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Clinical Practice Guideline

Radiation Therapy for Rectal Cancer: Executive Summary of an ASTRO Clinical Practice Guideline

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Abstract

Purpose: This guideline reviews the evidence and provides recommendations for the indications and appropriate technique and dose of neoadjuvant radiation therapy (RT) in the treatment of localized rectal cancer.

Methods: The American Society for Radiation Oncology convened a task force to address 4 key questions focused on the use of RT in preoperative management of operable rectal cancer. These questions included the indications for neoadjuvant RT, identification of appropriate neoadjuvant regimens, indications for consideration of a nonoperative or local excision approach after chemoradiation, and appropriate treatment volumes and techniques. Recommendations were based on a systematic literature review and created using a predefined consensus-building methodology and system for grading evidence quality and recommendation strength.

Results: Neoadjuvant RT is recommended for patients with stage II-III rectal cancer, with either conventional fractionation with concurrent 5-FU or capecitabine or short-course RT. RT should be performed preoperatively rather than postoperatively. Omission of preoperative RT is conditionally recommended in selected patients with lower risk of locoregional recurrence. Addition of chemotherapy before or after chemoradiation or after short-course RT is conditionally recommended. Nonoperative management is conditionally recommended if a clinical complete response is achieved after neoadjuvant treatment in selected patients. Inclusion of the rectum and mesorectal, presacral, internal iliac, and obturator nodes in the clinical treatment volume is recommended. In addition, inclusion of external iliac nodes is conditionally recommended in patients with tumors invading an anterior organ or structure, and inclusion of inguinal and external iliac nodes is conditionally recommended in patients with tumors involving the anal canal.

Conclusions: Based on currently published data, the American Society for Radiation Oncology task force has proposed evidence-based recommendations regarding the use of RT for rectal cancer. Future studies will look to further personalize treatment recommendations to optimize treatment outcomes and quality of life.

Preamble

As the 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 go through a rigorous 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. The complete disclosure policy for formal papers is online.

Selection of Task Force Members—The Guideline Subcommittee strives to avoid bias by selecting a multidisciplinary group of experts with variation in geographic region, gender, ethnicity, race, practice setting, and areas of expertise. 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. 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.

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 that 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, the Guideline Subcommittee will commission a replacement or reaffirmation within 5 years of publication.

Full-Text Guideline—The reader is encouraged to consult the full-text guideline supplement for the supportive text, abbreviations list, and additional information on rectal cancer because the executive summary contains limited information.

Introduction

Colorectal cancer has consistently been one of the top 3 causes of cancer incidence and mortality in the United States, with rectal adenocarcinomas representing about one-third of all colorectal cancers.[1] For many years, preoperative radiation therapy (RT) has widely been accepted as standard of care for locally advanced rectal cancer, with either standard fractionated chemoradiation (5000-5400 cGy in 180-200 cGy per fraction) or short-course RT (2500 cGy in 500 cGy per fraction). However, many questions remain about the optimal role of RT for rectal cancer, including indications, appropriate radiation regimens, role in nonoperative/local excision (LE) approaches, and treatment techniques. ASTRO previously developed a clinical document addressing some of these issues.[2] Subsequently, the treatment approach to rectal cancer has continued to evolve, with increasing interest in total neoadjuvant therapy (TNT), nonoperative management (NOM), and selective use of RT. Therefore, ASTRO commissioned a task force to formulate evidence-based recommendations for 4 clinical key questions (KQs) regarding the use of RT for rectal cancer.

Methods

Task Force Composition

The task force consisted of a multidisciplinary team of radiation, medical, and surgical oncologists; medical physicists; 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.

Document Review and Approval

The guideline was reviewed by 19 official peer reviewers and revised accordingly. The modified guideline was posted on the ASTRO website for public comment in April 2020. The final guideline was approved by the ASTRO Board of Directors and endorsed by the American College of Radiology, Canadian Association of Radiation Oncology, European Society for Radiotherapy and Oncology, the Royal Australian and New Zealand College of Radiologists, and the Society of Surgical Oncology.

Evidence Review

A systematic search of human subject studies retrieved from the database MEDLINE (through PubMed) was conducted. The inclusion criteria required studies to be published in English, from January 1999 through April 2019. It built upon a previous search of rectal cancer that included articles through July 2013 that were identified in PubMed, Embase, and the Cochrane Library. For the current guideline, the included studies evaluated adults with a diagnosis of operable primary rectal cancer treated with or without neoadjuvant therapy and either surgery or a nonoperative approach. For KQ1 and KQ2, the evidence base was restricted mostly to randomized controlled trials (RCTs) and meta-analyses. A small number of nonrandomized prospective studies with ≥50 patients were also included to address areas not covered by RCTs. For KQ3, RCTs, meta-analyses, prospective trials with ≥50 patients, and retrospective studies with ≥200 patients were included. For topics not well-addressed by prospective data, retrospective studies with ≥50 patients were considered. For KQ4, the evidence base consisted of RCTs, meta-analyses, prospective trials with ≥100 patients, retrospective studies with ≥150 patients, and dosimetric studies with ≥50 patients (≥10 patients for those looking at patient setup). The following concepts common to all KQs were searched using Medical Subject Heading (MeSH) terms and key search terms were used: rectal cancer, rectal neoplasms [MeSH], radiation; radiotherapy [MeSH], chemoradiation, chemoradiotherapy, and chemoradiotherapy [MeSH]. Additional terms specific to the KQs and hand searches supplemented the electronic searches. References selected and published in this document are representative and not all-inclusive.

All supplementary materials including the full-text guideline and evidence tables (which summarized the data used to formulate recommendations) are available at

Table 1 ASTRO recommendation grading classification system

ASTRO's recommendations are based on evaluation of multiple factors including the QoE, individual study quality, and panel consensus, all of which 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; RCT = randomized controlled trial.

* 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.

(https://doi.org/10.1016/j.prro.2020.08.004). The full-text guideline also includes Figure 1, which is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the number of articles screened, excluded, and included in the evidence review; Appendix 1 (peer reviewer's disclosure information); Appendix 2 (list of abbreviations); and Appendix 3 (literature search strategy).

Table 2 Recommendations for neoadjuvant RT indications

KQ1 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with rectal cancer, pelvic MRI with a rectal cancer protocol is recommended for preoperative clinical T and N staging.	Strong	Moderate [3-6]
2. For patients with stage II-III rectal cancer, neoadjuvant RT is recommended.	Strong	High [7-14]
3. For patients with stage II rectal cancer at lower risk of locoregional recurrence, omission of neoadjuvant RT is conditionally recommended after discussion with a multidisciplinary team. Implementation remark: Lower risk is defined as a cT3a/b N0 tumor that is >10 cm from the anal verge* and with mrCRM ≥2 mm and no mrEMVI.	Conditional	Moderate [5,6,11,15]
4. For patients with cT1-2N0 rectal cancer who may need an APR, neoadjuvant chemoradiation is conditionally recommended to improve the chance of sphincter preservation.	Conditional	Expert opinion [16-18]
5. For patients with rectal cancer where radiation is indicated, RT should be performed preoperatively rather than postoperatively.	Strong	High [8-10,16-18]

Abbreviations: APR = abdominoperineal resection; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; MRI = magnetic resonance imaging; RT = radiation therapy.
* cT3a/b = 1 to 5 mm extramural tumor spread; tumor height should be surgeon defined.

Scope of the guideline

This guideline covers only the subjects specified in the 4 KQs (see Table 2 in the full-text guideline for KQs and outcomes of interest). Outside the scope of this guideline are many other important questions that may be subjects of other guidelines, including indications, dose and technique for adjuvant therapy, RT in the setting of oligometastatic disease, locally recurrent disease, palliative RT, contact RT, proton RT, intraoperative RT, re-irradiation, and detailed discussions of surgical approaches and chemotherapy regimens.

Key Questions and Recommendations

Key Question 1: Indications for neoadjuvant RT (Table 2)

See evidence tables in supplementary materials for the data supporting recommendations for KQ1.

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

Pelvic magnetic resonance imaging (MRI) with a rectal cancer protocol is the primary imaging test recommended to determine the clinical T and N stage.[19] Endorectal ultrasound can be considered if MRI pelvis is unavailable, contraindicated, or equivocal. An important component of developing a high-quality, MRI-based rectal cancer staging protocol is the implementation of a synoptic form to ensure completeness of staging reports.[20]

For patients with clinical stage II-III rectal cancer, there is strong evidence to recommend neoadjuvant RT. Multiple prospective trials have demonstrated that neoadjuvant RT decreases the risk of local recurrence, even in the era of total mesorectal excision (TME).[7-11] These results were confirmed by several meta-analyses, which consistently found that the hazard ratio for local recurrence with RT was approximately 0.5 compared with surgery alone.[12-14]

Despite the strong evidence supporting the use of neoadjuvant RT for patients with stage II-III rectal cancer, a subset of patients may be at low risk for locoregional recurrence based on proximal tumor location and MRI-determined "safe" circumferential resection margin.[5,6,11,15] Based on this moderate evidence, a conditional recommendation may be made to omit neoadjuvant RT in favor of upfront surgery for patients in clinical stage IIA (cT3a/b N0) when the cancer is located >10 cm from the anal verge and there is a predicted circumferential resection margin ≥2 mm and the absence of extramural vascular invasion as determined by MRI with rectal cancer protocol. A critical component of this recommendation is the shared decision-making process within a multidisciplinary care team, high-quality surgical resection (ie, TME with negative margins) and follow-up of final pathologic staging to determine whether adjuvant therapy should be recommended in the setting of pathologic upstaging. Moving forward, improved stratification of risk within stage II-III rectal cancer is required to further individualize the use of neoadjuvant RT.

Sphincter preservation is a major quality of life (QoL) objective for many patients. Two phase 3 trials and a meta-analysis including those trials demonstrated that preoperative chemoradiation led to conversion of a group of patients initially deemed to require an abdominoperineal resection to low anterior resection.[16-18] Based on an extrapolation of this evidence, neoadjuvant RT (with concurrent chemotherapy) is conditionally recommended when sphincter preservation is being considered for a patient with a clinical stage I (cT1-T2 N0) tumor in a distal location. However, patients with early-stage tumors have not been shown to benefit from RT in terms of local control and preoperative RT may not result in sphincter preservation.[11]

Three prospective trials randomizing patients between preoperative and postoperative chemoradiation demonstrated improvements in disease-free survival and/or local recurrence-free survival with the preoperative approach.[8-10,16,17] Therefore, when RT is indicated for rectal cancer, the evidence strongly supports a recommendation favoring preoperative over postoperative treatment.

Key Question 2: Neoadjuvant regimens (Table 3)

See evidence tables in supplementary materials for the data supporting the recommendations for KQ2.

What are appropriate neoadjuvant regimens for operable rectal cancer when neoadjuvant therapy is indicated?

The German rectal trial[9] established reduced risk of relapse and increased rates of sphincter sparing surgery with neoadjuvant conventionally fractionated chemoradiation to 5040 cGy in 28 fractions. Doses of 5000 cGy in 200 cGy fractions have also become a standard approach based on favorable outcomes in several RCTs.[17,21,22,45] Based on these data, 5000 to 5040 cGy in 25 to 28 fractions with concurrent chemotherapy is recommended for patients undergoing neoadjuvant conventionally fractionated RT.[9,17,21,22,45]

The Swedish rectal trial[7] and Dutch rectal study,[11] as well as trials comparing neoadjuvant short-course RT to long-course chemoradiation,[32,47] establish 2500 cGy in 5 fractions without concurrent chemotherapy as a standard of care for patients undergoing neoadjuvant short-course RT. Among patients requiring neoadjuvant therapy, conventionally fractionated chemoradiation or short-course RT are recommended equally, given high-quality evidence that either approach improves local control,[7-11] and randomized studies suggesting similar efficacy and patient reported QoL outcomes for either treatment.[31,32,34,47]

Several RCTs have found no additional clinical benefit in terms of overall survival, disease-free survival, local control, pathologic complete response rate, tumor downstaging, or rates of sphincter-sparing surgery with the addition of oxaliplatin to neoadjuvant chemoradiation compared with standard 5-fluorouracil (5-FU) or capecitabine with RT.[26,27,48] Addition of oxaliplatin in these RCTs, however, was noted to markedly increase the rates of diarrhea.[27,48] Therefore, currently, there is not sufficient evidence that the addition of other agents to 5-FU or capecitabine provides clinical benefit in the neoadjuvant setting.

For patients requiring neoadjuvant therapy, use of neoadjuvant chemotherapy alone with selective use of neoadjuvant RT is an ongoing area of research to avoid the potential toxicities of pelvic RT. However, additional investigation of chemotherapy without RT is needed before a recommendation can be made for this approach outside of a clinical trial or multi-institutional registry setting.

Several studies have evaluated potential benefits of a TNT approach, where multiagent (FOLFOX (folinic acid, 5-fluorouracil, and oxaliplatin) or CAPOX (capecitabine and oxaliplatin) chemotherapy is added before or after chemoradiation or after short-course RT. Current prospective data suggest that addition of multiagent chemotherapy in the neoadjuvant setting improves downstaging[37] and tolerability[38,40] of chemotherapy compared with adjuvant treatment, while observational data suggest a possible disease-free survival benefit for TNT.[39] In this guideline, a TNT approach is conditionally recommended, but with differing qualities of evidence based on risk factors for disease recurrence.[37,40,49] Future studies will help to further establish risk stratification groups, clarify the ideal regimen for rectal cancer in the neoadjuvant setting, and clarify the optimal sequencing of chemotherapy and radiation in the setting of TNT.

The task force notes that recently published and presented studies provide additional information regarding TNT. In the 2019 publication of the German CAO/ARO/AIO-12 trial, patients treated with chemotherapy followed by chemoradiation had better compliance with chemotherapy, while patients treated with chemoradiation followed by chemotherapy had better compliance with chemoradiation and higher pCR.[49] The Rectal Cancer Followed by Preoperative Induction Therapy and Dedicated Operation (RAPIDO) trial compared preoperative chemoradiation versus preoperative, short-course radiation therapy followed by CAPOX or FOLFOX chemotherapy (*NCT01558921*). The PRODIGE 23 trial compared preoperative chemoradiation versus FOLFIRINOX chemotherapy followed by preoperative chemoradiation *(NCT0804790)*. Results from the RAPIDO and PRODIGE 23 trials have been presented but not yet published. Since all 3 of these trials were outside the

Table 3 Recommendations for neoadjuvant regimens

KQ2 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with rectal cancer receiving neoadjuvant chemoradiation, conventional fractionation from 5000-5040 cGy in 25-28 fractions with concurrent chemotherapy is recommended.	Strong	High [9,21,22]
2. For patients with rectal cancer receiving neoadjuvant short-course RT, 2500 cGy in 5 fractions without concurrent chemotherapy is recommended.	Strong	High [7,11]
3. For patients with rectal cancer undergoing neoadjuvant chemoradiation, only concurrent 5-fluorouracil or capecitabine is recommended with RT for radiosensitization.	Strong	High [21-28]
4. For patients with rectal cancer undergoing neoadjuvant therapy, chemotherapy alone (FOLFOX or CAPOX) is conditionally recommended only in the context of a clinical trial or multi-institutional registry.	Conditional	Low [29]
5. For patients with rectal cancer undergoing neoadjuvant therapy ***without*** tumor factors that portend increased recurrence risk, (1) chemoradiation or (2) short-course RT are recommended. Implementation remark: Risk factors for increased recurrence include cT3 tumors $\leq$5 cm from the anal verge or mrCRM <2 mm; cT4 tumor or cN2 disease, presence of mrEMVI.	Strong	High [7,11,30-35]
6. For patients with rectal cancer undergoing neoadjuvant therapy ***without*** tumor factors that portend increased recurrence risk, addition of multiagent (FOLFOX or CAPOX) chemotherapy (1) before or after chemoradiation or (2) after short-course RT is conditionally recommended. Implementation remark: Risk factors for increased recurrence include cT3 tumors $\leq$5 cm from the anal verge or mrCRM <2 mm; cT4 or cN2 disease, presence of mrEMVI.	Conditional	Low [4,36-40]
7. For patients with rectal cancer undergoing neoadjuvant therapy ***with*** tumor factors that portend increased recurrence risk, addition of multiagent (FOLFOX or CAPOX) chemotherapy (1) before or after chemoradiation or (2) after short-course RT is conditionally recommended. Implementation remark: Risk factors for increased recurrence include cT3 tumors $\leq$5 cm from the anal verge or mrCRM <2 mm; cT4 or cN2 disease, presence of mrEMVI.	Conditional	Moderate [4,24,36-40]
8. For patients with rectal cancer receiving neoadjuvant chemotherapy as a component of a total neoadjuvant therapy strategy, 3-4 months of either FOLFOX or CAPOX (without additional agents, targeted therapy, or immunotherapy) is recommended.	Strong	Moderate [37,40]
9. For patients with rectal cancer undergoing neoadjuvant chemoradiation with no further neoadjuvant chemotherapy planned, an interval of 6-11 weeks from the end of chemoradiation to surgery is recommended.	Strong	High ($\geq$6 weeks) [41-45] Moderate (6-11 weeks) [41-43,45]
10. For patients with rectal cancer undergoing neoadjuvant short-course RT with no further neoadjuvant chemotherapy planned, an interval of either $\leq$3 days or 4-8 weeks from the end of RT to surgery is recommended. Implementation remark: An interval of 4-8 weeks is preferred for patients who may benefit from tumor downstaging before resection.	Strong	Moderate [30,46]

Abbreviations: CAPOX = capecitabine and oxaliplatin; FOLFOX = folinic acid, 5-fluorouracil, and oxaliplatin; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; RT = radiation therapy.

inclusion criteria for this guideline, findings from these studies could not be incorporated into this guideline.

The optimal interval between completion of neoadjuvant chemoradiation and surgical resection remains uncertain.[18,43,45] As such, this guideline recommends an interval of 6 to 11 weeks between completion of chemoradiation and surgery for patients in whom no further neoadjuvant chemotherapy is planned, acknowledging that there is strong evidence for waiting ≥6 weeks and moderate evidence to support an optimal time frame within the 6 to 11 weeks window. Within this window, clinical judgment should be used to weigh the potential benefits of a longer interval to improve tumor downstaging versus the potential increase in operative complications that comes with this approach.

Traditionally, surgery was performed immediately (≤7 days) after the completion of neoadjuvant short-course RT for rectal cancer.[7,11] However, delaying surgery after short-course RT may allow for clinical downstaging before resection.[30,46] Balancing outcomes from the Stockholm III trial against the volume of data in which short-course RT is followed by immediate surgery,[7,11,30,46] a time interval of ≤3 days, or 4 to 8 weeks, between completion of short-course RT and surgical resection is recommended to allow for different clinical scenarios including the relative need for clinical downstaging.

Key Question 3: Nonoperative and local excision approaches (Table 4)

See evidence tables in supplementary materials for the data supporting the recommendations for KQ3.

Table 4 Recommendations for nonoperative or LE approaches

KQ3 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. NOM is conditionally recommended after multidisciplinary discussion if a cCR is achieved after neoadjuvant treatment in patients with rectal cancer who: a. would have a permanent colostomy or inadequate bowel continence after TME AND b. decline TME AND c. agree to close follow-up by a multidisciplinary team.	Conditional	Moderate [50-53]
2. Organ preservation through neoadjuvant chemoradiation followed by LE is conditionally recommended after multidisciplinary discussion for patients with cT2 N0 rectal cancer who: a. would have a permanent colostomy or inadequate bowel continence after TME AND b. decline TME AND c. are found to have ≤ypT1 disease and R0 margins upon LE AND d. agree to close follow-up by a multidisciplinary team.	Conditional	Moderate [54-56]
3. For patients with rectal cancer considering NOM or LE after RT, conventional fractionation from 5000-5400 cGy in 25-30 fractions with concurrent chemotherapy is recommended.	Strong	Moderate [50,54-56]
4. For patients with rectal cancer considering NOM, concurrent chemoradiation with or without induction or consolidation chemotherapy is conditionally recommended.	Conditional	Moderate [50-52,57]
5. 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 [51,54,55,58]
6. For patients with rectal cancer undergoing NOM or LE, surveillance is recommended with: • proctoscopy/sigmoidoscopy with DRE every 3 months for the first 2 years, then every 6-12 months thereafter, • rectal protocol MRI every 3-6 months for the first 2 years, then every 6-12 months thereafter, and • cross-sectional imaging of the chest, abdomen and pelvis every 6-12 months for the first 2 years, then every 12 months thereafter. Implementation remark: Follow-up should continue for a minimum of 5 years.	Strong	Moderate [51,54,55,58]

Abbreviations: cCR = complete clinical response; CT = computed tomography; DRE = digital rectal examination; LE = local excision; KQ = key question; MRI = magnetic resonance imaging; NOM = nonoperative management; RT = radiation therapy; TME = total mesorectal excision.

What are the appropriate indications for consideration of a nonoperative (NOM) or LE approach after definitive/preoperative chemoradiation?

There are increasing data indicating the safety and feasibility of NOM after a complete clinical response to neoadjuvant therapy.[50-52,59-61] However, given the rigor and nuance of the required follow-up, NOM should preferably be pursued at centers with experienced multidisciplinary teams. Given the potential QoL benefits noted with NOM compared with standard treatment[53] and patient interest in these QoL benefits,[62] NOM offers a potentially appealing option to discuss with patients during the shared decision-making process, especially for those who would have a permanent colostomy or inadequate bowel continence after total mesorectal excision (TME), and decline TME. Although data on NOM are encouraging, it is only moderate quality given the lack of RCTs comparing NOM to standard surgery, leading to the conditional recommendation for NOM.

Selected patients with cT2N0 rectal cancer may be treated with preoperative chemoradiation followed by restaging and transanal LE, instead of TME, thus allowing functional organ preservation. Ideal candidates are those with distally (<8-10 cm from the anal verge) located invasive tumors, favorable histology, and size <4 cm.[54-56] In such cases, it is critical that LE is performed by surgeons experienced with transanal LE techniques, preferably at centers with experienced multidisciplinary teams. It is important to note, however, TME conversion after LE for ypT2-3 may lead to major complications and poor functional outcomes.[54,56]

Doses between 5000 to 5400 cGy are recommended for both NOM and LE.[54,56,63,64] NOM has typically involved long-course RT with concurrent chemotherapy, either alone[50-52,58,60,65-67] or with induction or consolidation chemotherapy.[50-52,57,60,66] Although there is evidence of an increased pathologic complete response rate with a TNT approach for cT3 or node-positive patients,[55,68] given that no superiority of any chemoradiation regimen has been determined for NOM for oncologic control or QoL outcomes, all of these options are conditionally recommended. The Organ Preservation in Rectal Adenocarcinoma ([OPRA]; *NCT02008656*) trial has compared chemoradiation followed by chemotherapy versus chemotherapy followed by chemoradiation in the setting of NOM. The results from the OPRA trial have been presented but not yet published, so the findings could not be incorporated into this guideline. Longer-term, prospective, and ideally randomized data are needed to both confirm the initial oncologic and QoL results with NOM and to help determine the optimal neoadjuvant regimen.

The success of the NOM strategy is strongly dependent on proper patient assessment after neoadjuvant therapy and strict follow-up surveillance. Clinical response is typically assessed 2 to 3 months after completion of neoadjuvant therapy. The definition of complete clinical response is based on digital rectal examination (DRE), endoscopic features, and imaging studies, specifically rectal protocol MRI.[50,51,58,65] 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.[58]

Organ preservation strategies are associated with increased risk of tumor regrowth in patients treated with NOM, or local recurrence in patients treated with LE. If identified promptly, many of these patients could be salvaged with curative intent surgery. Current NOM and LE 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.[54-56,58] 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. 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.[69]

Key Question 4: Treatment volumes, dose-constraints, and techniques (Table 5)

See evidence tables in supplementary materials for the data supporting the recommendations for KQ4.

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

For patients with cT3-4 and/or cN+ rectal cancers, the task force recommends including the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes in the clinical target volume (CTV). If the primary tumor invades anterior structures or organs, nodal drainage may extend via the lymphatics of the involved organ.[71] Therefore, for patients with rectal tumors invading the prostate, seminal vesicles, cervix, vagina, and/or bladder, inclusion of the external iliac nodes in addition to the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes is conditionally recommended. Although lesions that extend to the anal canal can spread to the inguinal and external iliac nodes, limited data supports the inclusion of these lymph node regions in the CTV for patients with rectal cancer involving the anal canal.[71,81] Therefore, for patients with rectal tumors that extend into the anal canal, inclusion of the inguinal and external iliac nodes in addition to the rectum, mesorectal nodes, presacral nodes, internal

Table 5 Recommendations for appropriate treatment volumes and techniques

KQ4 Recommendations	Strength of Recommendation	Quality of Evidence (Refs)
1. For patients with cT3-4 and/or cN + rectal cancers, inclusion of the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes in the CTV is recommended.	Strong	High [70,71]
2. For patients with rectal tumors invading an anterior organ or structure (eg, prostate, seminal vesicles, cervix, vagina, and/or bladder), inclusion of the external iliac nodes in the CTV is conditionally recommended in addition to the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes.	Conditional	Low [71]
3. For patients with rectal cancer involving the anal canal, inclusion of inguinal and external iliac nodes in the CTV is conditionally recommended in addition to the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes.	Conditional	Expert opinion
4. For patients with rectal cancer treated with RT, an IMRT/VMAT technique is conditionally recommended. Implementation remark: IMRT/VMAT may be beneficial when the external iliac nodes and/or the inguinal nodes require treatment or when 3-D conformal techniques may confer a higher risk for toxicity.	Conditional	Low [72-77]
5. For patients with rectal cancer receiving IMRT/VMAT, daily image guidance to verify localization is conditionally recommended.	Conditional	Expert opinion
6. For patients with rectal cancer in whom the CTV does not include the inguinal nodes, simulation prone with a belly board is conditionally recommended.	Conditional	Low [78-80]

Abbreviations: 3-D = 3-dimensional; CTV = clinical target volume; IMRT = intensity modulated radiation therapy; KQ = key question; RT = radiation therapy; VMAT = volumetric modulated arc therapy.

iliac nodes, and obturator nodes is conditionally recommended.

Modulated RT techniques like intensity modulated radiation therapy (IMRT) and volumetric modulated arc therapy (VMAT) have the potential to reduce treatment-associated side effects to bladder, large bowel and small bowel by reducing the dose to these organs. In the RTOG 0822 phase 2 trial[82] of preoperative chemoradiation, using IMRT in combination with capecitabine and oxaliplatin did not reduce the rate of gastrointestinal toxicity compared with conventional radiation in a prior trial, RTOG 0247.[83] However, additional studies and a meta-analysis report that IMRT and VMAT result in reduced toxicity versus 3-D conformal radiation therapy.[72-77]

Modern planning techniques like 3-D conformal radiation therapy and IMRT/VMAT produce plans that are more conformal but less robust to daily variations in setup. This is particularly true of IMRT/VMAT because of the creation of concave dose distributions designed precisely to follow the contour of the target and spare critical structures. Recognizing the lack of published data, the task force conditionally recommends daily image guidance for patients with rectal cancer receiving IMRT/VMAT.

The choice of patient positioning is an important consideration in the treatment of rectal cancer.[78-80] The belly board can position abdominal organs more superiorly, displacing some of the small bowel out of the treatment field. The superiority of prone treatment with a belly board has been established in terms of dosimetric indices and differences in overlap between the target and organs at risk, but not in terms of patient outcomes. The limitations of these studies notwithstanding, the evidence is sufficient to make a conditional recommendation of simulation in the prone position with a belly board. However, in patients treated with IMRT/VMAT or with a colostomy, a supine position may also be suitable, particularly for patients whose CTV includes the inguinal lymph nodes. Regardless of whether a patient is treated in the supine or prone position, treating with a full bladder may further decrease dose to the small bowel. Additional treatment-planning studies will further identify optimal radiation treatment-planning techniques to minimize treatment toxicity.

Conclusions

Since the publication of the German Rectal Cancer Trial,[9,18] which established the role of neoadjuvant chemoradiation, TME, and adjuvant chemotherapy for locally advanced rectal cancer, the necessity and the optimal sequencing of all 3 of these treatment modalities have been challenged. In the era of personalized medicine, clinical decision making will look to move beyond traditional American Joint Committee on Cancer staging[84] to incorporate additional radiographic, pathologic, and molecular features which may influence treatment decisions to optimize treatment outcomes and QoL while mitigating risks of treatment related toxicities. Whenever possible, patient outcomes should be collected as part of clinical trials and prospective registries to strengthen the overall quality of evidence on this topic.

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Supplementary Materials

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