to an expected pCR rate of 15% with standard conventional CRT.[15,16] A pCR in the intention-to-treat (ITT) population was achieved in 17% of patients in the group that was treated with three cycles of FOLFOX followed by CRT ($P = .210$), and a pCR of 25% was achieved in the group that was treated with three cycles of FOLFOX following CRT ($P < .001$), thus the results for the consolidation group, but not the induction group fulfilled the predefined statistical hypothesis (Table 7). In the induction group, the median interval between completion of CRT and surgery was 45 days, whereas in the consolidation group, this interval was 90 days. There was lower adherence to chemotherapy when it followed CRT, compared to when it was delivered prior to CRT.

The OPRA trial compared induction chemotherapy followed by CRT versus CRT followed by consolidation chemotherapy, followed by selective watchful waiting or TME in both study arms.[20] DFS in both arms was 76%, which did not differ significantly from the 75% observed in historical controls treated with CRT, TME, and adjuvant chemotherapy,[51] therefore, the primary end point for this study, an improvement in DFS, was not met. OS data require additional follow-up. Grade 3 or greater AEs were not significantly different across groups. A secondary outcome, organ preservation (TME-free survival) in the ITT population at 3 years, was 51.3% in the consolidation group, compared to 41.5% in the induction group (RR, 1.31 [95% CI, 1.03 to 1.67]; Table 8).

Clinical Interpretation

In the OPRA trial, there was no difference in DFS between patients treated with TNT with either induction or consolidation chemotherapy and a selective NOM protocol compared to historical controls treated with CRT and TME. The enhanced tumor control with consolidation chemotherapy might be preferred for patients for whom enhanced local control is a goal, such as patients with cT4 or MRF-involved tumors. Induction chemotherapy is also a recommended option and may theoretically be preferred for patients who prioritize earlier control of micrometastases, such as those with EMVI or lymph node–positive disease, although data are not available for these subgroups.[15]

DURATION OF RT

Clinical Question 4

In the neoadjuvant setting, is short-course or long-course radiation recommended for patients with locally advanced rectal cancer?

Literature Review and Analysis

Four studies met the inclusion criteria for the comparison of short-term RT (5×5 Gy) versus long-course CRT. A systematic review and meta-analysis were used as a source of data for three studies,[29] and data were extracted directly from one study.[5] These studies accrued patients in a relatively earlier timeframe, compared to other studies that inform this guideline; the most recent was the Lithuanian trial, which accrued patients between 2007 and 2013 (Data Supplement, Table S2). In a meta-analysis of these four studies (Data Supplement, Fig S7), the RR of local recurrence was not significantly different between groups (RR, 0.73

TABLE 6. Studies of Consolidation Chemotherapy Versus Induction Chemotherapy in the Context of TNT

Study (author)	Treatment Arm (No. of cycles)	No.	Primary Outcome	Stage and Location
CAO/ARO/AIO-12 Phase II[15,16] (Germany)	Induction: FOLFOX (3 cycles) → FU + oxaliplatin CRT → surgery *v* Consolidation: 5FU + oxaliplatin CRT → FOLFOX (3 cycles) → surgery	156 150	pCR (compared with an established 15% rate with conventional CRT)	cT3 tumor <6 cm from the anal verge, cT3 tumor in the middle third of the rectum (6 to 12 cm) with extramural tumor spread into the mesorectal fat of more than 5 mm (cT3b), cT4 tumors, or lymph node involvement
OPRA Phase II[20] (United States)	Induction: mFOLFOX6 (8 cycles) or CAPEOX4 (5 cycles) → cape or FU CRT → TME or NOM watchful waiting *v* Consolidation: cape or FU CRT → mFOLFOX6 (8 cycles) or CAPEOX4 (5 cycles) → TME or NOM	158 166	DFS compared with historical controls	Eligibility: T3-4N0 Any T, N1-2 77% cT3 10% cT1-2 12.3% cT4 Most low rectal cancer

Abbreviations: Cape, capecitabine; CRT, chemoradiation; DFS, disease-free survival; fluoro + oxali, fluoropyrimidine + oxaliplatin; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FU, fluorouracil; mFOLFOX6, modified fluorouracil, leucovorin, and oxaliplatin; NOM, nonoperative management; pCR, pathologic complete response; TME, total mesorectal excision.

[95% CI, 0.48 to 1.11]). Additional relevant data are the 5-year locoregional recurrence rate (LRR) and locoregional failure rate (LRF) from the RAPIDO trial of short-course RT followed by chemotherapy compared to standard CRT with optional adjuvant chemotherapy. These LRR and LRF rates were 12% versus 8% ($P = .07$) and 10% versus 6% ($P = .027$) in the TNT and CRT groups, respectively. This compares to a 5-year LRR of 4.7% in the TNT arm of the PRODIGE-23 trial, in which patients were treated with FOLFIRINOX followed by CRT.[52]

Clinical Interpretation

The goal of RT is to reduce the risk of local recurrence. In addition, tumor downstaging provides a greater potential for sphincter preservation.[53] Previous analysis has shown that CRT rather than RT is associated with better efficacy in terms of reducing risk of local failure for patients with involved margins.[54] This analysis of four RCTs of short-course RT versus long-course CRT showed that there was no significant difference in local recurrence between the two, although

TABLE 7. CRT Followed by Chemotherapy (CRT → Chemotherapy) Versus Chemotherapy Followed by CRT (Chemotherapy → CRT) for Patients With Locally Advanced Rectal Cancer (CAO/ARO/AIO-12)[15,16]

Outcome Timeframe	Study Results	Absolute Effect Estimates: Chemotherapy (induction) → CRT	Absolute Effect Estimates: CRT→ Chemotherapy (consolidation)	Evidence Quality	Plain Language Summary
pCR[15]	OR, 1.62 (95% CI, 0.93 to 2.82) 284 participants in 1 study	170 responses per 1,000	257 responses per 1,000 Difference: 87 more per 1,000 (95% CI, 6 fewer to 210 more)	Moderate[a]	Chemotherapy after CRT may improve pCR, compared with chemotherapy before CRT
Sphincter-preserving surgery[15]	OR, 1.27 (95% CI, 0.76 to 2.11) 284 participants in 1 study	676 preserved per 1,000	726 preserved per 1,000 Difference: 50 more per 1,000 (95% CI, 63 fewer to 139 more)	Moderate[a]	There was a nonsignificantly higher rate of sphincter preservation with chemotherapy after CRT, compared with chemotherapy before CRT
Chemotherapy-related grade 3 to 4 AEs[15]	OR, 0.98 (95% CI, 0.56 to 1.70) 296 participants in 1 study	218 events per 1,000	215 events per 1,000 Difference: 3 fewer per 1,000 (95% CI, 83 fewer to 104 more)	Moderate[a]	Chemotherapy-related grade 3 to 4 AEs did not differ significantly between groups
Chronic grade 3 to 4 AEs[16] at 3 years	OR, 1.03 (95% CI, 0.38 to 2.79) 151 participants in 1 study	118 events per 1,000	121 events per 1,000 Difference: 3 more per 1,000 (95% CI, 70 fewer to 154 more)	Low[a,b]	Chronic grade 3 to 4 AEs did not differ significantly between groups after 3 years
DFS[16] 3-year	HR, 0.95 (95% CI, 0.63 to 1.45) 306 participants in 1 study	270 deaths or evidence of cancer per 1,000	258 deaths or evidence of cancer per 1,000 Difference: 12 fewer per 1,000 (95% CI, 90 fewer to 96 more)	Moderate[a]	There is no significant difference in DFS between groups

Abbreviations: AE, adverse event; CRT, chemoradiation; DFS, disease-free survival; HR, hazard ratio; OR, odds ratio; OS, overall survival; pCR, pathologic complete response.
[a]Unblinded.
[b]Fewer included patients.

TABLE 8. Neoadjuvant CRT → Chemotherapy Versus Neoadjuvant Chemotherapy → CRT + Selective NOM or TME in Patients With Stage II and III Rectal Adenocarcinoma (OPRA)[20]

Outcome Timeframe	Study Results	Absolute Effect Estimates: Chemotherapy → CRT (induction) + TME or NOM	Absolute Effect Estimates: CRT → Chemotherapy (consolidation) + TME or NOM	Evidence Quality	Plain Language Summary
DFS (primary end point) 3-year	RR, 1.03 (95% CI, 0.69 to 1.53) 324 participants in 1 study	228 deaths or recurrences per 1,000	235 deaths or recurrences per 1,000	Moderate[a]	DFS in both arms combined was not different from 75% observed in historical controls[51]
		Difference: 7 fewer per 1,000 (95% CI, 71 fewer to 121 more)			
cCR or nCR (offered NOM)	RR, 1.06 (95% CI, 0.92 to 1.21) 304 participants in 1 study	719 responses per 1,000	762 responses per 1,000	Moderate[a]	Rate of clinical complete or near-complete response did not differ significantly by timing of chemotherapy
		Difference: 43 more per 1,000 (95% CI, 58 fewer to 151 more)			
TME-free survival 3-year	RR, 1.31 (95% CI, 1.03 to 1.67) 324 participants in 1 study	399 TME-free per 1,000	523 TME-free per 1,000	Moderate[a]	Chemotherapy after CRT may improve TME-free survival, compared with chemotherapy before CRT
		Difference: 124 more per 1,000 (95% CI, 8 more to 251 more)			
Regrowth and TME recommended after NOM	RR, 0.69 (95% CI, 0.47 to 1.00) 225 participants in 1 study	400 salvage TME per 1,000	276 salvage TME per 1,000	Moderate[a]	After NOM, the rate of regrowth and recommended TME was higher in the group that had chemotherapy before CRT, compared with chemotherapy after CRT
		Difference: 124 more per 1,000 (95% CI, 212 more to 0 more)			
Grade ≥3 AEs	RR, 0.85 (95% CI, 0.64 to 1.12) 324 participants in 1 study	405 events per 1,000	344 events per 1,000	Moderate[a]	There was no significant difference in rate of grade 3 or greater AEs by timing of chemotherapy
		Difference: 61 fewer per 1,000 (95% CI, 142 fewer to 49 more)			

Abbreviations: AEs, adverse events; CT, chemotherapy; CRT, chemoradiation; DFS, disease-free survival; NOM, nonoperative management; OS, overall survival; OR, odds ratio; pCR, pathologic complete response; RR, relative risk; TME, total mesorectal excision.
[a]Unblinded.

the analysis included an outlier study.[19] A meta-analysis found that these results were consistent for patients with low rectal cancer and for patients with a delay or no delay before surgery.[29] In contrast, a different review reported that long-course CRT resulted in a better pCR than short-course RT, attributing this to the longer time period between radiation and surgery with long-course CRT.[53] The recently updated results from the RAPIDO trial, indicating a higher rate of local recurrence and local failure with short-course RT in the TNT arm, while maintaining the TNT benefit with respect to distant metastases and overall disease-related treatment failure, indicate that further refinement to appropriate delivery of TNT is needed.[27] Based on these findings, the Expert Panel recommends long-course CRT and awaits the results of trials such as CAO/ARO/AIO-18, which will provide further definitive data to inform this recommendation.

NONOPERATIVE MANAGEMENT

Clinical Question 5

Is NOM recommended for patients who have a cCR following initial therapy?

Literature Review and Analysis

A systematic review of 23 nonrandomized studies reported a rate of 2-year local regrowth, defined as clinical, endoscopic, or radiologic evidence of endoluminal tumor, of 15.7% (95% CI, 11.6 to 20.1) with an NOM protocol.[31] Salvage therapy was received by 95.4% (95% CI, 89.6 to 99.3) of patients with regrowth. There were no significant differences in DFS or OS in the two studies that reported these outcomes for patients who had a complete response and underwent NOM versus surgery. There are currently no randomized studies available to inform this recommendation. The OPRA phase II trial described previously compared two groups of patients randomly assigned to TNT with chemotherapy either before or after CRT, plus selective NOM or TME to historical controls treated with CRT + TME and adjuvant chemotherapy. As noted, there was no significant difference in DFS between either of the two randomized groups compared to the historical control group. TME-free survival at 3 years was 41% in the group that received chemotherapy before CRT and 53% in the group that received chemotherapy after CRT.

A limited number of RCTs in this review included patients who underwent NOM, either as part of the study protocol or because patients with cCR opted for NOM outside of the study protocol. Although determining the rate of cCR was not a primary objective of these studies, these rates and pCR from the RCTs that allowed NOM per study protocol are included in Table 9. In the OPRA trial of TNT, the combined rates of cCR and near-complete response (nCR) were 71% and 76% in the induction and consolidation chemotherapy groups, respectively. For patients who did not experience a complete or nCR in the OPRA trial, the median time from the day of restaging to the day of TME was 7 weeks (IQR, 3 to 9.5) in patients who were recommended TME at restaging and 30 weeks (IQR, 20 to 103) in patients who were recommended TME following regrowth. In addition, the cCR rates were generally much lower than the pCR rates in the RCTs, indicating the difficulties with detecting a preoperative response to neoadjuvant therapy. In the Accord 12/PRODIGE 2 trial of neoadjuvant CRT, the overall cCR rate was 8% of 201 patients with locally advanced rectal cancer, with rates being higher for T2 tumors (28%), and tumors <4 cm in diameter (14%).[55] In the RAPIDO RCT, where NOM was considered a protocol violation, of 14 patients with cCR in the TNT group who underwent NOM, two patients experienced distant metastases and one experienced local regrowth; of 11 with cCR in the CRT group, one developed distant metastases, one experienced local regrowth, and one experienced both local and distant regrowth.

Clinical Interpretation

Approximately 18%-26% of patients have a pCR following neoadjuvant CRT when the surgical specimen is examined (ie, no residual tumor cells).[56] There is increasing interest in organ preservation because this strategy is associated with better bowel function than therapy with neoadjuvant CRT and surgery.[26,57] However, as pCR and cCR are not always concordant, it is difficult to identify complete responders preoperatively.[31] A definition of cCR is provided following

TABLE 9. Rates of cCR and pCR in Included Randomized Controlled Trials With Patients Who Underwent NOM After Neoadjuvant Therapy

Study	Nonoperative Management	cCR	pCR
STELLAR[30]	NOM protocol allowed for patients with cCR who requested organ preservation or refused surgery	TNT: 11.1% CRT: 4.4%	pCR + sustained cCR: TNT: 21.8% CRT: 12.3%
CONVERT[7]	NOM strategy allowed for candidates for abdominoperineal resection and with cCR	Chemotherapy: 0.6% CRT: 1.5%	Chemotherapy: 11% CRT: 13.8%
OPRA[20]	NOM allowed for patients with cCR or nCR	cCR or nCR TNT (INCT): 71% TNT (CCRT): 76%	pCR + sustained cCR or nCR: TNT (INCT): 75% TNT (CCRT): 78%

Abbreviations: cCR, clinical complete response; CCRT; consolidation chemotherapy; CRT, chemoradiation; INCT, induction chemotherapy; nCR, near-complete response; NOM, nonoperative management; pCR, pathologic complete response; TNT, total neoadjuvant therapy.

Recommendation 5.1.[37] It is important to provide a robust definition of cCR because preliminary research has shown an association between local regrowth and distant metastases with NOM.[58] The OPRA trial investigators included clinical complete and near complete responses in their criteria, which resulted in a higher proportion of patients being eligible for a nonoperative approach, compared to offering NOM based on cCR alone. Sustained clinical response relative to previous evaluation was a requirement for remaining on the NOM protocol. Ultimately, there was no difference in 3-year DFS for these patients compared to historical controls treated with CRT, TME, and adjuvant chemotherapy. Also, those who were managed for local regrowth with TME showed no difference in DFS when compared with patients managed by TME following neoadjuvant therapy.[20,59] The surveillance protocol included digital rectal examination and flexible sigmoidoscopy every 4 months for the first 2 years from the time of assessment of response, continuing every 6 months for the following 3 years, in addition to MRI every 6 months for the first 2 years, and yearly for the following 3 years. The Expert Panel agreed that at this time, the available data are not sufficient to support a recommendation for NOM in patients with nCR.

MSI-HIGH AND/OR DMMR LOCALLY ADVANCED RECTAL CANCERS

Clinical Question 6

For MSI-high or dMMR rectal cancers, is immunotherapy recommended as an initial approach, compared to TNT or another treatment strategy?

Literature Review and Clinical Interpretation

dMMR occurs in approximately 5%-10% of rectal cancers.[38,60] The key evidence for this recommendation is the phase II prospective study of dostarlimab in patients with stage II or III dMMR rectal cancer. A cCR was demonstrated in the 12 patients who completed treatment and were followed for 6 months, and these patients experienced no grade 3 or greater AEs.[33] These results are supported by findings in other disease sites, such as colon cancer, in which a pCR to immunotherapy with ipilimumab and nivolumab was observed in 12 out of 20 dMMR patients.[61] On this basis, immunotherapy is recommended for patients with MSI-H or dMMR locally advanced rectal cancer. Where immunotherapy is contraindicated, patients may be offered the options outlined for patients with proficient mismatch repair or microsatellite stable tumors, considering that dMMR tumors have been shown to be sensitive to CRT[38] and that historically, fluorouracil-based chemotherapy has been less effective in patients with dMMR.[39]

FUTURE RESEARCH

The Expert Panel anticipates the results from several studies that are relevant for these guideline recommendations. The JANUS Rectal Cancer Trial (ClinicalTrials.gov identifier: NCT05610163) is investigating whether triplet chemotherapy after long-course CRT will result in improved cCR and DFS rates compared with doublet chemotherapy.[62] If the results of this trial show an improved rate of response with triplet chemotherapy, this could potentially increase the number of patients who are eligible for an NOM approach and would affect this guideline's recommendations for the recommended chemotherapy component of TNT in the future. The ENSEMBLE phase III trial with a similar hypothesis to JANUS is also underway in JAPAN, using short-course RT followed by triplet therapy with capecitabine, oxaliplatin, and irinotecan or doublet therapy with capecitabine and oxaliplatin (jRCTs031220342).[63] A multicenter trial is currently ongoing comparing TNT regimens (long-course RT followed by consolidation chemotherapy with or without oxaliplatin) for rectal cancers (mrT2-3N0-1) located distally, which could assist the Expert Panel to better understand the balance of benefit and increased rate of neurotoxicity associated with oxaliplatin (ClinicalTrials.gov identifier: NCT05000697).[9] In addition, the COMET trial is currently underway to assess the utility of MRI for assessing extranodal tumor deposits (ClinicalTrials.gov identifier: NCT03303547), which will help to further refine the risk factors that inform Recommendation 2.1.[64]

PATIENT AND CLINICIAN COMMUNICATION

The recommendations contained within this guideline require patient and clinician communication of the benefits and harms associated with each treatment option. TNT is a more intensive neoadjuvant therapy than CRT, which has historically been offered to patients, and thus, a discussion of the potential AEs is warranted. A nuanced discussion of the benefits and harms of chemotherapy alone versus CRT is important because although the risk of AEs is higher initially with FOLFOX chemotherapy alone, the event rates converge over time, and there may ultimately be a quality of life benefit with chemotherapy alone. The choice of TNT for patients without high-risk factors is a complex decision, weighing the risk of AEs against the potential for improved oncologic outcomes and achievement of a cCR, with the possible eligibility for NOM. If NOM is a goal of treatment, a discussion should occur between the patient and the clinician regarding the challenges with detecting a cCR, the requirements of surveillance, and other considerations noted in the qualifying statement to Recommendation 5.1. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[65]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to

medical care or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[66] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor-quality care than other Americans.[67-70] With respect to colorectal cancer specifically, compared with White patients, Black patients have a 20% higher incidence and 40% higher mortality and tend to be drastically under-represented in clinical trials.[46] In addition, there is a lack of inclusion of older patients with rectal cancer in the included studies for this review, which limits the generalizability of these recommendations to older adults with poorer performance status. Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. This factor is relevant for the recommendations contained within this guideline as recommendations for RT, for example, can be challenging to implement in locations where this modality is not readily available at a reasonable geographic distance. During the open comment process for this guideline, the Expert Panel also received feedback that MRI may not be readily available in some locations; however, an alternative method of imaging that could be recommended in place of MRI has not been validated, and therefore, imaging alternatives are not recommended within this guideline. In patients who cannot undergo MRI, endoscopic ultrasound and computed tomography may be considered, but are not recommended. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations. In addition, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[66]

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[71,72] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[73,74]

Discussion of cost can be an important part of shared decision making.[75] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease, and there are two or more treatment options that are comparable in terms of benefits and harms.[75]

Of note, medication prices may vary markedly, depending on negotiated discounts and rebates. Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which might have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[75]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data or agents that are not currently available in either the United States or Canada or are industry-sponsored. An informal review of the literature on this topic found evidence showing that the main cost drivers for locally advanced rectal cancer were outpatient care (29.9% of costs), radiotherapy (21.8%), index resection (20.6%), and chemotherapy (17.4%).[76] Several analyses found that short-course RT is more cost-effective than long-course CRT;[77-79] however, one review found that long-course CRT was more cost-effective for distal tumors.[80] For individual patients, treatment with TNT was found to be more cost-effective than CRT, followed by surgery and adjuvant chemotherapy, with the lesser effectiveness of the last option because of low adherence to the chemotherapy portion of treatment.[81]

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is not only to assess the suitability of the recommendations to implementation in the community setting but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among frontline practitioners and survivors of cancer and caregivers and also to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.aso.org/gastrointestinal-cancer-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, slide sets, and clinical tools and resources, visit

www.asco.org/gastrointestinal-cancer-guidelines. The Data Supplement for this guideline includes an additional evidence table and forest plots for included meta-analyses. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

GENDER-INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of individuals regardless of sexual orientation or gender identity.[84] Transgender and nonbinary people, in particular, may face multiple barriers to oncology care including stigmatization, invisibility, and exclusiveness. One way exclusiveness or lack of accessibility may be communicated is through gendered language that makes presumptive links between sex and anatomy.[85-88] With the acknowledgment that ASCO guidelines may impact the language used in clinical and research settings, ASCO is committed to creating gender-inclusive guidelines. For this reason, guideline authors use gender-inclusive language whenever possible throughout the guidelines. In instances in which the guideline draws upon data on the basis of gendered research (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

RELATED ASCO GUIDELINES

- Integration of Palliative Care Into Standard Oncology Care[82] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[65] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Treatment of Metastatic Colorectal Cancer[83] (http://ascopubs.org/doi/10.1200/JCO.22.01690)

AFFILIATIONS

[1]University of Arizona Cancer Center, Tucson, AZ
[2]American Society of Clinical Oncology, Alexandria, VA
[3]Vanderbilt Ingram Cancer Center, Nashville, TN
[4]Imperial College London, London, United Kingdom
[5]Netherlands Cancer Institute, Amsterdam, the Netherlands
[6]University of California Irvine Health, Irvine, CA
[7]Mount Sinai Comprehensive Cancer Center, Miami Beach, FL
[8]Case Comprehensive Cancer Center, Cleveland, OH
[9]Paltown Development Foundation/COLONTOWN, Crownsville, MD
[10]Columbia University, Herbert Irving Comprehensive Cancer Center, New York, NY
[11]Oregon Health & Science University, Portland, OR
[12]BC Cancer, Vancouver, BC, Canada
[13]MD Anderson Cancer Center, Houston, TX
[14]Hospital Alemão Oswaldo Cruz, São Paulo, Brazil
[15]Memorial Sloan Kettering Cancer Center, New York, NY
[16]Massachusetts General Hospital, Boston, MA
[17]Northwell Health, New Hyde Park, NY

CORRESPONDING AUTHOR

American Society of Clinical Oncology; e-mail: guidelines@asco.org.

EDITOR'S NOTE

This ASCO Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.org, is available at http://www.asco.org/gastrointestinal-cancer-guidelines.

EQUAL CONTRIBUTION

A.J.S. and S.G. were Expert Panel cochairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Locally Advanced Rectal Cancer: ASCO Guideline

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Aaron J. Scott
Stock and Other Ownership Interests: Johnson & Johnson/Janssen
Consulting or Advisory Role: Exelixis, QED Therapeutics, Pfizer
Research Funding: Exelixis, Genentech, Incyte, Five Prime Therapeutics, Merck
Travel, Accommodations, Expenses: Exelixis, QED Therapeutics

Jordan Berlin
Consulting or Advisory Role: Bayer Health, Ipsen, Mirati Therapeutics, Insmed, Merck KGaA, BioSapien, Merus, Bexion, Mekanistic Therapeutics, Bristol Myers Squibb/Celgene, Merck, Astellas Pharma, amplia, epsilon
Research Funding: Bayer (Inst), Incyte (Inst), EMD Serono (Inst), Lilly (Inst), Dragonfly Therapeutics (Inst), AbbVie (Inst), I-MAB (Inst), Astellas Pharma (Inst), Atreca (Inst), Day One Biopharmaceuticals (Inst), Bristol Myers Squibb/Celgene (Inst), Sumitomo Dainippon Pharma Oncology (Inst), 23andMe (Inst), Totus Medicines (Inst), Tyra Biosciences (Inst), HiberCell (Inst), Incendia Pharmaceuticals AB (Inst), ribosciences (Inst), Bristol Myers Squibb/Celgene (Inst), Volastra Therapeutics (Inst)
Other Relationship: Novocure, AstraZeneca, Boehringer Ingelheim

Gina Brown
Research Funding: Eisai (Inst)

Myriam Chalabi
Consulting or Advisory Role: MSD (Inst), Bristol Myers Squibb/Celgene (Inst), Numab (Inst), Kineta
Research Funding: Bristol Myers Squibb (Inst), Roche/Genentech (Inst), MSD (Inst), Agenus (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, Bristol Myers Squibb

May T. Cho
Employment: Replimune
Consulting or Advisory Role: Amgen, Eisai, Taiho Pharmaceutical, Astellas Pharma, Exelixis, Ipsen, Seagen, QED Therapeutics, Basilea, Genentech/Roche, AstraZeneca, BeiGene
Speakers' Bureau: Taiho Pharmaceutical, Pfizer, Natera, Bristol Myers Squibb/Celgene, Helsinn Therapeutics, Daiichi Sankyo/Astra Zeneca
Research Funding: Bristol Myers Squibb (Inst), Seagen (Inst), AstraZeneca/MedImmune (Inst), Incyte (Inst), Immunocore (Inst)
Travel, Accommodations, Expenses: AstraZeneca/MedImmune, Seagen

Mike Cusnir
Speakers' Bureau: Sirtex Medical, Guardant Health

Jennifer Dorth
Travel, Accommodations, Expenses: Varian Medical Systems

Manju George
Stock and Other Ownership Interests: Amgen, CRISPR therapeutics, Intellia Therapeutics, Editas Medicine, Johnson & Johnson/Janssen, Natera, Novavax, Guardant Health AMEA, Pfizer
Honoraria: Seagen, Daiichi Sankyo/Lilly, Astellas Pharma, Bayer, Natera
Patents, Royalties, Other Intellectual Property: Patent for a discovery in biomedical research

Lisa A. Kachnic
Honoraria: Varian Medical Systems
Consulting or Advisory Role: New B Innovation
Research Funding: Varian Medical Systems (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate
Travel, Accommodations, Expenses: Varian Medical Systems
Uncompensated Relationships: RTOG Foundation, NRG Oncology, NCI
Uncompensated Relationships: SWOG

Hagen F. Kennecke
Honoraria: Natera, Exelixis
Consulting or Advisory Role: Tersera
Speakers' Bureau: Natera
Research Funding: Taiho Pharmaceutical (Inst), Novartis (Inst), Exelixis (Inst)

Jonathan M. Loree
Consulting or Advisory Role: Taiho Pharmaceutical, Ipsen, Bayer, AMGEN, Pfizer, Advanced Accelerator Applications, Merck, SAGA Diagnostics, Guardant Health
Research Funding: Ipsen (Inst), Amgen (Inst), Personalis

Van K. Morris
Consulting or Advisory Role: Incyte, Regeneron, Novartis
Research Funding: Bristol Myers Squibb (Inst), EMD Serono (Inst), Pfizer (Inst), BioNTech (Inst), Bicara Therapeutics (Inst), Sumitomo Pharma Oncology (Inst), Redx Pharma (Inst)

Rodrigo Oliva Perez
Honoraria: Johnson & Johnson
Consulting or Advisory Role: Johnson & Johnson/MedTech
Research Funding: Medtronic (Inst)

J. Joshua Smith
Consulting or Advisory Role: Guardant Health, Foundation Medicine, GlaxoSmithKline
Travel, Accommodations, Expenses: GlaxoSmithKline
Other Relationship: Johnson & Johnson/Janssen

Sepideh Gholami
Consulting or Advisory Role: Genentech, Iota

No other potential conflicts of interest were reported.

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

TABLE A1. Management of Locally Advanced Rectal Cancer Expert Panel Membership

Name	Affiliation	Role or Area of Expertise
Sepideh Gholami, MD, MAS (cochair)	Northwell Health, New Hyde Park, NY	Surgical Oncology
Aaron J. Scott, MD (cochair)	University of Arizona Cancer Center, Tucson, AZ	Medical Oncology
Jordan Berlin, MD	Vanderbilt Ingram Cancer Center, Nashville, TN	Medical Oncology
Gina Brown, MBBS, MD	Imperial College London, London, UK	Radiology
Myriam Chalabi, MD, PhD	Netherlands Cancer Institute, Amsterdam, the Netherlands	Medical Oncology
May T. Cho, MD	University of California Irvine Health, Irvine, CA	Medical Oncology
Mike Cusnir, MD	Mount Sinai Comprehensive Cancer Center, Miami Beach, FL	Practice Guidelines Implementation Network
Jennifer Dorth, MD	Case Comprehensive Cancer Center, Cleveland, OH	Radiation Oncology
Manju George, DVM, PhD	Paltown Development Foundation/ COLONTOWN, Crownsville, MD	Patient Representative
Angelita Habr-Gama, MD, PhD	Hospital Alemão Oswaldo Cruz, São Paulo, Brazil	Surgical Oncology
Lisa A. Kachnic, MD	Columbia University, Herbert Irving Comprehensive Cancer Center, New York, NY	Radiation Oncology
Hagen F. Kennecke, MD	Oregon Health & Science University, Portland, OR	Medical Oncology
Jonathan M. Loree, MD	BC Cancer, Vancouver, BC, Canada	Medical Oncology
Van K. Morris, MD	MD Anderson Cancer Center, Houston, TX	Medical Oncology
Rodrigo Oliva Perez, MD, PhD	Hospital Alemão Oswaldo Cruz, São Paulo, Brazil	Surgical Oncology
J. Joshua Smith, MD, PhD	Memorial Sloan Kettering Cancer Center, Department of Surgery | Colorectal Service New York, NY	Surgical Oncology
Matthew R. Strickland, MD	Massachusetts General Hospital, Boston MA	Medical Oncology
Erin B. Kennedy, MHSc	American Society of Clinical Oncology, Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Quality of Evidence and Recommendation Rating Definitions

Term	Definition
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention.
Conditional/Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.
Good practice statement	Good practice statements represent the consensus of the Expert Panel and are used when high quality indirect evidence is available, but it would not be a good use of the Expert Panel's resources to conduct a formal systematic review.

NOTE. Source: GRADE Handbook (Schünemann et al[89]).