DRAFT – Public Comment

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

Source of support: This work was funded by the American Society for Radiation Oncology.

Disclaimer and Adherence: American Society for Radiation Oncology (ASTRO) guidelines present scientific, health, and safety information and may reflect scientific or medical opinion. They are available to ASTRO members and the public for educational and informational purposes only. Commercial use of any content in this guideline without the prior written consent of ASTRO is strictly prohibited.

Adherence to this guideline does not ensure successful treatment in every situation. This guideline should not be deemed inclusive of all proper methods of care or of all factors influencing the treatment decision, nor is it intended to be exclusive of other methods reasonably directed to obtaining the same results. ASTRO assumes no liability for the information, conclusions, and findings contained in its guidelines. This guideline cannot be assumed to apply to the use of these interventions performed in the context of clinical trials. This guideline is based on information available at the time the task force conducted its research and discussions on this topic. There may be new developments that are not reflected in this guideline and that may, over time, be a basis for ASTRO to revisit and update the guideline.

Table of Contents

Abstract **3**
Preamble **4**
1. Introduction **6**
2. Methods **6**
2.1. Task force composition 6
2.2. Document review and approval 7
2.3. Evidence review 7
2.4. Scope of the guideline 8
3. Key Questions and Recommendations **9**
3.1. KQ1: Indications for neoadjuvant RT (Table 3) 9
3.2. KQ2: Appropriate neoadjuvant regimens (Table 4) 12
3.3. KQ3: Indications for nonoperative (active surveillance) or local excision after definitive/preoperative chemoradiation) (Table 5) 16
4. Conclusions and Future Directions **20**
5. Acknowledgments **21**
Figure PRISMA 2020 Study Selection Diagram[93,94] **22**
References **23**
Appendix E1 Peer Reviewers and Disclosures (Comprehensive) **27**
Appendix E2 Abbreviations **27**
Appendix E3 PICOTS Questions / Literature Search Strategy **28**

Abstract

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 (ASTRO) 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 upfront surgery or neoadjuvant chemotherapy with a favorable treatment response. For patients with T3-T4 or node positive rectal cancer undergoing neoadjuvant therapy, 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 has 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 sequencing and treatment regimens to allow for more personalized recommendations based on individual risk stratification and treatment priorities towards improvement in quality of life.

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 **P**opulation, **I**ntervention, **C**omparator, **O**utcome, **T**iming, **S**etting (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 ≥75% (≥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.

Abbreviations: ASTRO = American Society for Radiation Oncology; QoE = quality of evidence; RCTs = randomized controlled trials.

*A lower quality of evidence, 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.

1. Introduction

Since the prior publication of the ASTRO clinical practice guideline, "Radiation Therapy for Rectal Cancer" in 2020,[3] large, randomized controlled trials (RCTs) have been published which challenge existing treatment paradigms. While neoadjuvant chemoradiation followed by total mesorectal excision (TME) and adjuvant chemotherapy was the prior standard of care,[4,5] more recent studies have explored both treatment intensification with the goal of improving disease outcomes, and also 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. 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. 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 guidelines and provide evidence-based recommendations for 3 clinical KQs regarding the use of RT for rectal cancer.

2. Methods

2.1. Task force composition

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

2.2. Document review and approval

The guideline update was reviewed by XX official peer reviewers (Appendix E1) and revised accordingly. The modified guideline was posted on the ASTRO website for public comment from May-June 2024. The final guideline was approved by the ASTRO Board of Directors and endorsed by the TBD.

2.3. Evidence review

ASTRO's guideline methodology includes the ability to publish 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 through 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 cancer. 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 including abstract only, 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]

2.4. Scope of the guideline

The scope of this focused update is existing treatment paradigms for localized rectal cancer. The impetus for this focused update is to primarily incorporate new practice-changing data on TNT, including different treatment sequencing and RT fractionation regimens which 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 standalone document and to serve as an update to KQs 1, 2, and 3. All recommendations (new, modified, and unchanged) 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 so consult the full-text version of the 2020 guideline for recommendations, text, and evidence tables supporting the unchanged recommendations and for clinical areas not addressed in this focused update.[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 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.

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 long-course chemoRT followed by surgery and postop chemo • Neoadjuvant strategy with long interval to surgery	• Overall survival • Local control • Disease-free survival • Pathologic complete response • Sphincter preservation • Acute and late grade ≥3 toxicity

		• Neoadjuvant strategy with short interval to surgery		
3	What are the appropriate indications for consideration of a nonoperative (active surveillance) or local excision approach after definitive/preoperative chemoradiation? **(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? **(Not updated, refer to 2020 guideline)[3]**			

Abbreviations: 3-D CRT= 3-dimensional conformal radiation therapy; chemo = chemotherapy; chemoRT = chemoradiation; CT = computed tomography; GI = gastrointestinal; HR-QoL = health-related quality of life; IMRT = intensity modulated radiation therapy; KQs = key questions; MRI = magnetic resonance imaging; PICO = Population, Intervention, Comparator, Outcome; preop = preoperative; postop = postoperative; RT = radiation therapy; TME = total mesorectal excision; VMAT = volumetric modulated arc therapy.

3. Key Questions and Recommendations

3.1. 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 radiation therapy for operable rectal cancer?

Table 3 Indications for neoadjuvant RT

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence
1. For patients with rectal cancer, pelvic MRI with a rectal cancer protocol is recommended for preoperative clinical T and N staging.	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.	Strong	High [5,19-25]
4. For patients with rectal cancer at lower risk of locoregional recurrence, omission of neoadjuvant RT is conditionally recommended for those undergoing: A. upfront surgery **OR**	Conditional	Moderate (A) [16,26-28]

B. neoadjuvant chemotherapy with a favorable response Implementation remark: Lower risk is defined as a cT2/T3a/b* N0-1 tumor >5 cm from the anal verge and with mrCRM ≥2 mm and no mrEMVI.		Moderate (B) 9,29-34
5. 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	Moderate 11,17,18
6. For patients with rectal cancer who wish to pursue nonoperative management, RT is recommended as part of a TNT regimen.	Strong	Moderate 8
7. For patients with cT1-2N0 rectal cancer who may need an APR, neoadjuvant RT is conditionally recommended to improve the chance of sphincter preservation.	Conditional	Expert Opinion
8. For patients with rectal cancer where radiation is indicated, RT should be performed preoperatively rather than postoperatively.	Strong	High 4,5,20,21,35,36

Abbreviations: APR = abdominoperineal resection; MMRd = mismatch repair deficient; KQ = key question; MMR = mismatch repair; mrEMVI = MRI-determined extramural vascular invasion; MRI = magnetic resonance imaging; MSI = microsatellite instability; MSI-H = microsatellite instability-high; RT = radiation therapy; TNT = total neoadjuvant therapy. *cT3a/b = 1 to 5 mm extramural tumor spread; tumor height should be surgeon defined.

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.[5,19-25,37] 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. The history and physical 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; proximal ≥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 a rectal cancer protocol has become central to selecting the appropriate treatment pathway. For patients without a contraindication, the recommendation for MRI staging of all patients remains unchanged.[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.[26,27,38,39] 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.[9,31,32,34]

It is now clear that patients with stage II or III rectal adenocarcinoma must be stratified into lower or higher risk groups. The most critical risk factor is the pretreatment, MRI-defined relationship of the disease to the mesorectal fascia/circumferential resection margin (mrCRM). In this guideline, lower risk patients are defined as having the mrCRM free of tumor or lymph node by ≥2 mm. Patients who are staged cT2 or T3a/b

and are >5 cm proximal to anal verge are at lower risk of locoregional recurrence (LRR). Patients lacking bulky nodal disease and without MRI-defined extramural vascular invasion are also considered low risk.[38]

Patients at lower risk of recurrence may be treated sufficiently with primary surgery without any neoadjuvant therapy. The OCUM (Optimal Surgery and MRI-Based Radiochemotherapy in Rectal Carcinoma) trial has now reported final and mature results.[26] In this prospective nonrandomized trial, patients with clear mrCRM excluding low tumors or T4 disease were treated with surgery alone 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 to preoperative short-course RT compared with surgery alone in either MRI-defined low-risk or high-risk cohorts.[39] A meta-analysis has also supported the option of surgery alone in patients with proximal rectal cancers.[28]

Select patients may be treated with neoadjuvant chemotherapy followed by surgery with omission of preoperative RT. 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.[37] Eligibility and subsequent treatment decision making were based on MRI staging (although endorectal ultrasound was allowed in the absence of available MRI). Omission of RT was based on a favorable response to neoadjuvant FOLFOX as defined as at least a 20% decrease in the size of the primary tumor after imaging and physical exam with proctoscopy by the primary surgeon. 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.[37] Subsequent analysis of patient-reported outcomes demonstrated the differences in toxicities that would be expected when comparing pelvic RT to intensive chemotherapy.[40] 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 almost identical trial design which has only presented initial results supporting the use of neoadjuvant chemotherapy and selective omission of RT.[31] Two phase 2 trials with similar protocol designs also reported results consistent with the PROSPECT trial.[29,30,34] 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.[9,16,26-34] 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. 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, T2/T3 N1 disease) may benefit from neoadjuvant chemotherapy rather than upfront surgery.

While 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. As discussed later, the OPRA trial has strengthened the evidence supporting NOM for patients achieving a complete clinical response (cCR) after TNT.[8] Even for patients with stage I rectal cancer who may need an abdominoperineal resection, neoadjuvant chemoradiation is conditionally recommended despite these patients not being included in prospective clinical trials.[4,35,36]

Molecular profiling has identified an important subset of cancers that may not require RT or surgery. Although lacking in randomized data and including only small numbers of patients, 2 prospective trials have observed extraordinarily high response rates to immune checkpoint inhibitors alone in patients whose tumors express MMRd or MSI-H status.[11,17] 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] Based on these data, initial treatment with immune checkpoint inhibitors alone are recommended for these patients followed by response assessment.[11,17,18] For patients with cCR omission of RT and surgery may be considered. 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.[9,14,32] With these increasing options, selection of a treatment pathway must be based on multidisciplinary discussion and consideration of the patient's individual goals and preferences.

3.2. 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?

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 chemoradiation with conventional fractionation, 5000-5600 cGy in 25-30 fractions with concurrent chemotherapy is recommended. Implementation remark: A prescribed dose >5040 cGy is preferred only for patients who may be considered for future nonoperative management.	Strong	High [5,8,41-45]

2. For patients with rectal cancer receiving neoadjuvant short-course RT, 2500 cGy in 5 fractions without concurrent chemotherapy is recommended.	Strong	High [6,19,22,46]
3. For patients with T3-T4 or node positive rectal cancer undergoing neoadjuvant therapy, a TNT approach is recommended.	Strong	High [6,10,14,47-54]
4. For patients with rectal cancer undergoing neoadjuvant therapy **without** tumor factors that portend increased local recurrence risk, chemotherapy before or after long-course chemoradiation, or after short-course RT is recommended. Implementation remark: Risk factors for increased local recurrence include cT3 tumors in the low rectum; mrCRM <2 mm; cT4 tumor; presence of mrEMVI; or lateral pelvic lymph nodes.	Strong	High [6,10,14,50-54]
5. 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. Implementation remark: Risk factors for increased local recurrence include cT3 tumors in the low rectum; mrCRM <2 mm; cT4 tumor; presence of mrEMVI; or lateral pelvic lymph nodes.	Strong	High [7,8,50,55]
6. 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. Implementation remark: Risk factors for increased local recurrence include cT3 tumors in the low rectum; mrCRM <2 mm; cT4 tumor; presence of mrEMVI; or lateral pelvic lymph nodes.	Conditional	Moderate [7]
7. 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. Implementation remark: Use mFOLFIRINOX with caution for elderly patients.	Strong	High [6,10,14,47-54]

Abbreviations: CAPOX = capecitabine and oxaliplatin; mFOLFOX = modified folinic acid, 5-Fluorouracil, and oxaliplatin; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; RT = radiation therapy; TNT = total neoadjuvant therapy.

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.[9,35,56,57] For patients being considered for NOM, the primary tumor can be treated with a sequential boost 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 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.[6,7] 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.[10,58] RAPIDO compared neoadjuvant short-course RT followed by CAPOX or FOLFOX4 chemotherapy to neoadjuvant chemoradiation and optional adjuvant chemotherapy.[6] When compared with the standard arm, 3-year disease-related treatment failure was improved for the TNT arm.[10] The STELLAR trial also evaluated TNT using short-course RT followed by CAPOX before surgery, compared with long-course chemoradiation followed by surgery.[49] The 3-year overall survival was improved for the TNT arm, although the reason for this improvement is unclear given similar LRR, DFS, and distant metastasis-free survival outcomes between the study arms.[49] 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 similarly 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.

The sequencing of chemotherapy relative to chemoradiation was evaluated in both the OPRA and CAO/ARO/AIO-12 studies.[8,12,55] 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.[8,12] After therapy patients went on to NOM if a cCR or near cCR was achieved. At median follow-up of 3 years there was no difference 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 to 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 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 and/or node-positive rectal adenocarcinoma received long-course chemoradiation with randomization to either induction or consolidation FOLFOX.[55] 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 difference in DFS was 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 increased rate of cCR and TME-free survival with this approach in OPRA.[8,12] For patients receiving TNT with 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,[59-62] 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 for the RAPIDO trial with 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. 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.[14,48,50-53] 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. For such patients with factors that portend increased local recurrence risk, 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.[7] 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.[12,55] 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. The use of TNT is associated with lower toxicity than

adjuvant chemotherapy.[54] 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 ≥ 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]

Prior to 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 cancer;[5] however, the optimal interval between completion of neoadjuvant chemoradiation and surgical resection remains uncertain,[63,64] 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 prior to long-course chemoradiation and planned resection. The optimal time 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 start of treatment to surgery/end of RT to surgery was approximately 24/23, and 21/20 weeks respectively.[6,49] In the consolidation arm of the OPRA trial, the time from start of treatment to surgery/end of RT to surgery was more than 34/28.5 weeks respectively.[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.

3.3. KQ3: Indications for nonoperative (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 for consideration of a nonoperative (active surveillance) or local excision approach after definitive/preoperative chemoradiation?

Table 5 Indications for nonoperative (active surveillance) or local excision after definitive/preoperative 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	Conditional	Moderate [8,55,65-68]

clinical response is achieved in patients with cT3-4 or any T, N+ rectal cancer who: • prefer an organ preservation approach, AND • undergo close follow-up by a multidisciplinary team.		
2. Organ preservation through neoadjuvant chemoradiation +/- local excision is conditionally recommended after multidisciplinary discussion if a near-complete response or 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 • undergo close follow-up by a multidisciplinary team.	Conditional	Moderate 69-71
3. For patients with rectal cancer considering NOM after RT, conventional fractionation of 5000-5600 cGy in 25-30 fractions with concurrent chemotherapy is recommended.	Strong	Moderate 68-71
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 69,72,73
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 with rectal protocol MRI, CT abdomen/pelvis, and proctoscopy/sigmoidoscopy with DRE 2-3 months after completion of treatment.	Strong	Moderate[8,12,67,69,72-76]
7. For patients with rectal cancer undergoing NOM or local excision, surveillance is recommended with: • proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6-12 months, AND • rectal protocol MRI every 3-6 months for the first 2 years, then every 6-12 months, AND • cross-sectional imaging 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.	Strong	Moderate 8,67,69,70,73-76

Abbreviations: CT = computed tomography; DRE = digital rectal examination; KQ = key question; MRI = magnetic resonance imaging; NOM = nonoperative management; RT = radiation therapy; TNT = total neoadjuvant therapy.

NOM, often termed "watch-and-wait" or "watchful waiting," has emerged as a significant paradigm shift in the treatment of rectal cancer. While there are no randomized trials comparing NOM with traditional trimodality therapies, there are increasing data indicating the safety and feasibility of NOM in patients who

have a cCR to neoadjuvant therapy.[8,12,66-68] Given the potential QoL benefits noted with NOM compared with treatment incorporating TME,[65,77] NOM offers a potentially appealing option to discuss with patients during shared decision-making. OPRA was a phase 2, multicenter clinical trial where patients 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 complete response 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 watchful waiting, 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] The DFS was the same in the patients who had incomplete response and underwent immediate TME and 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 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, exhibit favorable histology, and demonstrate a significant response to chemoradiation.[70,71,76] 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[70,71] and a single phase 3 trial.[76] 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.[69,76] In the 5-year update of this study, no significant differences were 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 group required completion of TME per protocol for ypT2-3 disease.[76] Therefore, for patients with cT2-3N0 rectal cancer who respond favorably to chemoradiation, organ preservation through transanal local excision is conditionally recommended.

Some studies have reported significant complications and poor functional outcomes with local excision after chemoradiation for ypT2-3 tumors.[70,76] Consequently, extrapolating from the data supporting NOM after

TNT,[12,77] 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 to omission of surgery in this patient population.

In the OPRA trial, 5000 to 5600 cGy was delivered using conventional fractionation to the primary tumor and involved nodes with either a simultaneous integrated boost and/or a sequential boost; therefore, this dose range is recommended for patients considering NOM after TNT.[8] While some studies report high rates of cCR with RT dose escalation, they have been limited in size, demonstrate early signs of increased toxicity such as rectal bleeding, and do not report long-term patient-reported QoL outcomes.[78,79] RT dose escalation via brachytherapy has similarly yielded high rates of organ preservation. While brachytherapy use is beyond the scope of this guideline, a recent RCT did show improvement in the 3-year organ preservation rate with the use of contact x-ray brachytherapy boost, compared to external beam RT boost.[80]

In the setting of local excision, a higher rate of toxicity was noted with 5400 cGy compared with 5040 cGy.[70] Although this may have been because of the concurrent oxaliplatin,[70,81-83] doses between 5000 to 5400 cGy are nonetheless recommended for patients considering local excision.[69,71,84,85] 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.[86] 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[66-68,74,87-90] or with induction or consolidation chemotherapy.[66-68,87,88,91] For cT1-2N0 patients, there are insufficient data to support the practice of additional chemotherapy before or after chemoradiation. Since 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 II/III 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. Tumor response to neoadjuvant chemoradiation may take longer than originally thought, and patients with a near cCR may eventually convert to a full cCR.[92] 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 rectal protocol MRI.[67,68,74,90] 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)

is able to identify responders with a high degree of accuracy and should be included in the selection of patients for NOM.[74]

Organ preservation strategies are associated with increased risk of tumor regrowth in patients treated with NOM, or local recurrence in patients treated with local excision. 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 and/or flexible sigmoidoscopy.[70,91] A few occur in the mesorectal nodes (<5% failure rate for those undergoing NOM) and are only identified by imaging.[88,92] As most tumor regrowth occurs in the first 2 years, current NOM and local excision protocols recommend DRE and flexible sigmoidoscopy every 3 months for the first 2 years and every 6 to 12 months for the following 3 years.[12,69-71,74] Rectal protocol MRI is recommended every 3 to 6 months for the first 2 years and every 6 to 12 months for at least the following 3 years. In selected cases, endorectal ultrasound may provide better visualization than MRI. As patients treated with organ preservation are at risk of distant metastases, they should also have surveillance with cross-sectional imaging 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 is not usually recommended beyond that time.[69,70] The long-term outcome of patients treated with NOM is currently unknown, and therefore, enrolling on a clinical trial or registering in a long-term survivorship and surveillance program is strongly encouraged.

4. 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 which may influence treatment decisions 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 trial access and representation among underrepresented minority patient populations. Lastly, with an increasing incidence of young onset rectal cancer, these discussions are critical to balance each patients' 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 task force members throughout the guideline's development. Those disclosures are published within this guideline. Where potential conflicts were detected, remedial measures to address them were taken.

Author 1: Varian (travel); **Author 2**: National Cancer Institute (rectal anal task force chair); **Author 3:** SSO (colorectal disease site work group chair); **Author 4:** Cancer Research UK City of London RadNet Centre (grant director); **Author 5:** Cancer Prevention and Research Institute of Texas (other-public health peer review panel), Fight Colorectal Cancer (ambassador-ended 5/2023); **Author 6**: *International Journal of Radiation Oncology, Biology, and Physics* (gastrointestinal [GI] section editor-ended 12/2023), ASTRO Radiation Oncology Healthcare Advisory Council (consultant); **Author 7:** Merck (research-PI), UpToDate (section editor), Varian (research-PI); **Author 8**: Intelligent Automation (research-PI-ended 9/2023), ViewRay (research-site PI-ended 10/2023); **Author 9:** Amgen (honoraria/meeting faculty-ended 5/2023), ASCO (GI guideline chair), Astellas (consultant-ended 7/2023), *European Society for Medical Oncology Gastrointestinal Oncology* (editorial board), Merck (honoraria/meeting faculty-ended 6/2023); **Author 10:** Alpha Tau (research-site PI), *ASTROnews* (editorial board), Iowa-Wide Oncology Research Coalition (grant review board); **Author 11**: Cigna, CVS Aetna, Johnson and Johnson, Merck, Organon, Pfizer, United Healthcare, Vertex, Viatris (all stocks); **Author 12:** ASTRO (GI scientific cmt, vice chair), Genentech (institutional research-PI). The 6 other authors reported no disclosures.

5. Acknowledgments

We are grateful to Yimin Geng, MSLIS, MS, the University of Texas-MD Anderson Cancer Center research medical librarian, for her assistance with creating the search strategy for this guideline. The task force also thanks Abhishek Kumar, MD, MAS, and Aaron Seo, MD, PhD, for literature review assistance.

The task force thanks the peer reviewers for their comments and time spent reviewing the guideline. See Appendix E1 for their names and disclosures.

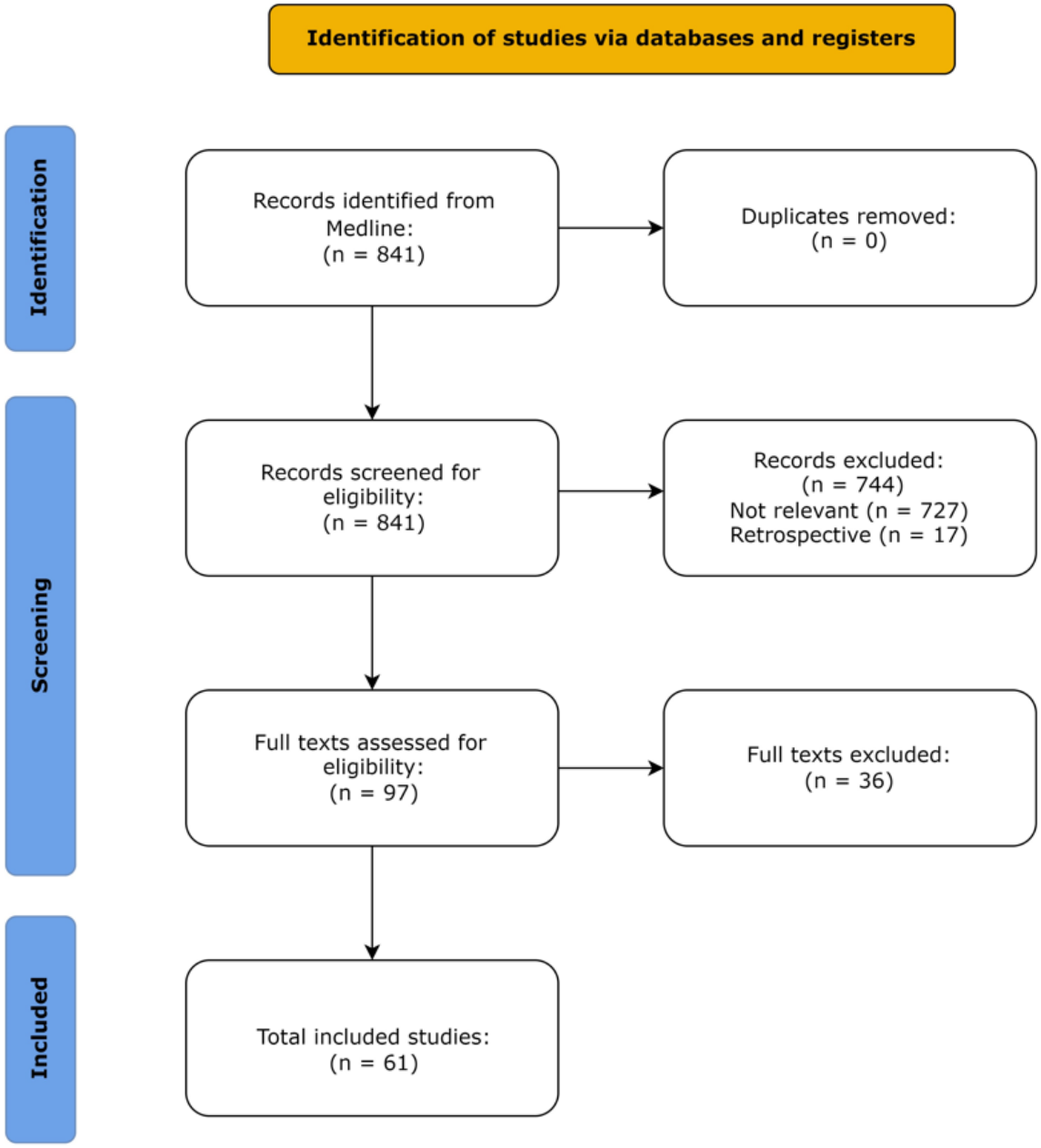

Figure PRISMA 2020 Study Selection Diagram[93,94]

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

References

1. Institute of Medicine (US) Committee on Standards for Developing Trustworthy Clinical Practice Guidelines. In: Graham R MM, Miller Wolman D, et al. *Clinical Practice Guidelines We Can Trust.* National Academies Press (US); 2011.
2. Institute of Medicine (US) Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Eden J LL, Berg A, et al. *Finding What Works in Health Care: Standards for Systematic Reviews.* National Academies Press; 2011.
3. Wo JY, Anker CJ, Ashman JB, et al. Radiation Therapy for Rectal Cancer: Executive Summary of an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol.* 2021;11(1):13-25.
4. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med.* 2004;351(17):1731-1740.
5. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol.* 2012;30(16):1926-1933.
6. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(1):29-42.
7. Dijkstra EA, Nilsson PJ, Hospers GAP, et al. Locoregional Failure During and After Short-course Radiotherapy Followed by Chemotherapy and Surgery Compared With Long-course Chemoradiotherapy and Surgery: A 5-Year Follow-up of the RAPIDO Trial. *Ann Surg.* 2023;278(4):e766-e772.
8. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. *J Clin Oncol.* 2022;40(23):2546-2556.
9. Schrag D, Shi Q, Weiser MR, et al. Preoperative Treatment of Locally Advanced Rectal Cancer. *N Engl J Med.* 2023;389(4):322-334.
10. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22(5):702-715.
11. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N Engl J Med.* 2022;386(25):2363-2376.
12. Verheij FS, Omer DM, Williams H, et al. Long-Term Results of Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy: The Randomized Phase II OPRA Trial. *J Clin Oncol.* 2024;42(5):500-506.
13. Battersby NJ, How P, Moran B, et al. Prospective Validation of a Low Rectal Cancer Magnetic Resonance Imaging Staging System and Development of a Local Recurrence Risk Stratification Model: The MERCURY II Study. *Ann Surg.* 2016;263(4):751-760.
14. Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. *Lancet Oncol.* 2010;11(3):241-248.
15. Ruppert R, Junginger T. Oncological outcome after MRI-based selection for neoadjuvant chemoradiotherapy in the OCUM Rectal Cancer Trial. *Br J Surg* 2018;105(11):1519-1529.
16. Taylor FG, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *J Clin Oncol.* 2014;32(1):34-43.
17. Chen G, Jin Y, Guan WL, et al. Neoadjuvant PD-1 blockade with sintilimab in mismatch-repair deficient, locally advanced rectal cancer: an open-label, single-centre phase 2 study. *Lancet Gastroenterol Hepatol.* 2023;8(5):422-431.
18. Bando H, Tsukada Y, Inamori K, et al. Preoperative Chemoradiotherapy plus Nivolumab before Surgery in Patients with Microsatellite Stable and Microsatellite Instability-High Locally Advanced Rectal Cancer. *Clin Cancer Res.* 2022;28(6):1136-1146.
19. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol.* 2005;23(24):5644-5650.
20. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol.* 2009;27(31):5124-5130.

21. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet.* 2009;373(9666):811-820.
22. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol.* 2011;12(6):575-582.
23. Abraha I, Aristei C, Palumbo I, et al. Preoperative radiotherapy and curative surgery for the management of localised rectal carcinoma. *The Cochrane database of systematic reviews.* 2018;10:Cd002102.
24. Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: A meta-analysis. *JAMA : the journal of the American Medical Association.* 2000;284(8):1008-1015.
25. Rahbari NN, Elbers H, Askoxylakis V, et al. Neoadjuvant radiotherapy for rectal cancer: meta-analysis of randomized controlled trials. *Ann Surg Oncol.* 2013;20(13):4169-4182.
26. Ruppert R, Junginger T, Kube R, et al. Risk-Adapted Neoadjuvant Chemoradiotherapy in Rectal Cancer: Final Report of the OCUM Study. *J Clin Oncol.* 2023;41(24):4025-4034.
27. Kreis ME, Ruppert R, Kube R, et al. MRI-Based Use of Neoadjuvant Chemoradiotherapy in Rectal Carcinoma: Surgical Quality and Histopathological Outcome of the OCUM Trial. *Ann Surg Oncol.* 2020;27(2):417-427.
28. Flanagan M, Clancy C, Sorensen J, et al. Neoadjuvant Short-Course Radiotherapy for Upper Third Rectal Tumors: Systematic Review and Individual Patient Data Metaanalysis of Randomized Controlled Trials. *Ann Surg Oncol.* 2021;28(9):5238-5249.
29. Shen Y, Wu Q, Meng W, Wei M, Deng X, Wang Z. Neoadjuvant chemotherapy (CAPOX) alone for low- and intermediate-risk stage II/III rectal cancer: Long-term follow-up of a prospective single-arm study. *Eur J Surg Oncol.* 2023;49(12):107115.
30. Zhang J, Li J, Huang M, et al. Neoadjuvant Modified FOLFOXIRI With Selective Radiotherapy in Locally Advanced Rectal Cancer: Long-term Outcomes of Phase II Study and Propensity-Score-Matched Comparison With Chemoradiotherapy. *Dis Colon Rectum.* 2023;66(7):934-945.
31. Mei WJ, Wang XZ, Li YF, et al. Neoadjuvant Chemotherapy With CAPOX Versus Chemoradiation for Locally Advanced Rectal Cancer With Uninvolved Mesorectal Fascia (CONVERT): Initial Results of a Phase III Trial. *Ann Surg.* 2023;277(4):557-564.
32. Rouanet P, Rullier E, Lelong B, et al. Tailored Strategy for Locally Advanced Rectal Carcinoma (GRECCAR 4): Long-term Results From a Multicenter, Randomized, Open-Label, Phase II Trial. *Dis Colon Rectum.* 2022;65(8):986-995.
33. Deng Y, Chi P, Lan P, et al. Neoadjuvant Modified FOLFOX6 With or Without Radiation Versus Fluorouracil Plus Radiation for Locally Advanced Rectal Cancer: Final Results of the Chinese FOWARC Trial. *J Clin Oncol.* 2019;37(34):3223-3233.
34. Zhang J, Huang M, Cai Y, et al. Neoadjuvant Chemotherapy With mFOLFOXIRI Without Routine Use of Radiotherapy for Locally Advanced Rectal Cancer. *Clin Colorectal Cancer.* 2019;18(4):238-244.
35. Park JH, Yoon SM, Yu CS, Kim JH, Kim TW, Kim JC. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. *Cancer.* 2011;117(16):3703-3712.
36. Song JH, Jeong JU, Lee JH, et al. Preoperative chemoradiotherapy versus postoperative chemoradiotherapy for stage II-III resectable rectal cancer: a meta-analysis of randomized controlled trials. *Radiat Oncol J.* 2017;35(3):198-207.
37. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg.* 2007;246(5):693-701.
38. Nougaret S, Castan F, de Forges H, et al. Early MRI predictors of disease-free survival in locally advanced rectal cancer from the GRECCAR 4 trial. *Br J Surg.* 2019;106(11):1530-1541.
39. Deng X, Liu P, Jiang D, et al. Neoadjuvant Radiotherapy Versus Surgery Alone for Stage II/III Mid-low Rectal Cancer With or Without High-risk Factors: A Prospective Multicenter Stratified Randomized Trial. *Ann Surg.* 2020;272(6):1060-1069.
40. Basch E, Dueck AC, Mitchell SA, et al. Patient-Reported Outcomes During and After Treatment for Locally Advanced Rectal Cancer in the PROSPECT Trial (Alliance N1048). *J Clin Oncol.* 2023;41(21):3724-3734.
41. De Caluwe L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. *The Cochrane database of systematic reviews.* 2013;2:CD006041.

42. Fiorica F, Cartei F, Licata A, et al. Can chemotherapy concomitantly delivered with radiotherapy improve survival of patients with resectable rectal cancer? A meta-analysis of literature data. *Cancer Treat Rev.* 2010;36(7):539-549.
43. Hearn N, Atwell D, Cahill K, et al. Neoadjuvant Radiotherapy Dose Escalation in Locally Advanced Rectal Cancer: a Systematic Review and Meta-analysis of Modern Treatment Approaches and Outcomes. *Clin Oncol (R Coll Radiol).* 2021;33(1):e1-e14.
44. Verweij ME, Hoendervangers S, Couwenberg AM, et al. Impact of Dose-Escalated Chemoradiation on Quality of Life in Patients With Locally Advanced Rectal Cancer: 2-Year Follow-Up of the Randomized RECTAL-BOOST Trial. *Int J Radiat Oncol Biol Phys.* 2022;112(3):694-703.
45. Wang J, Guan Y, Gu W, et al. Long-course neoadjuvant chemoradiotherapy with versus without a concomitant boost in locally advanced rectal cancer: a randomized, multicenter, phase II trial (FDRT-002). *Radiat.* 2019;14(1):215.
46. Socha J, Kairevice L, Kepka L, et al. Should Short-Course Neoadjuvant Radiation Therapy Be Applied for Low-Lying Rectal Cancer? A Systematic Review and Meta-Analysis of the Randomized Trials. *Int J Radiat Oncol Biol Phys.* 2020;108(5):1257-1264.
47. Dijkstra EA, Hospers GAP, Kranenbarg EM, et al. Quality of life and late toxicity after short-course radiotherapy followed by chemotherapy or chemoradiotherapy for locally advanced rectal cancer - The RAPIDO trial. *Radiother Oncol.* 2022;171:69-76.
48. Donnelly M, Ryan OK, Ryan EJ, et al. Total neoadjuvant therapy versus standard neoadjuvant treatment strategies for the management of locally advanced rectal cancer: network meta-analysis of randomized clinical trials. *Br J Surg.* 2023;110(10):1316-1330.
49. Jin J, Tang Y, Hu C, et al. Multicenter, Randomized, Phase III Trial of Short-Term Radiotherapy Plus Chemotherapy Versus Long-Term Chemoradiotherapy in Locally Advanced Rectal Cancer (STELLAR). *J Clin Oncol.* 2022;40(15):1681-1692.
50. Bisschop C, van Dijk TH, Beukema JC, et al. Short-Course Radiotherapy Followed by Neoadjuvant Bevacizumab, Capecitabine, and Oxaliplatin and Subsequent Radical Treatment in Primary Stage IV Rectal Cancer: Long-Term Results of a Phase II Study. *Ann Surg Oncol.* 2017;24(9):2632-2638.
51. Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM. Optimal timing of surgery after chemoradiation for advanced rectal cancer: Preliminary results of a multicenter, nonrandomized phase II prospective trial. *Ann Surg.* 2011;254(1):97-102.
52. Gollins S, West N, Sebag-Montefiore D, et al. A prospective phase II study of pre-operative chemotherapy then short-course radiotherapy for high risk rectal cancer: COPERNICUS. 2018;119(6):697-706.
53. Markovina S, Youssef F, Roy A, et al. Improved Metastasis- and Disease-Free Survival With Preoperative Sequential Short-Course Radiation Therapy and FOLFOX Chemotherapy for Rectal Cancer Compared With Neoadjuvant Long-Course Chemoradiotherapy: Results of a Matched Pair Analysis. *Int J Radiat Oncol Biol Phys.* 2017;99(2):417-426.
54. Fernandez-Martos C, Garcia-Albeniz X, Pericay C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trialdagger. *Ann Oncol.* 2015;26(8):1722-1728.
55. Fokas E, Schlenska-Lange A, Polat B, et al. Chemoradiotherapy Plus Induction or Consolidation Chemotherapy as Total Neoadjuvant Therapy for Patients With Locally Advanced Rectal Cancer: Long-term Results of the CAO/ARO/AIO-12 Randomized Clinical Trial. *JAMA Oncol.* 2022;8(1):e215445.
56. Allegra CJ, Yothers G, O'Connell MJ, et al. Neoadjuvant 5-FU or Capecitabine Plus Radiation With or Without Oxaliplatin in Rectal Cancer Patients: A Phase III Randomized Clinical Trial. *J Natl Cancer Inst.* 2015;107(11).
57. Hong TS, Moughan J, Garofalo MC, et al. NRG Oncology Radiation Therapy Oncology Group 0822: A Phase 2 Study of Preoperative Chemoradiation Therapy Using Intensity Modulated Radiation Therapy in Combination With Capecitabine and Oxaliplatin for Patients With Locally Advanced Rectal Cancer. *Int J Radiat Oncol Biol Phys.* 2015;93(1):29-36.
58. Conroy T, Etienne P, Rio E, et al. Total neoadjuvant therapy with mFOLFIRINOX versus preoperative chemoradiation in patients with locally advanced rectal cancer: 7-year results of PRODIGE 23 phase III trial, a UNICANCER GI trial. *J Clin Oncol.* 2023;41 (abstract).
59. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol.* 2017;18(3):336-346.

60. McLachlan SA, Fisher RJ, Zalcberg J, et al. The impact on health-related quality of life in the first 12 months: A randomised comparison of preoperative short-course radiation versus long-course chemoradiation for T3 rectal cancer (Trans-Tasman Radiation Oncology Group Trial 01.04). *Eur J Cancer.* 2016;55:15-26.
61. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol.* 2012;30(31):3827-3833.
62. Pietrzak L, Bujko K, Nowacki MP, et al. Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial. *Radiother Oncol.* 2007;84(3):217-225.
63. Akgun E, Caliskan C, Bozbiyik O, et al. Randomized clinical trial of short or long interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg.* 2018;105(11):1417-1425.
64. Lefevre JH, Mineur L, Kotti S, et al. Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6). *J Clin Oncol.* 2016;34(31):3773-3780.
65. Hupkens BJP, Martens MH, Stoot JH, et al. Quality of Life in Rectal Cancer Patients After Chemoradiation: Watch-and-Wait Policy Versus Standard Resection - A Matched-Controlled Study. *Dis Colon Rectum.* 2017;60(10):1032-1040.
66. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol.* 2017;2(7):501-513.
67. Dattani M, Heald RJ, Goussous G, et al. Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Systematic Review and Pooled Analysis. *Ann Surg.* 2018;268(6):955-967.
68. Chadi SA, Malcomson L, Ensor J, et al. Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis. *Lancet Gastroenterol Hepatol.* 2018;3(12):825-836.
69. Rullier E, Rouanet P, Tuech J, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2017;390(10093).
70. Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. *Lancet Oncol.* 2015;16(15):1537-1546.
71. Stijns RCH, de Graaf EJR, Punt CJA, et al. Long-term Oncological and Functional Outcomes of Chemoradiotherapy Followed by Organ-Sparing Transanal Endoscopic Microsurgery for Distal Rectal Cancer: The CARTS Study. *JAMA Surg.* 2019;154(1):47-54.
72. D'Alimonte L, Bao QR, Spolverato G, et al. Long-Term Outcomes of Local Excision Following Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer. *Ann Surg Oncol.* 2021;28(5):2801-2808.
73. Serra-Aracil X, Pericay C, Badia-Closa J, et al. Short-term outcomes of chemoradiotherapy and local excision versus total mesorectal excision in T2-T3ab,N0,M0 rectal cancer: a multicentre randomised, controlled, phase III trial (the TAU-TEM study). *Ann Oncol.* 2023;34(1):78-90.
74. Maas M, Lambregts DM, Nelemans PJ, et al. Assessment of Clinical Complete Response After Chemoradiation for Rectal Cancer with Digital Rectal Examination, Endoscopy, and MRI: Selection for Organ-Saving Treatment. *Ann Surg Oncol.* 2015;22(12):3873-3880.
75. Wang L, Zhang XY, Zhao YM, et al. Intentional Watch and Wait or Organ Preservation Surgery Following Neoadjuvant Chemoradiotherapy Plus Consolidation CAPEOX for MRI-defined Low-risk Rectal Cancer: Findings From a Prospective Phase 2 Trial (PKUCH-R01 Trial, NCT02860234). *Ann Surg.* 2023;277(4):647-654.
76. Rullier E, Vendrely V, Asselineau J, et al. Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. *Lancet Gastroenterol Hepatol.* 2020;5(5):465-474.
77. Custers PA, van der Sande ME, Grotenhuis BA, et al. Long-term Quality of Life and Functional Outcome of Patients With Rectal Cancer Following a Watch-and-Wait Approach. *JAMA Surg.* 2023;158(5):e230146.
78. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol.* 2015;16(8):919-927.
79. Gerard JP, Chapet O, Nemoz C, et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96-02 randomized trial. *J Clin Oncol.* 2004;22(12):2404-2409.
80. Gerard JP, Barbet N, Schiappa R, et al. Neoadjuvant chemoradiotherapy with radiation dose escalation with contact x-ray brachytherapy boost or external beam radiotherapy boost for organ preservation in early cT2-cT3

rectal adenocarcinoma (OPERA): a phase 3, randomised controlled trial. *Lancet Gastroenterol Hepatol.* 2023;8(4):356-367.
81. O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(18).
82. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol.* 2011;29(20):2773-2780.
83. Garcia-Aguilar J, Shi Q, Thomas CR, Jr., et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. *Ann Surg Oncol.* 2012;19(2):384-391.
84. Creavin B, Ryan E, Martin ST, et al. Organ preservation with local excision or active surveillance following chemoradiotherapy for rectal cancer. *Br J Cancer.* 2017;116(2):169-174.
85. Habr-Gama A, Lynn PB, Jorge JM, et al. Impact of Organ-Preserving Strategies on Anorectal Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. *Dis Colon Rectum.* 2016;59(4):264-269.
86. Chin RI, Roy A, Pedersen KS, et al. Clinical Complete Response in Patients With Rectal Adenocarcinoma Treated With Short-Course Radiation Therapy and Nonoperative Management. *Int J Radiat Oncol Biol Phys.* 2022;112(3):715-725.
87. Fiorica F, Trovo M, Anania G, et al. Is It Possible a Conservative Approach After Radiochemotherapy in Locally Advanced Rectal Cancer (LARC)? A Systematic Review of the Literature and Meta-analysis. *J Gastrointest Cancer.* 2019;50(1):98-108.
88. Martens MH, Maas M, Heijnen LA, et al. Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. *J Natl Cancer Inst.* 2016;108(12).
89. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? *Dis Colon Rectum.* 2013;56(10):1109-1117.
90. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg.* 2004;240(4):711-717; discussion 717-718.
91. Smith JJ, Strombom P, Chow OS, et al. Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients With a Complete Response After Neoadjuvant Therapy. *JAMA Oncol.* 2019:e185896.
92. Hupkens BJP, Maas M, Martens MH, et al. Organ Preservation in Rectal Cancer After Chemoradiation: Should We Extend the Observation Period in Patients with a Clinical Near-Complete Response? *Ann Surg Oncol.* 2018;25(1):197-203.
93. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Rev Esp Cardiol (Engl Ed).* 2021;74(9):790-799.
94. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ.* 2021;372:n160.

Appendix E1 Peer Reviewers and Disclosures (Comprehensive)

To be added after peer review

Appendix E2 Abbreviations

CAPOX = capecitabine and oxaliplatin
cGy = centigray
cCR = complete clinical response
DFS = disease-free survival
DRE = digital rectal examination

FOLFOX = folinic acid, 5-fluorouracil, and oxaliplatin
KQ = key question
LRR = locoregional recurrence
MMRd = mismatch repair deficient
MRI = magnetic resonance imaging
MSI/MSI-H = microsatellite instability/microsatellite instability-high
NOM = nonoperative management
mrCRM = MRI-determined circumferential resection margin
pCR = pathologic complete response
PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework
QoL = quality of life
RCT = randomized controlled trial
RT = radiation therapy
TME = total mesorectal excision
TNT = total neoadjuvant therapy

Appendix E3 PICOTS Questions / Literature Search Strategy

Search Limits:

Search Date(s):	10/12/23
Age Range	Adult (≥18 years old)
Language	English only
Species	Humans
Publication Types	• RCTs • Meta-analyses (of RCTs and prospective studies only) • Prospective studies with ≥50 patients or studies with biomarker selected patients (≥10 patients) (single arm, noncomparison studies included)
Timeframe	Focused update search 5/1/2019-10/20/2023

Universal Exclusion Criteria:

1. Preclinical/nonhuman studies
2. Health economics/cost analysis studies
3. Studies available in abstract only
4. Guidelines, review articles, case reports, comment or editorial
5. Pediatric patients
6. SEER and NCDB data (except potentially for health disparities data)
7. Otherwise not relevant or out of scope
8. Metastatic disease
9. Recurrent disease

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 1: What are the indications for neoadjuvant radiation therapy for operable rectal cancer?** To be addressed:

	• Patient selection based on MRI and other staging studies (e.g., how to synthesize NCCN/European/US-based risk groups) • Patients for whom chemo or immunotherapy alone may be appropriate neoadjuvant therapy • Role of pelvic RT in patients with operable rectal cancer • Patient selection based on MSI/MMR status
Definitions	• Indications: tumor location (upper rectum/rectosigmoid vs middle rectal vs lower rectal); tumor staging (T1-2N1 vs T3N0 vs T3-4N+), depth of extramural invasion (<5 mm vs ≥5 mm), threatened CRM, EMVI; MSI/MMR status • Omission of RT: neoadjuvant chemo alone vs neoadjuvant immunotherapy alone vs neoadjuvant RT
Condition or domain being studied	AJCC 8th edition stage II-III adenocarcinoma of the rectum
Participants/ population	Patients with pathologically confirmed rectal cancer
Intervention(s)/ exposure(s)	• Long-course preoperative RT • Long-course preoperative chemoRT • Short-course preoperative RT • Preoperative chemo • Preoperative immunotherapy
Comparator(s)/ control	• Surgery alone • Postoperative RT or chemoRT • Preoperative chemoRT
Outcomes: primary/critical	Overall survival, local control, disease-free survival
Outcomes: secondary/ important but not critical outcomes	• Disease-specific survival • Sphincter preservation • Acute and late grade ≥3 toxicity • HR-QoL
Timing	Any
Setting/context	Any
Study design	• Studies comparing preoperative long-course chemoRT to postoperative chemoRT or RT • Studies comparing preoperative short- course RT to surgery alone • Studies comparing preoperative short-course RT to postoperative chemoRT • Studies evaluating outcomes for patients with cT3-4 or N+ rectal cancer treated without neoadjuvant therapy • Studies comparing preoperative long-course chemoRT to preoperative chemo alone • Studies on preoperative immunotherapy • RCTs • Meta-analyses • Prospective studies with ≥50 patients or studies with biomarker selected patients (≥10 patients)
Summary of the key selection criteria	**Inclusion criteria:** Adults ≥18 years with operable rectal cancer treated with or without neoadjuvant chemoRT **Exclusion criteria:** • Patients **with operable rectal cancer receiving wide local excision alone**

855

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 2: What neoadjuvant regimens are appropriate for patients with operable rectal cancer?** To be addressed: • Short-course RT vs chemoRT, and situations where one may be preferred • Optimal integration and sequencing of chemo and RT in total neoadjuvant therapy (TNT) • Appropriate duration between completion of (chemo)radiation and surgery • Refer to KQ1 for selective chemo or immunotherapy alone for neoadjuvant therapy
Definitions	• Dose-fractionation regimens: numbers of RT fractions, dose per day, and total dose • Optimal RT treatment schema: short-course vs standard chemoRT and as part of TNT - potential impact of tumor location (upper rectum/rectosigmoid vs middle rectal vs lower rectal); tumor staging (T3 vs T4); nodal staging (N0 vs N1/2); threatened mesorectal fascia (yes vs no) • Timing of RT: upfront chemoRT vs neoadjuvant chemo followed by neoadjuvant RT vs neoadjuvant RT followed by neoadjuvant chemo • Optimal duration between RT and surgical resection: 6-8 weeks vs 11-12 weeks, and how it changes in the setting of TNT
Condition or domain being studied	AJCC 8th edition stage II-IIII adenocarcinoma of the rectum
Participants/ population	Patients with pathologically confirmed operable rectal cancer
Intervention(s)/ exposure(s)	• Preoperative short-course RT followed by surgery and postoperative chemo • Preoperative short-course RT followed by chemo followed by surgery • Preoperative chemo followed by short-course RT followed by surgery • Preoperative long-course chemoRT followed by chemo followed by surgery • Preoperative chemo followed by chemoRT followed by surgery • Neoadjuvant strategy with short interval to surgery
Comparator(s)/ control	• Preoperative long-course chemoRT followed by surgery and postoperative chemo (German rectal study arm) • Neoadjuvant strategy with long interval to surgery
Outcomes: primary/critical	Overall survival, local control, disease-free survival
Outcomes: secondary/ important but not critical outcomes	• pCR, cCR • Local control • Disease-specific survival • Sphincter preservation • Acute and late grade ≥3 toxicity • HR-QoL
Timing	Any
Setting/context	Any
Study design	• Studies comparing preoperative long-course chemoRT to short-course RT • Studies comparing preoperative chemo followed by long-course chemoRT followed by surgery vs preoperative long-course chemoRT followed by surgery followed by postoperative chemo

	• Studies comparing preoperative long-course chemoRT followed by chemo followed by surgery vs preoperative long-course chemoRT followed by surgery followed by postoperative chemo • Studies comparing preoperative chemo followed by long-course chemoRT followed by surgery vs preoperative long-course chemoRT followed by preoperative chemo followed by surgery • Studies comparing short-course RT followed by chemo followed by surgery vs preoperative long-course chemoRT followed by surgery followed by postoperative chemo • Studies comparing short interval to surgery vs long interval to surgery • RCTs • Meta-analyses • Prospective studies with ≥50 patients or studies with biomarker selected patients (≥10 patients)
Summary of the key selection criteria	**Inclusion criteria:** Adults ≥18 years with locally-advanced operable rectal cancer undergoing total mesorectal excision (TME) **Exclusion criteria:** • Patients **with operable rectal cancer receiving wide local excision alone**

856
857

Item	Details
Key Question and PICO(TSS) Framework	
Key clinical question(s)	**Key Question 3: What are the appropriate indications for consideration of a nonoperative (active surveillance) or local excision approach after definitive/preoperative chemoradiation?** To be addressed: • When a nonoperative (active surveillance) or local excision approach can be considered • Optimal integration and sequencing of therapy in a non-operative approach • Optimal methods of evaluating response and surveillance
Definitions	• Surgical approach after neoadjuvant therapy: TME vs wide local excision vs active surveillance • Neoadjuvant therapy: long-course chemoRT vs chemo followed by long-course chemoRT vs long-course chemoRT followed by chemo vs short-course RT vs short-course RT followed by chemo vs chemo followed by short-course RT vs immunotherapy for MSI patients • Optimal method/frequency of surveillance: MRI, flexible sigmoidoscopy and biopsy, restaging CT
Condition or domain being studied	AJCC 8th edition stage I-III adenocarcinoma of the rectum
Participants/ population	Patients with operable rectal cancer
Intervention(s)/ exposure(s)	1) Active surveillance 2) Local excision 3) 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

	4) method/frequency of surveillance: MRI, flexible sigmoidoscopy and biopsy, restaging CT
Comparator(s)/ control	1) TME (as comparator to active surveillance) 2) TME (as comparator to local excision) 3) Comparisons between the approaches described above 4) Other methods/frequencies of surveillance: MRI, flexible sigmoidoscopy and biopsy, restaging CT
Outcomes: primary/critical	Overall survival, local control, disease-free survival
Outcomes: secondary/ important but not critical outcomes	• pCR • cCR • TME-free survival rate • Local control/local regrowth • Disease-specific survival • Sphincter preservation • Salvage rate • Acute and late grade ≥3 toxicity • HR-QoL
Timing	Any
Setting/context	Any
Study design	• RCTs • Meta-analyses • Prospective studies with ≥50 patients or studies with biomarker selected patients (≥10 patients)
Summary of the key selection criteria	**Inclusion criteria:** Adults ≥18 years with operable rectal cancer **Exclusion criteria:** • **See universal exclusion list**

Abbreviations: cCR = clinical complete response; chemo = chemotherapy; chemoRT = chemoradiation/chemoradiotherapy; CRM = circumferential resection margin; CT = computed tomography; EMVI = extramural venous invasion; HR-QoL = health-related quality of life; MRI = magnetic resonance imaging; MSI = microsatellite instability; MMR = mismatch repair; pCR = pathological complete response; PICO = Population, Intervention, Comparator, Outcome; RT = radiation therapy; TME = total mesorectal excision; TNT = total neoadjuvant therapy.