

Clinical Practice Guideline

Radiation Therapy for Rectal Cancer: An ASTRO Clinical Practice Guideline Focused Update



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Purpose: With the results of several recently published clinical trials, this guideline focused update provides evidence-based recommendations for the indications and dose-fractionation regimens for neoadjuvant radiation therapy (RT), optimal sequencing of RT and systemic therapy in the context of total neoadjuvant therapy (TNT), and considerations for selective omission of RT and surgery for rectal cancer.

Methods: The American Society for Radiation Oncology convened a multidisciplinary task force to update 3 key questions that focused on the role of RT for patients with operable rectal cancer. The key questions addressed (1) indications for neoadjuvant RT, (2) selection of neoadjuvant regimens, and (3) indications for consideration of a nonoperative management (NOM) or local excision approach after definitive/preoperative chemoradiation. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for quality of evidence grading and strength of recommendation.

Results: For patients with stage II-III rectal cancer, neoadjuvant RT was strongly recommended; however, among patients deemed at lower risk of locoregional recurrence, consideration of omission of neoadjuvant RT was conditionally recommended in favor of neoadjuvant chemotherapy with a favorable treatment response or upfront surgery. For patients with T3-T4 and node-positive rectal cancer undergoing neoadjuvant RT, a TNT approach was strongly recommended. Among patients with higher risk of locoregional recurrence, TNT with chemotherapy before or after long-course chemoradiation was strongly recommended, whereas TNT with short-course RT followed by chemotherapy was conditionally recommended. For patients with rectal cancer for whom NOM is a priority, concurrent chemoradiation followed by consolidation chemotherapy was strongly recommended. Selection of RT dose-fractionation regimen, sequencing of therapies, and consideration of NOM should be determined by multidisciplinary consensus and based on disease extent, disease location, patient preferences, and quality of life considerations.

Conclusions: The task force proposed recommendations to inform best clinical practices on the use of RT for rectal cancer with strong emphasis on multidisciplinary care. Future studies should focus on further addressing optimal treatment regimens to allow for more personalized recommendations based on individual risk stratification and patient priorities regarding quality of life.

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Preamble

As a leading organization in radiation oncology, the American Society for Radiation Oncology (ASTRO) is dedicated to improving quality of care and patient outcomes. A cornerstone of this goal is the development and dissemination of clinical practice guidelines based on systematic methods to evaluate and classify evidence, combined with a focus on patient-centric care and shared decision making. ASTRO develops and publishes guidelines without commercial support, and members volunteer their time.

Disclosure Policy—ASTRO has detailed policies and procedures related to disclosure and management of industry relationships to avoid actual, potential, or perceived conflicts of interest. All task force members are required to disclose industry relationships and personal interests from 12 months before initiation of the writing effort. Disclosures for the chair and vice chair go through a review process with final approval by ASTRO's Conflict of Interest Review Committee. For the purposes of full transparency, task force members' comprehensive disclosure information is included in this publication. Peer reviewer disclosures are also reviewed and included (Supplementary Materials, [Appendix E1](#)). The complete disclosure policy for Formal Papers is online.

Selection of Task Force Members—ASTRO strives to avoid bias and is committed to creating a task force that includes a diverse and inclusive multidisciplinary group of experts considering race, ethnicity, gender, experience, practice setting, and geographic location. Representatives from organizations and professional societies with related

interests and expertise are also invited to serve on the task force.

Methodology—ASTRO's task force uses evidence-based methodologies to develop guideline recommendations in accordance with the National Academy of Medicine standards.^{1,2} The evidence identified from key questions (KQs) is assessed using the Population, Intervention, Comparator, Outcome, Timing, Setting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. [Table 1](#) describes ASTRO's recommendation grading system. See [Appendix E2](#) in Supplementary Materials for a list of abbreviations used in the guideline.

Consensus Development—Consensus is evaluated using a modified Delphi approach. Task force members confidentially indicate their level of agreement on each recommendation based on a 5-point Likert scale, from "strongly agree" to "strongly disagree." A prespecified threshold of $\geq 75\%$ ($\geq 90\%$ for expert opinion recommendations) of raters who select "strongly agree" or "agree" indicates consensus is achieved. Recommendation(s) that do not meet this threshold are removed or revised. Recommendations edited in response to task force or reviewer comments are resurveyed before submission of the document for approval.

Annual Evaluation and Updates—Guidelines are evaluated annually beginning 2 years after publication for new, potentially practice-changing studies that could result in a guideline update. In addition, ASTRO's Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Table 1 ASTRO recommendation grading classification system

ASTRO’s recommendations are based on evaluation of multiple factors including the QoE and panel consensus, which, among other considerations, inform the strength of recommendation. QoE is based on the body of evidence available for a particular key question and includes consideration of number of studies, study design, adequacy of sample sizes, consistency of findings across studies, and generalizability of samples, settings, and treatments.			
Strength of Recommendation	Definition	Overall QoE Grade	Recommendation Wording
Strong	• Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh benefits. • All or almost all informed people would make the recommended choice.	Any (usually high, moderate, or expert opinion)	“Recommend/Should”
Conditional	• Benefits are finely balanced with risks and burden, or appreciable uncertainty exists about the magnitude of benefits and risks. • Most informed people would choose the recommended course of action, but a substantial number would not. • A shared decision-making approach regarding patient values and preferences is particularly important.	Any (usually moderate, low, or expert opinion)	“Conditionally Recommend”
Overall QoE Grade	Type/Quality of Study	Evidence Interpretation	
High	• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.	The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.	
Moderate	• 1 well-conducted and highly generalizable RCT or a meta-analysis of such trials OR • 2 or more RCTs with some weaknesses of procedure or generalizability OR • 2 or more strong observational studies with consistent findings.	The true effect is likely to be close to the estimate of the effect based on the body of evidence, but it is possible that it is substantially different.	
Low	• 1 RCT with some weaknesses of procedure or generalizability OR • 1 or more RCTs with serious deficiencies of procedure or generalizability or extremely small sample sizes OR • 2 or more observational studies with inconsistent findings, small sample sizes, or other problems that potentially confound interpretation of data.	The true effect may be substantially different from the estimate of the effect. There is a risk that future research may significantly alter the estimate of the effect size or the interpretation of the results.	
Expert Opinion*	• Consensus of the panel based on clinical judgment and experience, due to absence of evidence or limitations in evidence.	Strong consensus (≥90%) of the panel guides the recommendation despite insufficient evidence to discern the true magnitude and direction of the net effect. Further research may better inform the topic.	
<i>Abbreviations:</i> ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials. *A lower QoE, including expert opinion, does not imply that the recommendation is conditional. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials, but there still may be consensus that the benefits of a treatment or diagnostic test clearly outweigh its risks and burden. ASTRO’s methodology allows for use of implementation remarks meant to convey clinically practical information that may enhance the interpretation and application of the recommendation. Although each recommendation is graded according to recommendation strength and QoE, these grades should not be assumed to extend to the implementation remarks.			

Introduction

Since the prior publication of the ASTRO clinical practice guideline, "Radiation Therapy for Rectal Cancer" in 2020,³ several randomized controlled trials (RCTs) have established newer treatment paradigms that challenge long-standing practices. Although neoadjuvant chemoradiation

followed by total mesorectal excision (TME) and adjuvant chemotherapy was the prior standard of care,^{4,5} more recent studies have explored treatment intensification, with the goal of improving disease outcomes, as well as treatment deintensification by omission of local therapies to potentially reduce treatment-related toxicities and improve quality of life (QoL).⁶⁻¹¹ These emerging treatment paradigms

allow for more personalized and nuanced treatment recommendations tailored to each individual patient's risk factors, tumor location, and priorities with respect to QoL. Specifically, prospective randomized trials, such as UNICANCER-PRODIGE 23 (Gastrointestinal Group and Partenariat de Recherche en Oncologie Digestive),¹⁰ RAPIDO (Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation),^{6,7} OPRA (Organ Preservation for Rectal Adenocarcinoma),^{8,12} and PROSPECT (Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients with Locally Advanced Rectal Cancer Undergoing Surgery),⁹ have explored the role of total neoadjuvant therapy (TNT), optimal sequencing of TNT, selective omission of radiation therapy (RT) and have more definitively established nonoperative management (NOM) as an acceptable treatment approach in select patients with appropriate follow-up. Additionally, for the first time, with the emergence of immunotherapy, biomarker-driven treatment has been explored and established among patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (MMRd) rectal cancers, heralding an exciting era of more personalized care.¹¹ To reflect the current landscape of rectal treatment guidelines more accurately, ASTRO recommissioned a task force to formulate a focused update of the rectal cancer guideline³ and provide evidence-based recommendations for 3 clinical KQs regarding the use of RT for rectal cancer.

Methods

Task force composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; and a patient representative. This guideline was developed in collaboration with the American Society of Clinical Oncology, the European Society for Radiotherapy and Oncology, and the Society of Surgical Oncology, who provided representatives and peer reviewers.

Document review and approval

The guideline update was reviewed by 20 official peer reviewers ([Appendix E1](#)) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from May to June 2024. The final guideline was approved by the ASTRO Board of Directors and endorsed by the European Society for Radiotherapy and Oncology, the Royal Australian and New Zealand College of Radiologists, and the Society of Surgical Oncology.

Evidence review

ASTRO's guideline methodology includes developing a focused update of a guideline when new practice-changing, published trials are considered important enough to

prompt changes to portions of a guideline. To facilitate this, using the PICOTS framework ([Table 2](#)), a systematic search of human participant studies retrieved from the Ovid MEDLINE database was conducted for English-language publications between April 2019 and October 2023 to incorporate new data published since the 2020 rectal cancer guideline.³ Allowable publication types included prospective clinical trials, RCTs, and meta-analyses (of RCTs and prospective studies only). The population of interest was adults (age ≥ 18 years) with pathologically confirmed rectal adenocarcinoma. Trial size required for inclusion was ≥ 50 patients for prospective studies or ≥ 10 for prospective studies with biomarker-selected patients. Universal exclusion criteria included preclinical and nonhuman studies; publication types such as abstracts, review articles, comments, or editorials; study types such as retrospective, dosimetric, health economics/cost analysis, or large registry/database studies; and treatment of recurrent or metastatic disease. For specific subquestions where limited data were available, expert opinion was relied upon to support recommendations. Full-text articles were assessed by the task force to determine the final included study list, resulting in 61 studies (see the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] diagram showing the number of articles screened, excluded, and included in the focused update evidence review and [Appendix E3](#) in Supplementary Materials for the literature search strategy, which includes the evidence search parameters and inclusion/exclusion criteria). The data used by the task force to formulate recommendations are summarized in evidence tables available in Supplementary Materials, [Appendix E4](#). References selected and published in this document are representative and not all-inclusive. Additional ancillary articles not in the evidence tables are included in the text; these were not used to support the evidence-based recommendations but may have informed expert opinion.

See the 2020 rectal cancer guideline for literature search details and methods before April 2019, noting that the 2020 guideline was built upon a previous search of rectal cancer that included articles through July 2013.³

Scope of the guideline

The scope of this focused update is existing treatment paradigms for localized rectal adenocarcinoma. The impetus for this focused update is to primarily incorporate new practice-changing data on TNT, including different treatment sequencing and RT fractionation regimens that have emerged as acceptable standards of care, selective omission of RT, NOM, and integration of immunotherapy for patients with MSI-H or MMRd rectal tumors.

This focused update is designed to function as a stand-alone document and to serve as an update to KQs 1, 2, and 3. All recommendations (new, modified, and unchanged)

Table 2 KQs in PICO format

KQ	Population	Intervention	Comparator	Outcomes
1	What are the indications for neoadjuvant RT for operable rectal cancer? (Updated)			
	Patients with pathologically confirmed rectal cancer	• Long-course preop chemoRT • Short-course preop RT • Preop chemo • Preop immunotherapy	• Surgery alone • Postop RT or chemoRT • Preop chemoRT	• Overall survival • Local control • Disease-free survival • Sphincter preservation • Acute and late grade ≥3 toxicity
2	What neoadjuvant regimens are appropriate for patients with operable rectal cancer? (Updated)			
	Same as KQ1	• Preop short-course RT followed by surgery and postop chemo • Preop short-course RT followed by chemo followed by surgery • Preop chemo followed by short-course RT followed by surgery • Preop long-course chemoRT followed by chemo followed by surgery • Preop chemo followed by chemoRT followed by surgery • Preop immunotherapy • Neoadjuvant RT with short interval to surgery (≤6 wk)	• Preop long-course chemoRT followed by surgery and postop chemo • Neoadjuvant RT with long interval to surgery (>6 wk)	• Overall survival • Local control • Disease-free survival • Pathologic complete response • Sphincter preservation • Acute and late grade ≥3 toxicity
3	What are the appropriate indications and considerations of a nonoperative (active surveillance) or local excision approach after definitive/preoperative chemoRT? (Updated)			
	Same as KQ1	• Active surveillance • Local excision • Long-course chemoRT, chemo followed by long-course chemoRT, long-course chemoRT followed by chemo, short-course RT, short-course RT followed by chemo, chemo followed by short-course RT • Method/frequency of surveillance (MRI, flexible sigmoidoscopy and biopsy, restaging CT)	• TME (comparator to active surveillance) • TME (comparator to local excision)	• Overall survival • Local control/regrowth • Disease-free survival • TME-free survival • Disease-specific survival • Pathologic and clinical complete response • Sphincter preservation • Salvage rate • Acute and late grade ≥3 toxicity • HR-QoL
4	What are the appropriate treatment volumes, dose constraints, and techniques for patients treated with RT? (KQ4 is not updated in this focused update, but the recommendations and text are included for ease of review by the reader) ³			
Abbreviations: chemo = chemotherapy; chemoRT = chemoradiation; CT = computed tomography; HR-QoL = health-related quality of life; KQ = key question; MRI = magnetic resonance imaging; PICO = Population, Intervention, Comparator, Outcome; preop = preoperative; postop = postoperative; RT = radiation therapy; TME = total mesorectal excision.				

for these KQs are included. The text explains new and modified recommendations, whereas recommendations from the 2020 guideline that have been deleted or superseded no longer appear. KQ4 (What are the appropriate treatment volumes, dose constraints, and techniques for patients treated with RT?) has not been modified from the 2020 rectal cancer guideline given that there have been no new randomized or prospective trials on these topics. KQ4, and the evidence table supporting KQ4, however, has been included for ease of review by the reader.³

The key outcomes of interest are oncologic results including overall survival, local control, disease-free

survival (DFS), acute and late toxicity, and QoL metrics. This guideline updates only the subjects specified in the KQs (Table 2). There are several important questions in the management of rectal cancer that are outside the scope of this guideline update, including management of non-adenocarcinoma histologies, indications, dose and technique for adjuvant therapy, RT in the setting of oligometastatic disease, locally recurrent disease, brachytherapy, palliative RT, contact RT, proton RT, intraoperative RT, reirradiation, and detailed discussions of surgical approaches and chemotherapy regimens.

Key Questions and Recommendations

KQ1: Indications for neoadjuvant RT (Table 3)

See evidence tables in Supplementary Materials, [Appendix E4](#), for the data supporting the recommendations for KQ1.

What are the indications for neoadjuvant RT for operable rectal cancer?

This guideline update highlights the increasing treatment options for patients with rectal adenocarcinoma. The clinical trials establishing the value of preoperative RT remain foundational evidence.^{5,19-25,40} To support the

clinical decision making now required to select these new treatment pathways, the role of clinical staging and molecular stratification has only increased in importance. Clinical evaluation should continue to include both a digital rectal examination (DRE) performed by an experienced examiner and a determination by the surgeon of tumor height (low = 0 to <5 cm from the anal verge; mid = 5 to <10 cm; high ≥ 10 cm). This measurement is most accurately assessed by rigid proctoscopy, but flexible endoscopy is more commonly performed in the modern office setting. Beyond the physical exam, pelvic magnetic resonance imaging (MRI) with rectal protocol has become central to selecting the appropriate treatment pathway. For those without a contraindication,

Table 3 Indications for neoadjuvant RT

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with rectal cancer, pelvic MRI with rectal protocol is recommended for preoperative clinical T and N staging. (<i>Unchanged from 2020 guideline</i>)	Strong	Moderate 13-16
2. For patients with rectal cancer, testing the biopsy specimen for MMR/MSI is recommended.	Strong	Moderate 11,17,18
3. For patients with stage II or III rectal cancer, neoadjuvant RT is recommended. <u>Implementation remark:</u> For patients at lower risk of locoregional recurrence, neoadjuvant RT may not always be appropriate.	Strong	High 5,19-25
4. For patients with stage II or III rectal cancer at lower risk of locoregional recurrence who attain a favorable response to neoadjuvant chemotherapy, omission of neoadjuvant RT is conditionally recommended. <u>Implementation remarks:</u> • Lower risk is defined as a cT2 or cT3a/b tumor >5 cm from the anal verge, with radiographically <4 lymph nodes >1 cm in the short axis and with mrCRM ≥ 2 mm and no mrEMVI. • Favorable response is defined as >20% decrease in the size of the primary tumor on imaging and endoscopic evaluation.	Conditional	High 9,26-32
5. For patients with stage II or III rectal cancer at lower risk of locoregional recurrence, upfront surgery with omission of neoadjuvant RT is conditionally recommended. <u>Implementation remark:</u> Lower risk is defined as a cT2 or cT3a/b tumor >5 cm from the anal verge, with radiographically <4 lymph nodes >1 cm in the short axis and with mrCRM ≥ 2 mm and no mrEMVI.	Conditional	Moderate 16,33-35
6. For patients with stage II or III rectal cancer who wish to pursue nonoperative management, RT is recommended as part of a total neoadjuvant therapy regimen.	Strong	Moderate 8
7. For patients with cT1-2N0 rectal cancer who may need an abdominoperineal resection, neoadjuvant RT is conditionally recommended to improve the chance of sphincter preservation.	Conditional	Low 36,37
8. For patients with rectal cancer where radiation is indicated, RT should be performed preoperatively rather than postoperatively. (<i>Unchanged from 2020 guideline</i>)	Strong	High 4,5,20,21,38,39
9. For patients with MMRd/MSI-H rectal cancer, omission of neoadjuvant RT is recommended after a clinical complete response to upfront treatment with checkpoint inhibitors.	Strong	Low 11,17,18

Abbreviations: KQ = key question; MMRd = mismatch repair deficient; MMR = mismatch repair; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; MRI = magnetic resonance imaging; MSI = microsatellite instability; MSI-H = microsatellite instability-high; RT = radiation therapy.

the recommendation for all patients with rectal cancer to undergo pelvic MRI staging remains unchanged from the 2020 guideline.¹³⁻¹⁶ Since the 2020 guideline publication, several new studies have been published, further strengthening the role of MRI in the initial risk stratification for patients with stage II or III disease.^{33,34,41,42} Additional studies have gone further to include MRI after an initial course of neoadjuvant chemotherapy in the assessment of disease response to facilitate subsequent treatment decision making.^{9,28,29,31}

It is now clear that patients with stage II or III rectal adenocarcinoma should be stratified into lower or higher risk groups. The most critical risk factor for local recurrence is the pretreatment MRI-defined relationship of the disease to the mesorectal fascia/circumferential resection margin (mrCRM). It is also clear that definitions of how to optimally classify “lower risk” have continued to change over time, reflecting improved staging techniques and recognition of predictive value of radiographic baseline imaging. Notably, the 2020 guideline defined “lower risk” as a T3N0 tumor that is >10 cm from the anal verge and with CRM ≥ 2 mm, whereas in the current guideline, the definition of “lower risk” has been expanded to include patients with tumors that are staged cT2 or T3a/b >5 cm from the anal verge, have the mrCRM free of tumor or lymph node by ≥ 2 mm, and lack MRI-defined extramural vascular invasion.^{16,33-35} Patients with radiographically <4 lymph nodes >1 cm in the short axis with favorable response to chemotherapy may also be at lower risk of locoregional recurrence (LRR).⁹ In contrast, presence of pelvic sidewall (lateral) lymph nodes and tumor deposits on MRI have been associated with worse DFS.^{43,44}

Select patients may be treated with neoadjuvant chemotherapy followed by surgery with omission of preoperative RT after multidisciplinary team-based evaluation and decision making. The PROSPECT trial is an important phase 3 trial comparing standard long-course chemoradiation to a regimen of neoadjuvant chemotherapy with selective omission of RT in lower-risk rectal cancer.⁹ Eligibility and subsequent treatment decision making were based on MRI staging (although endorectal ultrasound was allowed in the absence of available MRI). Patients were required to have cT3N0 or cT2-3, with <4 lymph nodes with a short axis >10 mm, no tumor visible within 3 mm of the radial margin, and be eligible for sphincter-preserving surgery.⁹ Omission of RT was based on a favorable response to neoadjuvant folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) defined as >20% decrease in the size of the primary tumor after imaging and physical exam with proctoscopy by the primary surgeon within 28 days after completion of FOLFOX. The trial demonstrated that neoadjuvant chemotherapy followed by surgery with omission of preoperative RT was not inferior with respect to oncologic outcomes in this select group of patients. Neoadjuvant chemotherapy with

FOLFOX was associated with significantly greater grade 3 to 4 toxicities, especially neuropathy and neutropenia. All patients, regardless of treatment arm, were recommended to receive adjuvant FOLFOX.⁹ Subsequent analysis of patient-reported outcomes demonstrated significantly lower rates of fatigue, neuropathy, and better sexual function among patients with selective omission of RT.⁴⁵ The CONVERT (Neoadjuvant Chemotherapy With CAPOX Versus Chemoradiation for Locally Advanced Rectal Cancer With Uninvolved Mesorectal Fascia) trial is a second phase 3 trial with an almost identical trial design, which has only presented initial results supporting the use of neoadjuvant chemotherapy and selective omission of RT.²⁸ Two phase 2 trials with similar protocol designs also reported results consistent with the PROSPECT trial.^{26,27,31} Based on these data, for patients with rectal cancer at lower risk of recurrence, the omission of RT is conditionally recommended for those undergoing upfront surgery or neoadjuvant chemotherapy with a favorable response.^{9,16,26-31,33-35} Selection of lower risk patients for omission of RT must currently be determined by each institutional multidisciplinary team but requires high-quality surgery with TME weighing patient preferences and clinical factors such as fertility preservation. Moreover, selection between upfront surgery and neoadjuvant chemotherapy must also be determined by the institutional multidisciplinary team based on the specific clinical situation and patient preferences. For example, patients with otherwise low risk but node-positive disease (eg, cT2-3N1 disease) who plan to undergo surgical resection may benefit from neoadjuvant chemotherapy rather than upfront surgery.

Patients at lower risk of recurrence may be treated sufficiently with upfront surgery with high-quality TME without any neoadjuvant therapy. The OCUM (Optimal Surgery and MRI-Based Radiochemotherapy in Rectal Carcinoma) trial has now reported final and mature results with 5-year outcomes.³³ In this prospective, nonrandomized trial, patients with clear mrCRM excluding low tumors or T4 disease were treated without neoadjuvant chemoradiation and found to have a 3.8% risk of local recurrence. A multicenter randomized study from China was underpowered but could not clearly demonstrate a benefit of preoperative short-course RT compared with surgery alone in either MRI-defined low-risk or high-risk cohorts.⁴² A meta-analysis has also supported the option of surgery alone in patients with high/upper third rectal cancers.³⁵

Sphincter preservation is a major QoL objective for many patients. Although the omission of preoperative RT may be of value for certain patients wishing to avoid the toxicities of pelvic RT, other patients may prioritize the avoidance of surgery. The OPRA trial has strengthened the evidence supporting NOM for patients achieving a complete clinical response (cCR) after TNT.⁸ Two phase 3 trials and a meta-analysis including those trials demonstrated that preoperative chemoradiation led to conversion of a

group of patients initially deemed to require an abdominoperineal resection to low anterior resection.^{4,38,39} However, this endpoint is subjective because it is based on the surgeon's preoperative assessment of the need for abdominoperineal resection, and the rate of sphincter preservation was ultimately equivalent in the preoperative and postoperative arms. These trials included only stage II and III patients, for whom neoadjuvant RT is already the standard of care. Based on an extrapolation of this evidence, neoadjuvant RT is conditionally recommended when sphincter preservation is being considered for a patient with a stage I (T1-T2 N0) tumor in a distal location.^{5,20,21,38,39}

Three prospective trials randomizing patients between preoperative and postoperative chemoradiation demonstrated improvements in DFS and/or local recurrence-free survival with the former approach.^{5,20,21,38,39} The German rectal trial also reported fewer acute and long-term toxicities in the patients treated with preoperative chemoradiation.^{4,5} However, a fourth trial from Korea did not show significant differences in either oncologic outcomes or toxicities.³⁸ A meta-analysis, which included this Korean trial, confirmed a significant reduction in local recurrence and acute toxicity in the patients treated preoperatively.³⁹ Therefore, when RT is indicated for rectal cancer, the evidence strongly supports a recommendation favoring preoperative over postoperative treatment.

Molecular profiling has identified an important subset of patients with rectal cancer who may not require RT or surgery. Although lacking in randomized data and including only small numbers of patients with limited follow-up, 2 prospective trials have observed extraordinarily high response rates to immune checkpoint inhibitors alone in patients whose tumors express MMRd or who have MSI-H status, determined by immunohistochemistry for the detection of loss of expression of MLH1, MSH1, MSH6, and PMS2.^{11,17} Based on these data, initial treatment with immune checkpoint inhibitors alone is recommended for these patients followed by response assessment.^{11,17,18} Of note, a third trial included nivolumab sequentially between preoperative chemoradiation and surgery, showing a pathologic complete response (pCR) rate of 60% in patients with MSI-H.¹⁸ The AZUR-1 trial (NCT05723562), a global, multicenter, single-arm, open-label, phase 2 study of dostarlimab monotherapy in patients with MMRd/MSI-H tumors is ongoing for confirmation. For patients with cCR, omission of RT, chemotherapy, and surgery may be considered. Because of limited follow-up with this approach, however, close posttreatment surveillance is important. In a phase 2 trial of dostarlimab, patients were assessed for clinical response with endoscopic evaluation and DRE at 6 weeks, 3 months, 6 months, and then every 4 months after treatment initiation.¹¹ MRI with rectal protocol and positron emission tomography/computed tomography (CT) was also performed at 3 months, 6 months, and then every 4 months after treatment initiation.¹¹ Although these tumors may only represent 5% to 10% of the patients

diagnosed with rectal adenocarcinoma, the testing of all biopsy specimens for MMRd/MSI-H status is recommended to appropriately identify which patients would benefit from immune checkpoint inhibitor therapy.^{11,17,18} With these increasing options, treatment selection must be based on multidisciplinary discussion and consideration of the patient's individual goals and preferences.

KQ2: Appropriate neoadjuvant regimens (Table 4)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ2.

What neoadjuvant regimens are appropriate for patients with operable rectal cancer?

The German rectal cancer trial established that preoperative chemoradiation using a dose of 5040 cGy in 28 fractions reduces the risk of local recurrence with less toxicity than postoperative treatment.⁴ A preoperative dose of 5000 to 5040 cGy using 180 to 200 cGy per fraction has been adopted and validated in multiple trials.^{9,38,70,71} For patients being considered for NOM, the primary tumor can be treated with a sequential or simultaneous integrated boost (SIB) up to 5600 cGy, respecting bowel tolerance limits, given that a median dose of 5400 cGy was used in the OPRA study.¹²

The Swedish and Dutch rectal cancer trials demonstrated that preoperative short-course RT using a dose of 2500 cGy in 5 fractions to the pelvis reduces the relative risk of local recurrence by >50%.^{19,22}

TNT was shown to improve pCR rates, metastasis-free survival, and DFS for patients with high-risk rectal cancer in the PRODIGE 23 and RAPIDO trials.^{6,10} The PRODIGE 23 study evaluated a TNT regimen of sequential mFOLFIRINOX for 6 cycles, long-course chemoradiation, resection, and adjuvant FOLFOX.¹⁰ When compared with the standard arm of long-course chemoradiation followed by surgery and adjuvant FOLFOX, 3-year DFS, and most recently 7-year overall survival, was improved for TNT.^{10,72} Of note, both arms included adjuvant FOLFOX in this trial. RAPIDO compared neoadjuvant short-course RT followed by capecitabine and oxaliplatin (CAPOX) or FOLFOX4 chemotherapy with neoadjuvant chemoradiation and optional adjuvant chemotherapy.⁶ When compared with the standard arm, 3-year disease-related treatment failure was improved for the short-course RT (TNT) arm.⁶ The STELLAR trial also evaluated TNT using short-course RT followed by CAPOX before surgery, compared with long-course chemoradiation followed by surgery.⁶³ The 3-year overall survival was improved for the TNT arm, although the reason for this improvement is unclear given similar LRR, DFS, and

Table 4 Appropriate neoadjuvant regimens for operable rectal cancer

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with rectal cancer receiving neoadjuvant RT with conventional fractionation, 5000-5600 cGy in 25-31 fractions with concurrent capecitabine or continuous infusion 5-fluorouracil is recommended. <u>Implementation remark:</u> A prescribed dose >5040 cGy is considered <i>only</i> for patients who may be candidates for future nonoperative management.	Strong	High (5000-5040 cGy) 5,8,50-54 Moderate (>5040-5600 cGy) 8,53
2. For patients with rectal cancer receiving neoadjuvant short-course RT, 2500 cGy in 5 fractions without concurrent chemotherapy is recommended. (<i>Unchanged from 2020 guideline</i>)	Strong	High 6,19,22,55
3. For patients with rectal cancer undergoing neoadjuvant chemoradiation, only concurrent 5-fluorouracil or capecitabine is recommended with RT for radiosensitization. (<i>Unchanged from 2020 guideline</i>)	Strong	High 50,51,56-60
4. For patients with cT3-4 or cN+ rectal cancer undergoing neoadjuvant therapy, a TNT approach is recommended. <u>Implementation remark:</u> For patients at lower risk of recurrence, TNT may not always be appropriate.	Strong	High 6,10,14,61-68
5. For patients with rectal cancer undergoing neoadjuvant therapy without tumor factors that portend increased local recurrence risk, TNT with chemotherapy before or after long-course chemoradiation or after short-course RT is recommended. <u>Implementation remarks:</u> • Risk factors for increased local recurrence include cT3 tumors in the low rectum (<5 cm from anal verge); mrCRM <2 mm; cT4 tumor; presence of mrEMVI; or lateral pelvic lymph nodes. • For patients at lower risk of recurrence, TNT may not always be appropriate.	Strong	High 6,9,10,14,64-68
6. For patients with rectal cancer undergoing neoadjuvant therapy with tumor factors that portend increased local recurrence risk, TNT with chemotherapy before or after long-course chemoradiation is recommended. <u>Implementation remark:</u> Risk factors for increased local recurrence include cT3 tumors in the low rectum (<5 cm from anal verge); mrCRM <2 mm; cT4 tumor; presence of mrEMVI; or lateral pelvic lymph nodes.	Strong	High 7,8,64,69
7. For patients with rectal cancer undergoing neoadjuvant therapy with tumor factors that portend increased local recurrence risk, TNT with short-course RT followed by chemotherapy is conditionally recommended. <u>Implementation remark:</u> Risk factors for increased local recurrence include cT3 tumors in the low rectum (<5 cm from anal verge); mrCRM <2 mm; cT4 tumor; presence of mrEMVI; or lateral pelvic lymph nodes.	Conditional	Moderate 7,15,16
8. For patients with rectal cancer receiving neoadjuvant chemotherapy as a component of TNT, the following regimens are recommended: • 3-4 months of FOLFOX or CAPOX (1) before or after chemoradiation OR (2) after short-course RT • 3 months of induction mFOLFIRINOX before chemoradiation <u>Implementation remark:</u> Use mFOLFIRINOX with caution especially for patients who are elderly, have poor performance status, or have significant comorbidities.	Strong	High (FOLFOX/CAPOX) 6,14,61-68 Moderate (mFOLFIRINOX) 10
Abbreviations: CAPOX = capecitabine and oxaliplatin; mFOLFOX = modified folinic acid, 5-fluorouracil, and oxaliplatin; mFOLFIRINOX = modified folinic acid, 5-fluorouracil, irinotecan, and oxaliplatin; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; RT = radiation therapy; TNT = total neoadjuvant therapy.		

distant metastasis-free survival outcomes between the study arms.⁶³ These trials largely enrolled high-risk patients. In PRODIGE 23, 93% of patients had nodal involvement or threatened circumferential resection margins.¹⁰ The RAPIDO trial only enrolled high-risk patients; eligibility criteria included T4 or N2 disease, extramural vascular invasion, pelvic side wall nodal involvement, and involved circumferential resection margins.⁶ TNT is therefore recommended for patients with T3-T4 or node-positive rectal cancer, acknowledging that various chemotherapy regimens, treatment sequences, and use of either short-course RT or long-course chemoradiation have been used in TNT trials. However, TNT may not always be appropriate for low-risk patients.

The sequencing of chemotherapy relative to chemoradiation was evaluated in both the OPRA and CAO/ARO/AIO-12 studies.^{8,12,69} OPRA was a phase 2 randomized study of patients with stage II or III rectal adenocarcinoma treated with induction chemotherapy followed by long-course chemoradiation or long-course chemoradiation followed by consolidation chemotherapy, with both arms compared with historical controls.^{8,12} After therapy, patients went on to NOM if a cCR or near cCR was achieved. At a median follow-up of 3 years, there were no differences in DFS, local recurrence-free survival, distant metastasis-free survival, or overall survival.⁸ There were higher rates of TME-free survival in the consolidation chemotherapy arm at 53% compared with 41% in the induction chemotherapy arm.⁸ Updated results of the OPRA study after a median follow-up of 5 years confirmed a higher rate of 3-year TME-free survival in the consolidation chemotherapy arm, along with similar 5-year DFS rates in both arms.¹²

Sequencing of therapies within TNT was also evaluated in the CAO/ARO/AIO-12 study, in which patients with cT3-4 or node-positive rectal adenocarcinoma received long-course chemoradiation with randomization to either induction or consolidation FOLFOX.⁶⁹ Patients treated with induction chemotherapy had better compliance with chemotherapy, while patients treated with consolidation chemotherapy had improved compliance with chemoradiation and higher pCR. No differences in DFS or incidence of metastasis were observed between arms. These data support a TNT strategy with long-course chemoradiation and either induction or consolidation chemotherapy, with both approaches receiving a strong recommendation for treatment with *preoperative* intent. However, as addressed in KQ3, consolidation chemotherapy may be preferred for patients under consideration for NOM, given the increased rate of cCR and TME-free survival with this approach in OPRA.^{8,12} For patients receiving TNT with preoperative short-course RT, consolidation chemotherapy is recommended based on the RAPIDO study.⁶

High-quality evidence that predated use of TNT suggests similar efficacy and patient-reported QoL outcomes for use of either long-course chemoradiation or short-

course RT,⁷³⁻⁷⁶ with both regimens recommended equally in the 2020 ASTRO guideline.³ Long-course chemoradiation and short-course RT have not been directly compared in the context of TNT, with both showing efficacy in phase 3 trials.^{6,10} In an update of the RAPIDO trial with a 5-year follow-up, the improvement in disease-related treatment failure driven by a reduction in distant metastatic disease persisted for the TNT arm.⁷ However, an increase in LRR was observed in the short-course TNT arm compared with the standard long-course chemoradiation arm.⁷ The mesorectum was breached more often in the short-course TNT arm, which may have contributed to the difference in LRR. It is not possible to discern if the increase in LRR would have been mitigated by use of long-course chemoradiation because only short-course RT was used in the TNT arm.

These phase 3 studies, in addition to multiple phase 2 studies and meta-analyses, support either short-course RT or long-course chemoradiation use as part of a TNT strategy, with both regimens recommended equally for patients without tumor factors that portend increased local recurrence risk.^{14,62,64-67} Patients with cT3 tumors in the low rectum (defined as <5 cm from the anal verge), mrCRM <2 mm, cT4 tumor, presence of MRI-defined extramural vascular invasion, or lateral pelvic lymph nodes have higher risk of local recurrence.^{41,43,44} For such patients with factors that portend increased local recurrence risk, TNT with chemotherapy before or after long-course chemoradiation is recommended, while TNT with short-course RT followed by consolidation chemotherapy is conditionally recommended, weighing the overall disease-related treatment failure benefit demonstrated in the RAPIDO study against the reported increased risk in LRR and uncertainties about factors that may have contributed to the increased LRR.^{6,7,10,14} For patients with a particularly high risk of distant metastatic disease, use of short-course RT or induction chemotherapy may facilitate earlier initiation of chemotherapy, although it is noted that in unselected populations, neither the AIO-12 nor OPRA trial detected a detrimental impact on development of distant metastases when multiagent chemotherapy was delayed with long-course chemoradiation being given first.^{12,69} Patient preferences need to be considered in deciding between various TNT regimens.

There is no consensus defining the optimal combination or sequence of multiagent chemotherapy during TNT, although the optimal length of neoadjuvant systemic therapy in the TNT strategy is 3 to 4 months.^{6,10} FOLFOX, CAPOX, or mFOLFIRINOX can be used. However, caution needs to be exercised when using mFOLFIRINOX, especially in elderly patients and patients with poor performance status or significant comorbidities. The use of TNT is associated with lower toxicity than adjuvant chemotherapy.⁶⁸ In RAPIDO, use of doublet treatment in the experimental arm was associated with a 48% risk of grade ≥ 3 adverse events, with diarrhea representing the

most common grade ≥ 3 toxicity. In PRODIGE 23, a similar 47% risk of grade ≥ 3 adverse events was reported for triplet therapy with mFOLFIRINOX, with grade 3-4 neutropenia and diarrhea observed in 17% and 11% of patients, respectively.¹⁰ In PRODIGE 23, granulocyte colony-stimulating factor was administered in 27% of patients with bolus fluorouracil omitted to reduce febrile neutropenia.¹⁰ Risk factors for recurrence, age, performance status, comorbidities, and patient preferences must be considered when selecting doublet or triplet chemotherapy in the context of TNT. If triplet therapy is pursued, an induction chemotherapy approach is favored in alignment with PRODIGE 23.¹⁰

Before the adoption of TNT, the German rectal trial established a standard interval of approximately 6 weeks between the completion of neoadjuvant chemoradiation and surgical resection for patients with rectal cancer⁵; however, the optimal interval between completion of neoadjuvant chemoradiation and surgical resection remains uncertain,^{77,78} with an interval of 6 to 11 weeks recommended in prior ASTRO practice guidelines.³ This interval remains appropriate for patients who are not receiving TNT or those receiving induction chemotherapy before long-course chemoradiation and planned resection. The optimal timing of surgery following TNT with the addition of consolidation chemotherapy has not been established. In the experimental arm of the RAPIDO and STELLAR studies, the median time from end of RT to surgery was approximately 23 and 20 weeks, respectively.^{6,63} In the OPRA trial, the median time from completion of all treatment to restaging was similar in the induction and consolidation arms (around 8 weeks); however, the median time from completion of RT to restaging was longer in the consolidation arm (28.5 weeks vs 8 weeks).⁸ The improvement in pCR after consolidation chemotherapy in TNT can be attributed to the addition of the consolidation chemotherapy, longer interval between chemoradiation and surgery, or both.

KQ3: Indications for nonoperative management (active surveillance) or local excision after definitive/preoperative chemoradiation) (Table 5)

See evidence tables in Supplementary Materials, Appendix E4, for the data supporting the recommendations for KQ3.

What are the appropriate indications and considerations of a nonoperative management (active surveillance) or local excision approach after definitive/preoperative chemoradiation?

NOM, often termed “watch-and-wait” or “watchful waiting,” has emerged as a significant paradigm shift in

the treatment of rectal cancer. Although there are no randomized trials comparing NOM with traditional trimodality therapies, there are more prospective data supporting the safety and feasibility of NOM in patients who have a cCR to neoadjuvant therapy.^{8,12,79-81} Given the potential QoL benefits noted with NOM compared with treatment incorporating TME,^{87,88} NOM offers a potentially appealing option to discuss with patients during shared decision making. OPRA was a phase 2, multicenter clinical trial where patients with cT3-4 or node-positive disease were randomized to either induction chemotherapy followed by chemoradiation or chemoradiation followed by consolidative chemotherapy.⁸ After neoadjuvant treatment, patients were restaged, and those that had a cCR or near cCR underwent NOM. Those that had an incomplete response went on to TME. Among those in the induction chemotherapy arm, 71% of patients went on to NOM, and in the consolidation chemotherapy arm, 76% of patients went on to NOM. Although the trial was not powered to compare arms, consolidation chemotherapy seemed to lead to higher rates of organ preservation than induction (5-year TME-free survival 39% in the induction versus 54% in the consolidation chemotherapy arm).¹² The results from the OPRA trial also demonstrated equivalent DFS to historical controls with the use of NOM after TNT compared with universal TME. Of all cases of tumor regrowth, 94% occurred within 2 years and 99% occurred within 3 years after restaging.¹² DFS was the same in the patients who had incomplete response and underwent immediate TME and in those patients who developed local recurrence and required salvage TME, suggesting NOM with salvage surgery did not compromise overall outcomes.¹² However, given the potential for local tumor regrowth, it is imperative that patients who opt for NOM are followed closely. Although these data are encouraging, the overall quality of evidence for NOM is considered moderate as no studies have randomized patients to NOM versus standard surgery, leading to the conditional recommendation for NOM.

An alternative organ-preserving approach for selected patients with cT2-3N0 rectal cancer is preoperative chemoradiation followed by transanal full-thickness wide local excision. This approach is particularly suitable for tumors that are distal (generally <8-10 cm from the anal verge), are <4 cm in size, and demonstrate a significant response to chemoradiation.^{37,47,86} The local excision procedure must be conducted by surgeons skilled in transanal techniques and within hospitals with experienced multidisciplinary teams. Evidence supporting this method comes from multiple phase 2 trials^{37,47} and a single phase 3 trial.⁸⁶ The GRECCAR-2 study randomized patients with T2 or T3 low (≤ 8 cm from anal verge) rectal cancer who responded well to chemoradiation (residual tumor ≤ 2 cm) to local excision versus TME.^{36,86} In the 5-year update of this study, no significant differences were

Table 5 Indications for nonoperative management or local excision after chemoradiation

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. Organ preservation through TNT followed by NOM is conditionally recommended after multidisciplinary discussion if a complete clinical response is achieved in patients with cT3-4 or cN+ rectal cancer who: • prefer an organ preservation approach, AND • will undergo close follow-up by a multidisciplinary team.	Conditional	Moderate 8,69,79-81
2. Organ preservation through neoadjuvant chemoradiation and local excision is conditionally recommended after multidisciplinary discussion if a near-complete response is achieved in patients with cT2-3N0 rectal cancer who: • have tumors in the low-to-mid rectum, maximum size 4 cm, AND • prefer an organ preservation approach, AND • will undergo close follow-up by a multidisciplinary team.	Conditional	Moderate 36,37,47
3. For patients with rectal cancer considering NOM after RT, conventional fractionation of 5000-5600 cGy in 25-31 fractions with concurrent chemotherapy is recommended.	Strong	Moderate 8,36,37,47,81
4. For patients with rectal cancer considering local excision after RT, conventional fractionation of 5000-5040 cGy in 25-28 fractions with concurrent chemotherapy is recommended.	Strong	Moderate 36,82,83
5. For patients with rectal cancer for whom NOM is a priority, concurrent chemoradiation followed by consolidation chemotherapy is recommended.	Strong	Moderate 8
6. For patients with rectal cancer considering NOM, assessment for response is recommended by pelvic MRI with rectal protocol, CT abdomen/pelvis, and proctoscopy/sigmoidoscopy with DRE 2-3 months after completion of treatment. (<i>Unchanged from 2020 guideline</i>)	Strong	Moderate 8,12,36,80,82-86
7. For patients with rectal cancer undergoing NOM or local excision, active surveillance is recommended with: • proctoscopy/sigmoidoscopy with DRE every 3-4 months for the first 2 years, then every 6-12 months, AND • pelvic MRI with rectal protocol every 3-6 months for the first 2 years, then every 6-12 months, AND • CT of the chest, abdomen, and pelvis every 6-12 months for the first 2 years, then every 12 months. Implementation remark: Continue follow-up for a minimum of 5 years. (<i>Unchanged from 2020 guideline</i>)	Strong	Moderate 8,36,37,80,83-86
Abbreviations: CT = computed tomography; DRE = digital rectal examination; KQ = key question; MRI = magnetic resonance imaging; NOM = non-operative management; RT = radiation therapy; TNT = total neoadjuvant therapy.		

detected between the arms in terms of local control (7% vs 7%), DFS (70% vs 72%), and overall survival (84% vs 82%), with the caveat that 35% of patients in the local excision group required completion of TME per protocol for ypT2-3 disease.⁸⁶ Therefore, for patients with cT2-3N0 rectal cancer who have a near cCR to chemoradiation, organ preservation through transanal local excision is conditionally recommended. Among patients with cT2N0 disease who achieve a cCR to chemoradiation, NOM with close surveillance with a multidisciplinary team may be reasonable, although data for this select cohort is limited.⁴⁹

Some studies have reported significant complications and poor functional outcomes with local excision with completion TME after chemoradiation for ypT2-3 tumors.^{37,86} Consequently, extrapolating from the data supporting NOM after TNT,^{12,88} for patients who have a cCR, omission of surgery is favored over local excision. However, to date, there have been no studies directly comparing local excision with omission of surgery in this patient population. An alternative organ-sparing approach was evaluated in a phase 2 trial in which patients with early-stage rectal cancer were treated with induction chemotherapy followed by local excision.⁸⁹

In the OPRA trial, 5000 to 5600 cGy was delivered using conventional fractionation to the primary tumor and involved nodes with either a SIB and/or a sequential boost; therefore, this dose range is recommended for patients considering NOM after TNT.⁸ Intensity modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) may be beneficial in patients undergoing dose escalation to protect normal structures. Commonly used approaches for dose escalation in patients considering NOM include (1) initial course of 4500 cGy in 25 fractions to the pelvis, followed by sequential boost of 900 cGy in 5 fractions to the primary tumor and involved nodes, using 3-D conformal RT or IMRT/VMAT; or (2) SIB of 4500 cGy to the pelvis and 5000 cGy to the primary tumor and involved nodes, followed by sequential boost of additional 400 cGy in 2 fractions to the primary tumor and involved nodes using IMRT/VMAT. Image-guided RT may also be beneficial in patients undergoing dose escalation. Although some studies reported high rates of cCR with RT dose escalation beyond 5600 cGy, they were limited in size, demonstrated early signs of increased toxicity such as rectal bleeding, and did not report long-term patient-reported QoL outcomes.^{90,91} RT dose escalation via brachytherapy has similarly yielded high rates of organ preservation. Although brachytherapy use is beyond the scope of this guideline, a recent phase 3 RCT did show improvement in the 3-year organ preservation rate with the use of contact x-ray brachytherapy boost (9000 cGy in 3 fractions) compared with external beam RT boost (900 cGy in 5 fractions), when added to long-course chemoradiation (4500 cGy in 25 fractions).⁹² The 3-year organ preservation rate was 81% with contact brachytherapy boost and 59% with external beam RT boost for all patients and 97% with contact brachytherapy boost and 63% with external beam RT boost for patients with tumors <3 cm in size. Consensus recommendations have previously been published specifically on contact brachytherapy for rectal cancer.⁹³

In the setting of local excision, a higher rate of toxicity was noted with 5400 cGy compared with 5040 cGy.³⁷ Although this may have been because of the concurrent oxaliplatin,^{37,46,59,94} doses of 5000 to 5040 cGy are nonetheless recommended for patients considering local excision.^{36,47,95,96} Short-course RT followed by chemotherapy is not routinely recommended as part of NOM because of limited data; however, it could be considered in the setting of a clinical trial or cancer registry.⁹⁷ The ACO/ARO/AIO-18.1 phase 3 trial, which evaluates short-course RT followed by chemotherapy versus conventionally fractionated chemoradiation followed by chemotherapy, will provide insight into which approach yields superior rates of organ preservation (NCT04246684).

NOM has typically involved long-course RT with concurrent chemotherapy, either alone^{49,79-81,84,98-100} or with induction or consolidation chemotherapy.^{8,79-81,98,99,101} For cT1-2N0 patients, there are insufficient data to support the practice of additional chemotherapy before or after chemoradiation. Because the OPRA trial showed that patients with consolidation chemotherapy had higher rates of organ preservation as compared with those treated with induction chemotherapy,^{8,12} for patients with rectal cancer for whom NOM is a priority, concurrent chemoradiation followed by consolidation chemotherapy is recommended.⁸ The ongoing JANUS phase 2/3 trial (NCT05610163) is assessing the efficacy of triplet versus doublet chemotherapy in achieving cCR among patients with locally advanced rectal cancer.

The success of the NOM strategy is strongly dependent on proper patient assessment after neoadjuvant therapy and strict follow-up surveillance with multidisciplinary teams that have experience with NOM. Tumor response to neoadjuvant chemoradiation may take longer than originally thought, and patients with a near cCR may eventually convert to a full cCR.¹⁰² Therefore, response is now typically assessed 2 to 3 months after completion of neoadjuvant therapy. The definition of cCR is based on DRE, endoscopic features, and imaging studies, specifically pelvic MRI with rectal protocol.^{80,81,84,100} On MRI, complete response is characterized by a uniform dark scar on T2-weighted sequences, while restricted diffusion on diffusion-weighted imaging and intermediate T2 signal are considered indications of persistent tumor. The combination of the 3 diagnostic modalities (ie, DRE, flexible sigmoidoscopy, and MRI) can identify responders with a high degree of accuracy and should be included in the selection of patients for NOM.⁸⁴ An international consensus statement has specified the criteria for cCR or near cCR based on DRE, flexible sigmoidoscopy, and MRI.¹⁰³ The same consensus statement also did not recommend biopsy as mandatory for those with cCR or near cCR.

Organ preservation strategies are associated with risk of tumor regrowth in patients treated with NOM or local recurrence in patients treated with local excision. In the International Watch and Wait Database study, patients undergoing NOM had 25% 2-year incidence of local regrowth.¹⁰⁴ If identified promptly, many of these patients can be salvaged with curative intent surgery. Most tumor regrowth and local recurrences occur in the bowel wall and can be identified by DRE or flexible sigmoidoscopy.^{37,101} A few occur in the mesorectal nodes (<5% failure rate for those undergoing NOM) and are only identified by imaging.^{99,102} Because most tumor regrowth occurs in the first 2 years, current NOM and local excision protocols recommend DRE and flexible sigmoidoscopy every 3 to 4 months for the first 2 years and every 6 to 12 months for

the following 3 years.^{12,36,37,47,84} Pelvic MRI with rectal protocol is recommended every 3 to 6 months for the first 2 years and every 6 to 12 months for the following 3 years. Because patients treated with organ preservation are at risk of distant metastases, they should also have surveillance with CT of the chest, abdomen, and pelvis every 6 to 12 months for the first 2 years and then annually.^{8,12} The risk of local recurrence for patients who had local excision diminishes 5 years after treatment and therefore, routine imaging with MRI or CT is not usually recommended beyond that time.^{36,37} The long-term outcome of patients treated with NOM is currently unknown and therefore, enrolling in a clinical trial or registering in a long-term survivorship and surveillance program is strongly encouraged.

Conclusions and Future Directions

The landscape of rectal cancer treatment has dramatically evolved over the last decade. There are more clinically appropriate and reasonable approaches to the treatment of localized rectal cancer that exist today than ever before, which necessitates complex and nuanced multidisciplinary discussions to arrive at optimal treatment paradigms for each individual patient based on tumor characteristics, molecular profiling, and patient preferences. In the era of personalized and patient-centered medicine, clinical decision making will continue to move beyond traditional American Joint Committee on Cancer staging, incorporating additional radiographic, pathologic, and molecular features that may influence treatment recommendations. Patients and providers will ideally be able to further tailor treatment decisions, including optimal treatment sequencing and RT dose, and potentially incorporate liquid biopsies such as those for biomarker-driven response assessment, to optimize treatment outcomes and QoL while mitigating risks of treatment-related toxicities. Future studies should look to improve disparities in rectal cancer outcomes and improve access to clinical trials and representation among underrepresented minority patient populations. Lastly, with an increasing incidence of young-onset rectal cancer, these discussions are critical to balance each patient's priorities for QoL that encompasses fertility preservation, sexual health, neuropathy, bowel function, and sphincter preservation.

Disclosures

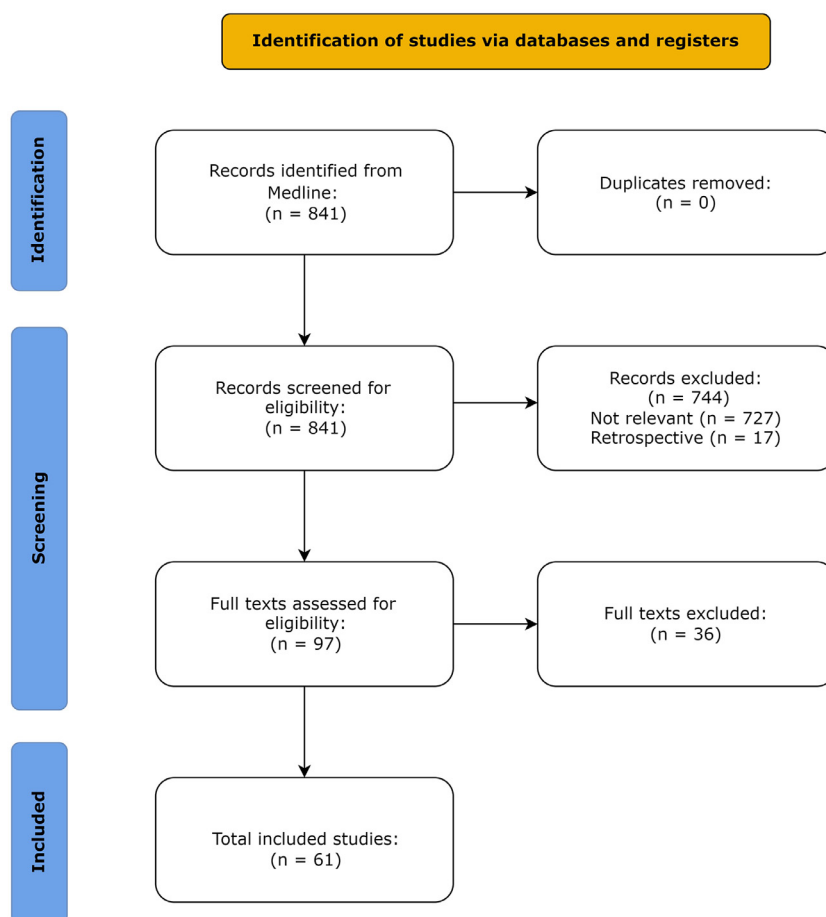
All task force members' disclosure statements were reviewed before being invited and were shared with other

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PRISMA PRISMA 2020 study selection diagram^{105,106}

Abbreviation: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Re-Publication of KQ4 Recommendations (2020) (Table 6) and Text

This section is included for ease of review by the reader; however, the information was not reviewed or modified from the 2020 guideline, given that there have been no new randomized or prospective trials on these topics.³

“What are the appropriate treatment volumes, dose constraints, and techniques for patients treated with RT?”

For patients with cT3-4 and/or cN + rectal cancers, the task force recommends including the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes in the clinical target volume (CTV). Pooled analyses have demonstrated that these sites are at increased risk of local recurrence for patients with locally advanced rectal cancer.^{107,108} For further clarification in specific clinical scenarios, international guidelines for optimal target delineation for rectal cancer are available.¹¹⁸ Generally, similar considerations should be given to treatment

volumes and treatment techniques for both conventionally fractionated chemoradiation and short-course RT.

Similar analyses have shown that if the primary tumor invades anterior structures or organs, nodal drainage may extend via the lymphatics of the involved organ.¹⁰⁸ Therefore, for patients with rectal tumors invading the prostate, seminal vesicles, cervix, vagina, and/or bladder, inclusion of the external iliac nodes in addition to the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes is conditionally recommended.

Although lesions that extend to the anal canal can spread to the inguinal and external iliac nodes, limited data supports the inclusion of these lymph node regions in the CTV for patients with rectal cancer involving the anal canal.^{108,119} While some data may suggest low rates of inguinal recurrence, for patients with rectal tumors that extend into the anal canal, inclusion of the inguinal and external iliac nodes in addition to the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes is conditionally recommended.

Table 6 Recommendations for appropriate treatment volumes and techniques

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with cT3-4 and/or cN + rectal cancers, inclusion of the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes in the CTV is recommended.	Strong	High 107,108
2. For patients with rectal tumors invading an anterior organ or structure (eg, prostate, seminal vesicles, cervix, vagina, and/or bladder), inclusion of the external iliac nodes in the CTV is conditionally recommended in addition to the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes.	Conditional	Low 108
3. For patients with rectal cancer involving the anal canal, inclusion of inguinal and external iliac nodes in the CTV is conditionally recommended in addition to the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes.	Conditional	Expert Opinion
4. For patients with rectal cancer treated with RT, an IMRT/VMAT technique is conditionally recommended. <u>Implementation remark:</u> IMRT/VMAT may be beneficial when the external iliac nodes and/or the inguinal nodes require treatment or when 3-D conformal techniques may confer a higher risk for toxicity.	Conditional	Low 109-114
5. For patients with rectal cancer receiving IMRT/VMAT, daily image guidance to verify localization is conditionally recommended.	Conditional	Expert Opinion
6. For patients with rectal cancer in whom the CTV does not include the inguinal nodes, simulation prone with a belly board is conditionally recommended.	Conditional	Low 115-117
<i>Abbreviations:</i> 3-D = 3-dimensional; CTV = clinical target volume; IMRT = intensity modulated radiation therapy; KQ = key question; RT = radiation therapy; VMAT = volumetric modulated arc therapy.		

Modulated RT techniques like intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have the potential to reduce treatment-associated side effects to bladder, large bowel, and small bowel by reducing the dose to these organs. In the RTOG 0822 phase 2 trial⁷¹ of preoperative chemoradiation, using IMRT in combination with capecitabine and oxaliplatin did not reduce the rate of gastrointestinal toxicity compared with conventional radiation in a prior trial, RTOG 0247.¹²⁰ Of note, the RTOG 0822 trial used concurrent capecitabine and oxaliplatin, which is not the current standard. A meta-analysis found that IMRT lowered the incidence of grade ≥ 2 acute toxicity for overall gastrointestinal toxicity, as well for diarrhea and proctitis.¹⁰⁹ Additional studies report that IMRT and VMAT result in reduced toxicity versus 3-dimensional conformal radiation therapy (3-D CRT).¹¹⁰⁻¹¹⁴ The effect seems to be more consistent for diarrhea and genitourinary toxicities compared with other endpoints. The use of modulated RT techniques does not appear to affect tumor control. Therefore, the task force felt the evidence of improved toxicity is sufficient to make a conditional recommendation for the use of IMRT or VMAT over 3-D CRT, particularly when the external iliac nodes with or without the inguinal nodes require treatment or when 3-D CRT techniques may confer a higher risk for toxicity.

Modern planning techniques like 3-D CRT and IMRT/VMAT produce plans that are more conformal but less

robust to daily variations in setup. This is particularly true of IMRT/VMAT because of the creation of concave dose distributions designed precisely to follow the contour of the target and spare critical structures. Recognizing the lack of published data, the task force conditionally recommends daily image guidance for patients with rectal cancer receiving IMRT/VMAT. Image guidance with volumetric imaging (eg, cone-beam and megavoltage computed tomography) can help account for differences in bladder filling, rectal filling, and movement of the small bowel. Daily alignment to bony anatomy using planar orthogonal imaging is acceptable if planning margins are sufficient to mitigate daily variations in soft tissue anatomy.

The choice of patient positioning is an important consideration in the treatment of rectal cancer.¹¹⁵⁻¹¹⁷ Patient positioning can affect the relative positions of the target and normal tissues. Furthermore, patient positioning decisions can also affect setup reproducibility during treatment. Options for patient positioning include supine and prone. The decision to treat supine or prone impacts the positioning of the peritoneal cavity and small bowel more than other organs at risk. The belly board can position abdominal organs more superiorly, displacing some of the small bowel out of the treatment field. A study of rectal cancer patients comparing prone and supine positioning showed that prone positioning with a belly board reduces overlap between the small bowel and the planning target volume, relative to supine positioning.¹¹⁷ A

separate study investigating 5 treatment planning techniques in both supine and prone positioning found that all treatment techniques provide superior sparing of organs at risk in the prone position.¹¹⁶ In the prone position, the use of a belly board reduces dose to the small bowel over a wide range of dose levels compared with not using a belly board.¹¹⁵ The superiority of prone treatment with a belly board has been established in terms of dosimetric indices and differences in overlap between the target and organs at risk, but not in terms of patient outcomes. The limitations of these studies notwithstanding, the evidence is sufficient to make a conditional recommendation of simulation in the prone position with a belly board. However, in patients treated with IMRT/VMAT or with a colostomy, a supine position may also be suitable, particularly for patients whose CTV includes the inguinal lymph nodes. Regardless of whether a patient is treated in the supine or prone position, treating with a full bladder may further decrease dose to the small bowel.

Based on the available evidence, the task force was not able to provide specific recommendations regarding dose constraints. Additional treatment-planning studies are needed to identify optimal dose constraints to minimize treatment toxicity.”

Supplementary materials

Supplementary material associated with this article can be found in the online version at [doi:10.1016/j.prro.2024.11.003](https://doi.org/10.1016/j.prro.2024.11.003).

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