Radiation Therapy for Rectal Cancer: An ASTRO Clinical Practice Guideline

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Task Force Members’ Disclosure Statements

All task force members’ disclosure statements were rigorously reviewed prior to being invited and were shared with other task force members throughout the guideline’s development. Those disclosures are published within this report. Where potential conflicts were detected, remedial measures to address them were taken.

Daniel Chang: Varian (research grants, honoraria, travel expenses), Viewray (stock); Patrick Kelly: Viewray (research grants); Jeffrey Olsen: *International Journal of Radiation Oncology, Biology, Physics* (Associate Editor); Syntactx Clinical Events Committee Chair (Initiated 4.1.20, after draft development); Ann Raldow: Intelligent Automation (consultant); Karyn Stitzenberg (Society of Surgical Oncology representative): Johnson and Johnson, Merck, Pfizer, Myriad Genetics, United Healthcare, Vertex Pharmaceuticals, Mygen (all stock); Q. Jackie Wu: National Institute of Health/National Cancer Institute (research grants), Varian (research grants).

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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, beginning 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 — The 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 Population, Intervention, Comparator, Outcome, Timing, Setting (PICOTS) framework. A systematic review of the KQs is completed, which includes creation of evidence tables that summarize the evidence base task force members use to formulate recommendations. Table 1 describes ASTRO’s recommendation grading system.

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.
### 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.

<table>
<thead>
<tr>
<th>Strength of Recommendation</th>
<th>Definition</th>
<th>Overall QoE Grade</th>
<th>Recommendation Wording</th>
</tr>
</thead>
</table>
| 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” |

<table>
<thead>
<tr>
<th>Overall QoE Grade</th>
<th>Type/Quality of Study</th>
<th>Evidence Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>• 2 or more well-conducted and highly generalizable RCTs or meta-analyses of such trials.</td>
<td>The true effect is very likely to lie close to the estimate of the effect based on the body of evidence.</td>
</tr>
</tbody>
</table>
| 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.
1. Introduction

Colorectal cancer has consistently been one of the top 3 causes of cancer incidence and mortality in the United States. Rectal adenocarcinomas represent about one-third of all colorectal cancers, with an estimated incidence of 43,340 cases in the United States in 2020. The incidence of rectal cancer has been increasing among young adults, leading to heightened interest in this disease. 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. The American Society for Radiation Oncology (ASTRO) previously developed a clinical document addressing some of these issues. 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.

2. Methods

2.1. 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.

2.2. Document Review and Approval

The guideline was reviewed by 19 official peer reviewers (see Appendix 1 for the reviewer’s disclosure information) 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 TBD.
2.3. Evidence Review

A systematic search was conducted of human subject studies indexed in MEDLINE (through PubMed), 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 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 in order 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). Both Medical Subject Heading (MeSH) terms and key search terms were utilized and terms common to all searches included: 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.

The data supplement (link) includes evidence tables that summarize the data used by the task force to formulate recommendations. References selected and published in this document are representative and not all-inclusive. The outcomes of interest are listed in Table 2. See Appendix 2 for a list of abbreviations, Appendix 3 for the detailed search protocol and Figure 1 for 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.

2.4. Scope of the Guideline

This guideline covers only the subjects specified in the KQs (Table 2). 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; intra-operative RT; re-irradiation; and detailed discussions of surgical approaches and chemotherapy regimens. While outside the scope of this guideline, efforts to proactively address potential survivorship issues including fertility and sexual dysfunction should be made, especially given the increasing incidence of rectal cancer among young adults.
### Table 2. KQs in Population, Intervention, Comparator, Outcome (PICO) format

<table>
<thead>
<tr>
<th>KQ</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| 1  | What are the indications for neoadjuvant RT for operable rectal cancer? | Patients with pathologically confirmed rectal cancer | • Long-course preop RT  
• Long-course preop chemoradiation  
• Short-course preop RT | • Surgery alone  
• Postop RT | • 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? | Patients with pathologically confirmed operable rectal cancer | • Preop short-course RT followed by surgery and postop chemo  
• Preop short-course RT followed by chemo followed by surgery  
• Preop long-course chemoradiation followed by chemo followed by surgery  
• Preop chemo followed by long-course chemoradiation followed by surgery  
• Preop chemo followed by surgery  
• Neoadjuvant strategy with short interval to surgery | • Preop long-course chemoradiation 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 |
| 3  | What are the appropriate indications for consideration of a nonoperative (active surveillance) or local excision approach after definitive/preop chemoradiation? | Patients with operable rectal cancer | • Definitive chemoradiation  
• Active surveillance  
• Local excision | • Total mesorectal excision | • Overall survival  
• Local control/regrowth  
• Disease-free survival  
• Pathologic and clinical complete response  
• Sphincter preservation  
• Salvage rate  
• Acute and late grade ≥3 toxicity |
| 4  | What are the appropriate treatment volumes, dose-constraints, and techniques for patients treated with RT? | Patients with pathologically confirmed operable rectal cancer | • IMRT/VMAT  
• 3-D CRT  
• Elective LN Coverage  
• Dose escalated RT | • Standard 3-D CRT with classic pelvic fields | • Acute grade ≥3 GI toxicity  
• Local control  
• Disease-free survival  
• Acute and late grade ≥3 toxicity  
• HR-QoL |

**Abbreviations:** 3-D CRT = 3-dimensional conformal radiation therapy; chemo = chemotherapy; GI = gastrointestinal; HR-QoL = health-related quality of life; IMRT = intensity-modulated radiation therapy; KQs = key questions; LN = lymph node; preop = preoperative; postop = postoperative; RT = radiation therapy; VMAT = volumetric modulated arc therapy.
3. Key Questions and Recommendations

3.1. Key Question 1: Indications for neoadjuvant RT (Table 3)

See data supplement (link) for the evidence supporting the recommendations for KQ1.

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

Table 3. Recommendations for neoadjuvant RT indications

<table>
<thead>
<tr>
<th>KQ1 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (Refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with rectal cancer, pelvic MRI with a rectal cancer protocol is recommended for preoperative clinical T and N staging.</td>
<td>Strong</td>
<td>Moderate 4-7</td>
</tr>
<tr>
<td>2. For patients with stage II-III rectal cancer, neoadjuvant RT is recommended.</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td>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.</td>
<td>Conditional</td>
<td>Moderate 6,7,12,16</td>
</tr>
<tr>
<td>Implementation Remark: Lower risk is defined as a T3a/bN0 tumor that is &gt;10 cm from the anal verge* and with mrCRM ≥2 mm and no mrEMVI.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. For patients with T1-2N0 rectal cancer who may need an APR, neoadjuvant RT is conditionally recommended to improve the chance of sphincter preservation.</td>
<td>Conditional</td>
<td>Expert Opinion 17-19</td>
</tr>
<tr>
<td>5. For patients with rectal cancer where radiation is indicated, RT should be performed preoperatively rather than postoperatively.</td>
<td>Strong</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9-11,17-19</td>
</tr>
</tbody>
</table>

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.

* T3a/b = 1-5 mm extramural tumor spread; tumor height should be surgeon defined.

Clinical staging, including physical examination and radiographic imaging, is critical to selecting the appropriate treatment pathway for patients with 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.\(^{20}\) Endorectal ultrasound can be considered if MRI pelvis is unavailable, contraindicated, or equivocal. The major phase III trials establishing the role of neoadjuvant RT did not require MRI for study enrollment. However, in the years since those trials were designed, multiple prospective studies have established the value of MRI to risk-stratify patients into subgroups who may not require radiation or who may benefit from intensification of neoadjuvant treatment.\(^{4-7}\) The oncologic outcomes of the prospective observational Mercury II study are pending and may provide additional evidence supporting the value of MRI in treatment decision making for low rectal cancer.\(^{4}\)
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.\textsuperscript{21}

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).\textsuperscript{8-12} 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 to surgery alone.\textsuperscript{13-15} The long-term follow-up of the Dutch TME study identified an overall survival (OS) benefit with preoperative RT in the subgroup of patients with stage III disease and negative circumferential resection margins (CRMs), but this OS benefit was not observed in the entire study population.\textsuperscript{12}

While acknowledging 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” CRM.\textsuperscript{6,7,12,16} Omission of neoadjuvant RT in favor of surgery alone may be considered in these patients to avoid the acute and chronic toxicities associated with pelvic RT. Based on this moderate evidence, a conditional recommendation may be made to omit neoadjuvant RT in favor of upfront surgery in clinical stage IIA (T3a/bN0) patients when the cancer is located ≥10 cm from the anal verge and there is a predicted CRM ≥2 mm and the absence of extramural vascular invasion as determined by MRI with rectal cancer protocol. Tumor height (low = 0-5 cm from the anal verge; mid = 5-10 cm; proximal ≥10 cm) should be defined by the surgeon at initial diagnosis. Classically, this measurement has been by rigid proctoscopy, but flexible endoscopy is more commonly performed in the modern office setting. 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 if adjuvant therapy should be recommended in the setting of pathologic upstaging.

Sphincter preservation is a major quality-of-life (QoL) objective for many patients. Two phase III 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.\textsuperscript{17-19} However, this endpoint is subjective because it is based on the surgeon’s preoperative assessment of the need for abdominoperineal resection, and the rate of sphincter preservation was ultimately equivalent in the preoperative and postoperative arms. These trials included only stage II-III patients, for whom neoadjuvant RT is already the standard of care. 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 stage I (T1-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. Thus, some patients with early-stage tumors may experience the acute and late toxicities of pelvic radiation without a commensurate benefit.\textsuperscript{22}

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,\textsuperscript{9-11,17,18} One of these trials, the German rectal trial, also reported fewer acute and long-term toxicities in the patients treated with preoperative chemoradiation.\textsuperscript{10,19} However, a fourth trial from Korea did not show significant differences in either oncologic outcomes or toxicities.\textsuperscript{18} A meta-analysis, which included this Korean trial, confirmed a significant reduction in local recurrence and acute toxicity in the patients treated preoperatively.\textsuperscript{17} Therefore, when RT is indicated for rectal cancer, the evidence strongly supports a recommendation favoring preoperative over postoperative treatment.

3.2. Key Question 2: Neoadjuvant regimens (Table 4)

See data supplement (link) for the evidence supporting the recommendations for KQ2.

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

Table 4. Recommendations for neoadjuvant regimens

<table>
<thead>
<tr>
<th>KQ2 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (Refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with rectal cancer receiving neoadjuvant chemoradiation, conventional fractionation from 5000 to 5040 cGy in 25 to 28 fractions with concurrent chemotherapy is recommended.</td>
<td>Strong</td>
<td>High 10,23,24</td>
</tr>
<tr>
<td>2. For patients with rectal cancer receiving neoadjuvant short-course RT, 2500 cGy in 5 fractions without concurrent chemotherapy is recommended.</td>
<td>Strong</td>
<td>High 8,12</td>
</tr>
<tr>
<td>3. For patients with rectal cancer undergoing neoadjuvant chemoradiation, only concurrent 5-fluorouracil or capecitabine is recommended with RT for radiosensitization.</td>
<td>Strong</td>
<td>High 23-30</td>
</tr>
<tr>
<td>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.</td>
<td>Conditional</td>
<td>Low 31</td>
</tr>
<tr>
<td>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.</td>
<td>Strong</td>
<td>High 8,12,32-37</td>
</tr>
</tbody>
</table>
### Implementation remark: Risk factors for increased recurrence include: T3 tumors ≤ 5 cm from the anal verge or mrCRM < 2 mm; cT4 tumor or cN2 disease, presence of mrEMVI.

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: T3 tumors ≤ 5 cm from the anal verge or mrCRM < 2 mm; cT4 or cN2 disease, presence of mrEMVI.

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: T3 tumors ≤ 5 cm from the anal verge or mrCRM < 2 mm; cT4 or cN2 disease, presence of mrEMVI.

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: T3 tumors ≤ 5 cm from the anal verge or mrCRM < 2 mm; cT4 or cN2 disease, presence of mrEMVI.

8. For patients with rectal cancer receiving neoadjuvant chemotherapy as a component of a total neoadjuvant therapy strategy, 3 to 4 months of either FOLFOX or CAPOX (without additional agents, targeted therapy, or immunotherapy) is recommended.

9. For patients with rectal cancer undergoing neoadjuvant chemoradiation with no further neoadjuvant chemotherapy planned, an interval of 6 to 11 weeks from the end of chemoradiation to surgery is recommended.

10. For patients with rectal cancer undergoing neoadjuvant short-course RT with no further neoadjuvant chemotherapy planned, an interval of either ≤ 3 days or 4 to 8 weeks from the end of RT to surgery is recommended.

   Implementation Remark: An interval of 4 to 8 weeks is preferred for patients who may benefit from tumor downstaging prior to resection.

**Abbreviations:** cGy = centigray; KQ = key question; mrCRM = MRI-determined circumferential resection margin; mrEMVI = MRI-determined extramural vascular invasion; RT = radiation therapy.

The German rectal trial\textsuperscript{10} 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. A meta-analysis based on 5 RCTs revealed that while there is no improvement in survival, the addition of concurrent chemotherapy to conventionally fractionated RT increases the 5-year local control and pathologic complete response (pCR) rates compared to preoperative RT alone.23 This was confirmed by another meta-analysis evaluating 7 RCTs which demonstrated that preoperative chemoradiation significantly reduced the recurrence rate compared to preoperative RT alone24 although there was no difference in distant metastasis rate or OS. 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. For patients receiving conventionally fractionated treatment, after an initial 4500 cGy in 25 fractions delivered to the pelvis, a boost of 540 cGy in 3 fractions to the tumor plus margin may be delivered to achieve 5040 cGy composite dose to the tumor, involved mesorectum, and involved nodal regions.10

The Swedish rectal trial,8 which predated implementation of TME, randomized patients to hypofractionated “short-course” RT prior to surgery compared to surgery alone. Both a local control and OS benefit was observed for neoadjuvant radiation at a median follow-up of 13 years. This was confirmed by the Dutch rectal study12 which utilized similar arms to the Swedish trial and confirmed a local control benefit for short-course RT in the era of TME. These studies, as well as additional trials comparing neoadjuvant short-course RT to long-course chemoradiation,34,49 establish 2500 cGy in 5 fractions without concurrent chemotherapy as a standard of care for patients undergoing neoadjuvant short-course RT.

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. Emerging data on neoadjuvant chemotherapy alone in selected populations appears promising.31,50,51 The FOWARC study was designed to compare the efficacy of fluorouracil and leucovorin with RT versus mFOLFOX6 with or without RT for the neoadjuvant treatment of locally advanced rectal cancer.31,52 The final results have shown improved pCR with the inclusion of RT, with no significant differences in disease-free survival or local recurrence rate, although the trial design did not allow for a noninferiority comparison.52 Given these results, 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. Ongoing trials will provide additional insight about this approach including the PROSPECT trial (NCT01515787).51

Several RCTs have found no additional clinical benefit in terms of OS, disease-free survival, local control, pCR rate, tumor downstaging, or rates of sphincter sparing surgery with the addition of oxaliplatin to neoadjuvant chemoradiation compared to standard 5-FU or capecitabine with RT.28,29,53 Addition of oxaliplatin in these RCTs, however, was noted to markedly increase the rates of diarrhea such as in the NSABP R-04 study29 or grade 3 or 4 adverse events, such as in the STAR-01 study.53 These results were not uniformly noted.
across all studies, however, as the German CAO/ARO/AIO-04 study demonstrated an increased disease-free survival with the addition of oxaliplatin, with suggestion of a survival benefit in younger patients.\textsuperscript{54,55} A single arm phase II study found the addition of bevacizumab to S-1 chemotherapy increased postoperative toxicity without clinical benefit.\textsuperscript{30} Weighing results of the CAO/ARO/AIO-04 study against other trials, there is not sufficient evidence that the addition of other agents to 5-FU or capecitabine provides clinical benefit in the neoadjuvant setting.

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,\textsuperscript{8-12} and randomized studies suggesting similar efficacy and patient reported QoL outcomes for either treatment.\textsuperscript{33,34,36,49} In a subset analysis of distal tumors (<5 cm from the anal verge) in the TROG randomized trial, there appeared to be more local recurrences in the short-course RT arm, compared to the conventionally fractionated chemoradiation arm, but this difference was not statistically significant.\textsuperscript{34}

Several studies have evaluated potential benefits of a TNT approach, where multiagent (FOLFOX or CAPOX) chemotherapy is added before or following chemoradiation or following short-course RT. Current prospective data suggest that addition of multiagent chemotherapy after chemoradiation in the neoadjuvant setting improves downstaging\textsuperscript{39} and tolerability\textsuperscript{40,42} of chemotherapy compared to adjuvant treatment, while observational data suggests a possible disease-free survival benefit for TNT.\textsuperscript{41} Possible risks of TNT include delaying local treatment and potential over-treatment, in particular, for patients with stage II disease without other risk factors for increased recurrence.

In this guideline, a TNT approach is conditionally recommended, but with differing levels of evidence based on risk factors for disease recurrence including clinical T4 or N2 stage, low (<5 cm) tumors, threatening of the CRM, or presence of extramural vascular invasion as determined by MRI.\textsuperscript{4,34} For patients with clinical factors that portend increased recurrence risk, TNT is conditionally recommended with moderate-quality evidence. In this setting, there is a potential benefit from earlier treatment of micrometastatic disease, and a downstaging benefit which may facilitate margin negative resection, as well as improved tolerability of TNT compared to adjuvant chemotherapy. Patients with persistent close circumferential margin after upfront chemoradiation or short-course RT may derive particular downstaging benefit from addition of chemotherapy after radiation, although the long-term impact on clinical outcome remains unclear. A TNT approach is also conditionally recommended for patients with lower risk disease to improve tolerability of therapy, acknowledging a lower level of evidence in this setting and possible risk of overtreatment. If a TNT approach is considered, addition of 3 to 4 months of FOLFOX or CAPOX chemotherapy is consistent with evidence that suggest TNT has the potential to optimize compliance compared with adjuvant chemotherapy, without compromising a patient’s risk of surgical complications.\textsuperscript{39,42,56} This guideline allows for addition of FOLFOX or
CAPOX chemotherapy to be given either before or after chemoradiation or following short-course RT,
acknowledging absence of outcome data to support a specific sequence. For patients with threatened CRM or
other high-risk features, delivery of RT or chemoradiation before FOLFOX or CAPOX chemotherapy may
improve the extent of downstaging, although absence of high-quality data precludes recommendation of a
specific sequence.

The German rectal trial\textsuperscript{19} established a standard interval of 6 to 7 weeks between the completion of
neoadjuvant chemoradiation and surgical resection for patients with rectal cancer. Subsequently, retrospective
studies and at least 2 RCTs\textsuperscript{45,46} have examined the benefits of increasing this interval beyond 6 to 7
weeks. These studies have suggested somewhat inconsistent findings. While some studies have suggested an
increase in the rate of pCR with an increased interval, the largest RCT, the GRECCAR-6 trial,\textsuperscript{46} did not
demonstrate an improvement in tumor downstaging. Moreover, increasing the interval between completion
of chemoradiation and surgery from 7 to 11 weeks resulted in increased perioperative complications and
worse surgical quality, based on fewer patients resected with a completely intact mesorectum. As a result of
these conflicting findings, the optimal interval between completion of neoadjuvant chemoradiation and
surgical resection remains uncertain. 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 judgement 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.\textsuperscript{8,12} However, delaying surgery after short-course RT may allow for clinical
downstaging prior to resection. In the Stockholm III study,\textsuperscript{32} short-course RT with immediate surgery (≤7 days)
was compared to short-course RT with delayed surgery (4-8 weeks), and long-course RT (5000 cGy in 25
fractions) with delayed surgery (4-8 weeks). In a pooled secondary analysis of the short-course cohorts, no
differences were seen in the incidence of local failure, OS, or late complications between the immediate
surgery and delayed surgery cohorts. Subset analyses including data from the Dutch TME trial suggest reduced
morbidty for patients undergoing resection within 3 days of completion of short-course RT.\textsuperscript{48} Balancing
outcomes from Stockholm III against the volume of data in which short-course RT is followed by immediate
surgery, 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.
3.3. Key Question 3: Nonoperative and local excision approaches (Table 5)

See data supplement (link) for the evidence supporting the recommendations for KQ3.

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

Table 5. Recommendations for nonoperative or LE approaches

<table>
<thead>
<tr>
<th>KQ3 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (Refs)</th>
</tr>
</thead>
</table>
| 1. NOM is conditionally recommended after multidisciplinary discussion if a cCR is achieved following neoadjuvant treatment in patients with rectal cancer who:  
  a. would have a permanent colostomy or inadequate bowel continence following TME AND  
  b. decline TME AND  
  c. agree to close follow-up by a multidisciplinary team. | Conditional                  | Moderate 57-60               |
| 2. Organ preservation through neoadjuvant chemoradiation followed by LE is conditionally recommended after multidisciplinary discussion for patients with T2 N0 rectal cancer who:  
  a. would have a permanent colostomy or inadequate bowel continence following 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 61-63               |
| 3. For patients with rectal cancer considering NOM or LE following RT, conventional fractionation from 5000 to 5400 cGy in 25 to 30 fractions with concurrent chemotherapy is recommended. | Strong                      | Moderate 57,61-63            |
| 4. For patients with rectal cancer considering NOM, concurrent chemoradiation with or without induction or consolidation chemotherapy is conditionally recommended. | Conditional                  | Moderate 57-59,64            |
| 5. For patients with rectal cancer considering NOM, assessment for response is recommended with MRI pelvis, computed tomography abdomen/pelvis, and proctoscopy/sigmoidoscopy with DRE 2 to 3 months following completion of treatment. | Strong                      | Moderate 58,61,62,65         |
| 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 to 12 months thereafter, CT chest/abdomen/pelvis every 6 to 12 months for the first 2 years, then every 12 months thereafter, and MRI every 3 to 6 months for the first 2 years, then every 6 to 12 months thereafter. | Strong                      | Moderate 58,61,62,65         |
Abbreviations: cGy = centigray; cCR = complete clinical response; CT = computed tomography; DRE = digital rectal exam; LE = local excision; KQ = key question; MRI = magnetic resonance imaging; NOM = nonoperative management; RT = radiation therapy; TME=total mesorectal excision.

There are increasing data indicating the safety and feasibility of NOM following a complete clinical response (cCR) to neoadjuvant therapy. However, given the rigor and nuance of the required follow-up, NOM should preferably be pursued at centers with experienced multidisciplinary teams. In a meta-analysis of NOM following a cCR, the majority of patients avoided regrowth; the only factor associated with regrowth was increasing T-stage. Several series have reported a distant metastasis rate between 5% to 9% among patients with an initial cCR who underwent NOM. While a recent retrospective study showed that most distant metastases were found in patients who also had local tumor regrowth, the overall rate of distant metastases and the OS rate in patients undergoing NOM after cCR were no different from patients undergoing TME that had pCR. Given the potential QoL benefits noted with NOM compared with standard treatment and patient interest in these QoL benefits, 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, inadequate bowel continence following TME, and decline TME. While data on NOM is encouraging, it is only moderate in 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 local excision, 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. In such cases, it is critical that LE is performed by surgeons experienced with transanal local excision techniques, preferably at centers with experienced multidisciplinary teams. Multi-institutional phase II and III trials support this approach, with 1 trial not requiring TME if ypT2 disease was found (ACOSOG Z6041), and 2 trials requiring TME if ypT2-3 disease was found in the surgical specimen (GRECCAR 2, CARTS).

Therefore, organ preservation through neoadjuvant chemoradiation followed by LE is conditionally recommended for patients with cT2 N0 rectal cancer who are subsequently found to have ≤ypT1 disease and R0 margins (defined as ≤1 mm) upon LE who also agree to close follow-up by a multidisciplinary team. It is important to note, however, TME conversion after LE for ypT2-3 may lead to major complications and poor functional outcomes. Although there are data on LE that include patients with cT3 and/or cN+ disease, such data are limited. If organ preservation is desired for patients with cT3 and/or cN+ disease, QoL might be best served by instead pursuing NOM for those who achieve cCR. Functional outcomes and QoL are
variably impacted by chemoradiation and LE depending on the neoadjuvant regimen, patient gender and tumor distance from the anal verge.\textsuperscript{63,77} The majority of series of NOM utilized RT doses between 4500 to 5400 cGy.\textsuperscript{57,61,69,78} While some studies report high rates of cCR with radiation 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.\textsuperscript{79,80} Although dose has not been shown to affect local regrowth,\textsuperscript{57} as most NOM series involved at least 5000 cGy, a dose of 5000 to 5400 cGy is recommended. In the setting of LE, although a higher rate to toxicity was noted with 5400 cGy compared to 5040 cGy in the ACOSOG trial, this may have been instead due to the concurrent oxaliplatin.\textsuperscript{29,53,62,81} Other prospective series have not reported an increased toxicity with 5400 cGy, therefore, doses between 5000-5400 cGy are recommended for both NOM and LE.\textsuperscript{61,63,75,76} Short-course RT without chemotherapy is not recommended as part of NOM because of limited data\textsuperscript{82} and some data suggesting that it may result in lower cCR rates.\textsuperscript{83} However, there are data noting similar oncologic and QoL outcomes with neoadjuvant short-course RT followed by chemotherapy as compared to long-course chemoradiation when TME is part of the treatment plan.\textsuperscript{26,41} At this time, NOM via sequential short-course RT and chemotherapy is recommended only in the setting of a cancer registry or clinical trial.

NOM has typically involved long-course RT with concurrent chemotherapy, either alone,\textsuperscript{57-59,65,67,71,78,84} or with induction or consolidation chemotherapy.\textsuperscript{57-59,64,67,71} For T1-2NO patients, there are insufficient data to support the practice of additional chemotherapy before or after CRT. Although there is evidence of an increased pCR rate with a TNT approach for T3 or node positive patients,\textsuperscript{62,85} 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 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.\textsuperscript{86} Therefore, response is now typically assessed 2 to 3 months after completion of neoadjuvant therapy. The definition of cCR is based on digital rectal exam (DRE), endoscopic features, and imaging studies, specifically MRI.\textsuperscript{57,58,65,84} 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.\textsuperscript{65} 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. Most re-growths and local recurrences occur in the bowel wall and can be identified by DRE and/or flexible sigmoidoscopy.\textsuperscript{62,64} A few occur in the mesorectal nodes and are only identified by imaging. As most tumor re-growths occur during the first 2 years, 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.\textsuperscript{61-63,65} 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 computed tomography of the chest, abdomen and pelvis every 6 to 12 months for the first 2 years and then annually.\textsuperscript{87} The risk of local recurrence for LE patients diminishes 5 years after treatment and therefore, routine imaging is not necessary beyond that time.\textsuperscript{61,62} The long-term outcome of patients treated with NOM is currently unknown, and therefore registering in a long-term survivorship and surveillance program is strongly encouraged.

3.4. Key Question 4: Treatment volumes, dose-constraints, and techniques (Table 6)

See data supplement (link) for the evidence supporting the recommendations for KQ4.

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

Table 6. Recommendations for appropriate treatment volumes, dose-constraints, and techniques

<table>
<thead>
<tr>
<th>KQ4 Recommendations</th>
<th>Strength of Recommendation</th>
<th>Quality of Evidence (Refs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. For patients with T3-4 and/or N+ rectal cancers, inclusion of the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes in the CTV is recommended.</td>
<td>Strong</td>
<td>High 88,89</td>
</tr>
<tr>
<td>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.</td>
<td>Conditional</td>
<td>Low 89</td>
</tr>
<tr>
<td>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.</td>
<td>Conditional</td>
<td>Expert Opinion</td>
</tr>
<tr>
<td>4. For patients with rectal cancer treated with RT, an IMRT/VMAT technique is conditionally recommended.</td>
<td>Conditional</td>
<td>Low 90-95</td>
</tr>
</tbody>
</table>
4.6.20

**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.

| 5. For patients with rectal cancer receiving IMRT/VMAT, daily image guidance to verify localization is conditionally recommended. |
|---|---|---|
| 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**

**Expert Opinion**

**Low 96-98**

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

For patients with T3-4 and/or N+ rectal cancers, the task force recommends including the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes in the CTV. For further clarification in specific clinical scenarios, international guidelines for optimal target delineation for rectal cancer are available.\(^9\) Pooled analyses have demonstrated that these sites are at increased risk of local recurrence for patients with locally advanced rectal cancer.\(^8,8^9\)

Similar analyses have shown that if the primary tumor invades anterior structures or organs, nodal drainage may extend via the lymphatics of the involved organ.\(^8^9\) 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.\(^8^9,1^00\) While some data may suggest low rates of inguinal recurrence, for patients with rectal tumors that extend into the anal canal, inclusion of the inguinal and external iliac nodes in addition to the rectum, mesorectal nodes, presacral nodes, internal iliac nodes, and obturator nodes is conditionally recommended.

Modulated RT techniques like intensity-modulated radiation therapy (IMRT), including static field 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\(^1^0^1\) of preoperative chemoradiation, using IMRT in combination with capecitabine and oxaliplatin did not reduce the rate of gastrointestinal toxicity compared to conventional radiation in a prior trial, RTOG 0247.\(^1^0^2\) Of note, the RTOG 0822 trial used concurrent capecitabine and oxaliplatin, which is not the current standard. Other studies have demonstrated that IMRT can decrease toxicity.\(^9^1-9^5\) A meta-analysis found that IMRT lowered the incidence of grade ≥2 acute toxicity for overall gastrointestinal, diarrhea, proctitis and overall genitourinary
In addition, IMRT also lowered the incidence of grade ≥3 acute toxicity for overall gastrointestinal toxicity, diarrhea and proctitis. Additional studies report that IMRT and VMAT result in reduced toxicity versus three-dimensional conformal radiation therapy (3-D CRT). The effect seems to be more consistent for diarrhea and genitourinary toxicities compared to other endpoints. The use of modulated treatments does not appear to affect tumor control. Therefore, the task force felt the evidence of improved toxicity is sufficient to make a conditional recommendation for the use of IMRT or VMAT over 3-D CRT, particularly when the external iliac nodes and/or the inguinal nodes require treatment or when 3-D CRT techniques may confer a higher risk for toxicity. Additional treatment planning studies are needed to identify optimal dose constraints to minimize treatment toxicity.

Modern planning techniques like 3-D CRT and IMRT/VMAT produce plans that are more conformal but less robust to daily variations in setup. This is particularly true of IMRT/VMAT because of the creation of concave dose distributions designed precisely to follow the contour of the target and spare critical structures. Recognizing the lack of published data, the task force conditionally recommends daily image guidance for rectal cancer patients receiving IMRT/VMAT. Image guidance with volumetric imaging (eg, cone-beam and megavoltage computed tomography) can help account for differences in bladder filling, rectal filling, and movement of the small bowel. Daily alignment to bony anatomy using planar orthogonal imaging is acceptable if planning margins are sufficient to mitigate daily variations in soft tissue anatomy.

The choice of patient positioning is an important consideration in the treatment of rectal cancer. Patient positioning can affect the relative positions of the target and normal tissues. Furthermore, patient positioning decisions can also affect setup reproducibility during treatment. Options for patient positioning include supine and prone. The decision to treat supine or prone impacts the positioning of the peritoneal cavity and small bowel more than other organs at risk. The belly board can position the belly more superiorly, displacing some of the small bowel out of the treatment field. A study of rectal cancer patients comparing prone and supine positioning showed that prone positioning with a belly board reduces overlap between the small bowel and the planning target volume, relative to supine positioning. A separate study investigating treatment planning techniques in both supine and prone positioning found that all treatment techniques provide superior sparing of organs at risk in the prone position. In the prone position, the use of a belly board reduces dose to the small bowel over a wide range of dose levels compared to not using a belly board. 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 clinical target volume include
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.

4. Conclusion/Future Directions

Since the publication of the German Rectal Cancer Trial\textsuperscript{10,19} 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 has been challenged. In the era of personalized medicine, clinical decision making will look to move beyond traditional American Joint Committee on Cancer (AJCC) staging\textsuperscript{103} to incorporate additional radiographic, pathologic, and molecular features which may influence treatment decisions in order to optimize treatment outcomes and QoL while mitigating risks of treatment related toxicities.

Moving forward, improved stratification of risk within stage II-III rectal cancer is required to further individualize the use of neoadjuvant RT. Advancements in MRI will be central to this progress, including field strength, coil technology, identification of novel MRI contrast agents, and multiparametric imaging. For patients with intermediate-risk stage II-III disease, the results of the PROSPECT trial (NCT01515787) may provide further clarification regarding omission of routine neoadjuvant chemoradiation in this setting.

Additionally, future studies will help to clarify the ideal sequence and regimen for rectal cancer neoadjuvant therapy, and further establish risk stratification groups. Although adoption of a TNT approach has been increasing, ongoing studies including the RAPIDO trial (NCT01555821) and the German CAO/ARO/AIO-18 trial will directly compare chemoradiation alone with TNT-based approaches to better characterize potential advantages of this strategy. Studies will also need to clarify the optimal sequencing of chemotherapy and chemoradiation in the setting of 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.\textsuperscript{56} Although only concurrent 5-fluorouracil or capecitabine are considered current standard of care radiosensitizers during chemoradiation, trials such as the ongoing NRG-GI002 study (NCT029221256) will evaluate addition of concurrent targeted therapies or immunotherapy to current standard of care.

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. Studies, including the Organ Preservation in Rectal Adenocarcinoma (OPRA) study which seeks to further investigate the optimal sequencing of TNT in the setting of NOM, and the Magnetic Resonance Tumour Regression Grade as Biomarker for Stratified Management of Rectal Cancer Patients (TRIGGER, NCT02704520) which seeks to
incorporate and evaluate MRI tumor regression grading as a predictive biomarker for NOM, are ongoing. Results from these trials will provide measurable progress in these areas. Lastly, additional treatment planning studies will further identify optimal radiation treatment planning techniques to minimize treatment toxicity. 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.

5. Acknowledgements

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See Appendix 1 for their names and disclosures.
**Figure 1. PRISMA Diagram**, based on Moher et al, 2009\(^{104}\)

* Includes both original and updated searches

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

**Appendix 1. Peer Reviewers and Disclosures**

Added prior to publication
Appendix 2. Abbreviations

3-D CRT = 3-dimensional conformal radiation therapy

cGy = centigray

cCR = complete clinical response

CRM = circumferential resection margin

CVT = clinical target volume

DRE = digital rectal exam

Fx = fraction

IMRT = intensity-modulated radiation therapy

KQ = key question

LE = local excision

MRI = magnetic resonance imaging

NOM = nonoperative management

OS = overall survival

pCR = pathologic complete response

PICOTS = Population, Intervention, Comparator, Outcome, Timing, Setting framework

QoL = quality of life

RCT = randomized clinical trial

RT = radiation therapy

TME = total mesorectal excision

TNT = total neoadjuvant therapy
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