Appropriate Customization of Radiation Therapy for Stage II and III Rectal Cancer: An ASTRO Best Practice Statement

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Conflict of Interest Disclosure Statement:

Working Group

Before initiation of this Best Practice Statement, all members of the working group were required to complete disclosure statements. These statements are maintained at the ASTRO headquarters in Fairfax, VA and pertinent disclosures are published with the report. The ASTRO Conflict of Interest Disclosure Statement seeks to provide a broad disclosure of outside interests. Where a potential conflict is detected, remedial measures to address any potential conflict are taken and will be noted in the
disclosure statement. Theodore Hong, MD, was part of an advisory board for Illumina. Parag Parikh, MD receives research funding, honoraria, and travel expenses from Varian and research funding from Philips. He also owns stock in Holaira, Inc. Joseph Herman, MD has received research funding from Nucletron to conduct prospective clinical trials on endorectal brachytherapy. Brian Czito, MD has received research funding from Abbvie and honoraria from UptoDate. He also participates in an advisory board for Pfizer. John Kim, MD has received research funding from Philips. George Fisher, MD, PhD has received research funding from Bristol Myers Squibb, Genentech, Sanofi-Aventis, Novartis, Tercica, New Link Genetics, Polaris Group, Advanced Accelerator Applications, Gilead, and Faster Cures. He also serves on advisory boards for Genentech and Faster Cures. Nancy Baxter, MD, PhD receives research funding from Pfizer. The working group chairs and the chairs of the Best Practices Subcommittee reviewed these disclosures and determined that they do not present a conflict with respect to these members’ work on this Best Practice Statement.

**Expert Panel**

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Introduction

Treatment of rectal cancer has made great strides over the last five decades with improvements in surgical techniques and the use of combined modality therapy. Prior to the use of the total mesorectal excision (TME) technique, surgery alone resulted in local recurrence rates of 30-60% for locally advanced disease. The use of adjuvant 5-fluorouracil (5-FU)-based chemoradiation reduced local failure rates to 10-12% and improved overall survival compared to surgery alone, leading to the 1990 National Cancer Institute (NCI) consensus statement recommending adjuvant chemotherapy and radiotherapy for all patients with stage II or III (T3-4 or node positive) rectal cancer. The phase III randomized German Rectal Study subsequently demonstrated an improvement in the 10-year cumulative incidence of local relapse and reduced acute and overall toxicity rates with the use of pre-operative versus post-operative chemoradiation. This study has established the standard of care for stage II or III rectal cancer as neoadjuvant 5-FU-based chemotherapy with conventionally fractionated radiotherapy to 50.4 Gy.

However, a number of important questions remain regarding how to define subgroups of stage II and III and individualize use of multimodality therapy. With 5-year survival rates upwards of 75% for these patients, weighing potential long-term effects of surgery, radiotherapy and chemotherapy must be considered in determining appropriate management strategies. Given the potential morbidity associated with a multimodality approach, there are emerging efforts to identify subgroups of patients who can safely forgo a component of standard management without sacrificing disease control.

There have been attempts to further stratify Stage II and III rectal cancer patients by risk to identify subgroups that could potentially be over-treated using tri-modality therapy. In a pooled analysis of prospective and randomized datasets of patients treated with or without chemotherapy and/or radiation after radical rectal resection, Gunderson et al. identified three risk groups among Stage II and
III rectal cancer based on recurrence rates: 1) intermediate risk, characterized by tumor, node, metastasis classification system (TNM) stage T1–2N1 and T3N0 lesions; (2) moderately high risk, with stage T1-2N2, T3N1, T4N0 lesions; and (3) high risk in patients with stage T3N2, T4N1, T4N2 tumors.\textsuperscript{11,12}

Patients in the intermediate group, with a single high-risk factor, were shown to have better overall survival and disease control than patients with moderately high or high risk tumors. These data suggest that different adjuvant treatment strategies may be indicated for each risk group. However, the challenge remains in determining which patients can be spared adjuvant chemoradiation. This question is further complicated by the fact that chemoradiation is administered pre-operatively when pathologic staging is not available. Pre-operative imaging may not correctly identify all patients with involved lymph nodes, making it difficult to omit radiotherapy within the setting of uncertainty regarding clinical staging.

With significant reductions in local recurrence rates in more modern surgical series with the use of TME,\textsuperscript{13,14} pre-operative chemoradiation may not be as essential to eradicate disease often left behind with older surgical techniques. Neoadjuvant FOLFOX chemotherapy alone has also been evaluated in a small, single institution pilot study\textsuperscript{15} and is being evaluated in a large, randomized Phase III trial as a potential alternative to pre-operative chemoradiation, although results will not be available for many years.\textsuperscript{16}

Radical rectal surgery is also associated with significant morbidity.\textsuperscript{17-23} Patients with distal rectal tumors may require either permanent colostomy, often associated with poor body image and quality of life,\textsuperscript{20-23} or a low anterior resection with a coloanal anastomosis, which is often associated with impaired bowel function.\textsuperscript{22,23} Moreover, 20% of patients who receive neoadjuvant chemoradiation experience a pathologic complete response (pCR), in which no residual tumor is appreciable in the surgical specimen.\textsuperscript{24,25} These patients have particularly favorable outcomes, compared to those with residual cancer at the time of TME,\textsuperscript{25,26} and may not derive additional benefit from radical surgery.
Recent studies have demonstrated the feasibility of eliminating surgery entirely for patients achieving clinical complete response (cCR) to chemoradiotherapy, suggesting that surgery can be omitted, particularly in the group of patients for whom an operation would result in a permanent colostomy.\textsuperscript{27-30}

**Scope and purpose**

While the establishment of tri-modality therapy for rectal cancer, including surgery, radiotherapy, and chemotherapy, is the result of decades of randomized trials designed to address key questions, ambiguity remains due to patient and disease heterogeneity and the emerging attempt to better customize treatment strategies. Moreover, a growing body of evidence indicates that subgroups of stage II and III patients have differing risk profiles and warrant a more tailored therapeutic approach that spares unnecessary morbidity while achieving good outcomes. The current standard approach using the same therapeutic regimen for all Stage II or II rectal cancer patients suggests additional study is required to further refine specific approaches. Ultimately, the goal will be to intensify treatment for tumors demonstrating aggressive biologic behavior and limit treatment for more indolent tumors. Without better validated biomarkers, clinicians are faced with making decisions about therapy based on stage, tumor location, and other clinical factors. Currently, there are limited data and clinical guidance available to help clinicians navigate the emerging options and, therefore, the American Society for Radiation Oncology (ASTRO) proposed the development of a Best Practice Statement to address two clinical situations that provide opportunities for a more individualized approach. Specific questions addressed included:

- How to appropriately individualize the use of (neo)adjuvant radiation therapy for patients with T3-4 or node positive rectal cancer.
How to appropriately customize non-surgical therapy for rectal cancer patients who are medically inoperable or who have low-lying tumors and are attempting to avoid an abdominoperineal resection.

We thus sought to employ the RAND/ University of California-Los Angeles (UCLA) Appropriateness Methodology to define best practice with respect to neoadjuvant or adjuvant radiation therapy and non-operative management among stage II or III rectal cancer patients. Specific clinical scenarios incorporating known risk factors for recurrence were developed to help stratify these patients into more discrete subgroups and were presented to a multi-specialty expert panel to determine appropriate management for these cases. The Best Practice Statement also addresses radiation techniques, such as intensity modulated radiotherapy (IMRT), and other clinical considerations. We believe that a Best Practice Statement on this subject will be useful for oncology and for day to day management of rectal cancer patients.

Methods and Materials

Process

The ASTRO Board of Directors approved the creation of a Best Practice Statement on how to appropriately customize radiation therapy for stage II and III rectal cancer in May 2013. A working group of physicians from radiation oncology, medical oncology, and surgery who specialize in gastrointestinal cancers oversaw a comprehensive literature review conducted by ASTRO staff and developed the scenarios and definitions during a series of discussions by conference call and electronic mail. A multidisciplinary expert panel was selected to review the literature and rate the scenarios. The working group reconvened to interpret the ratings from the expert panel and draft the Best Practice Statement. The document was reviewed by the expert panel, the Best Practices Subcommittee, and the
Clinical Affairs and Quality Committee. It also underwent public comment during March and April 2015. The final draft was submitted to the Board of Directors for approval in June 2015.

This Best Practice Statement uses the RAND/UCLA Appropriateness Method, which was created during the 1980s with the goal of offering a rigorous way to “combine the best available scientific evidence with the collective judgment of experts to yield a statement regarding the appropriateness of performing a procedure at the level of patient-specific symptoms, medical history and test results.”\(^{31}\) This method has been applied to a wide range of medical disciplines, including a number of other oncology topics,\(^{32-36}\) and incorporates a multidisciplinary expert panel to rate the scenarios in order to mitigate the fact that physicians often rate treatments they deliver as more appropriate than those they do not.\(^ {37,38}\)

For this Best Practice Statement, each scenario was rated Appropriate, May Be Appropriate, or Rarely Appropriate. An Appropriate rating indicates that the expected benefit for the patient is sufficiently greater than the risks under most circumstances to make it worthwhile and reasonable to use the treatment. However, because a therapy is Appropriate does not mean it is required in all patients like those described in the scenario. Similarly, a Rarely Appropriate rating shows that the anticipated risks are considered higher than the benefits in most patients with the characteristics in that scenario, but should not be taken to mean that it is never reasonable to apply the intervention under those circumstances. Treatments rated May Be Appropriate have evidence that is limited, mixed, or subject to disagreement or the balance of the risks and benefits is currently unclear. However, the therapy may be appropriate and reasonable for some patients similar to those in the scenario.

Literature review
A systematic literature review was carried out using MEDLINE PubMed, Embase, and the Cochrane Library to identify studies published between January 1990 and July 2013 that evaluated patients 18 years or older with stage II or III rectal cancer receiving radiotherapy and/or chemotherapy. Both resectable and medically inoperable patients were included. The electronic searches were supplemented by hand searches and a total of 1571 articles were initially retrieved. These were screened based on the exclusion criteria to remove articles that were: case reports, stage I or IV only, non-English language, recurrent disease, abstract only, phase I studies, focused on tolerability or dosage without survival or recurrence outcomes, or otherwise not relevant. For trials of neoadjuvant or adjuvant radiation therapy, studies that were retrospective or had ten patients or fewer were also excluded. Where the same study was reported at multiple time points, only the latest one was retained. Ultimately, 228 full-text articles were selected for inclusion and the data were abstracted to create detailed literature tables. Literature summaries were also developed.

Clinical scenarios and definitions of terms

The scenarios were split into four sections: neoadjuvant therapy, adjuvant therapy, medically inoperable patients, and patients seeking to avoid abdominoperineal resection (APR). First, the working group compiled a list of factors that might influence physicians’ choice of therapy. Second, factors relevant to each section were combined to create a set of scenarios representing patients a radiation oncologist might see in practice, along with potentially appropriate therapies. Both the factors included and the treatments assessed varied by section and are described in the Results. The Best Practice also included two questions addressing the relative appropriateness of delivering neoadjuvant and adjuvant radiation with three-dimensional conformal radiation therapy (3D-CRT) versus IMRT. There were 237
total initial scenarios. A definition list was also created to give a common understanding of the terms across all participants in the project.

**Expert Panel**

The expert panel was charged with rating the scenarios based on the literature review and definitions developed by the working group. The panel was composed of physicians in radiation oncology (including both specialists and a non-specialist in gastrointestinal tumors), medical oncology, colorectal surgery, gastroenterology, and general internal medicine. Prospective participants were identified through nominations from ASTRO committees and external outreach to other medical specialty societies. Invited panelists were selected by the best practices subcommittee based on specialty, geographic region, practice setting, and availability for the in-person meeting. The final ten-member panel (Table 1) was made up of eight physicians who worked in academic settings and two who were in private or community-based practice.

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<tr>
<th>Specialty</th>
<th>Name</th>
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<tr>
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**Rating process and panel meeting**
For each scenario, the panel rated the appropriateness of the treatment from 1 to 9. A “1” indicated much greater anticipated harm than benefit and a “9” much higher expected benefit than harm. A “5” signified balanced harm and benefit or that the rater felt unable to reach a conclusion. Additionally, panelists were instructed to envision an “average patient” treated by an “average physician” in an “average facility” and not to consider cost or cost-effectiveness. Prior to rating, an orientation to the rating procedure and materials was held. The expert panel rated the scenarios in two rounds. The initial rating was performed independently via an online survey during February and March, 2014.

A face-to-face meeting of the expert panel was held on April 5th, 2014 in Alexandria, Virginia and was overseen and moderated by a moderator experienced in the RAND process. Each panelist received an individualized form showing their own rating per indication and the median and mean distance from the median for the entire panel. During the meeting, the panelists discussed the scenarios and then re-rated them using the same survey and process. Panelists were not forced to reach agreement.

The expert panel was asked in July 2014 to rate three scenarios a third time due to inconsistencies in the second round results and the resulting ratings replaced those from the second round.

Statistical analyses

Ratings for the first and second rounds were analyzed by a statistician using SAS statistical software. For the third round, due to the small number of ratings, Excel was used. For all rounds, the median and the mean distance from the median were calculated for each scenario. The median was used to measure central tendency because the responses were ordinal and the distance between points on the scale was not fixed. Average distance from the median was used to measure dispersion. Treatments were rated Rarely Appropriate when the median was 1 to 3 without disagreement, May Be Appropriate when
it was 4 to 6 or there was disagreement, and Appropriate when it was 7 to 9 without disagreement.

Disagreement was defined as \( \geq 3 \) ratings from 1 to 3 and \( \geq 3 \) from 7 to 9 on the same item.

**Results**

The expert panel evaluated 237 scenarios during the initial round of rating and 209 during the second. The scenarios were organized in four sections and an additional question on IMRT. Throughout the scenarios, only patients with stage II or III rectal cancer were included. In the first round, 28.3% (67 scenarios) were rated Appropriate, 38.4% (91 scenarios) were rated May Be Appropriate, and 33.3% (79 scenarios) were rated Rarely Appropriate. There was disagreement on 7.2% (17 scenarios). After face-to-face discussion, 27.3% (57 scenarios) were rated Appropriate, 44.0% (92 scenarios) were rated May Be Appropriate, and 28.7% (60 scenarios) were rated Rarely Appropriate. There was only one second round scenario with disagreement. Three scenarios were rated a third time due to an inconsistency in the ratings during the second round. As a result, one scenario moved from a rating of May Be Appropriate to Rarely Appropriate and one scenario changed from a rating of Rarely Appropriate to May Be Appropriate. The third scenario remained the same.

**Neoadjuvant therapy**

The first section included 105 scenarios. It considered the role of the distance of the distal edge of the tumor from the anal verge, distance from the radial tumor edge to edge of mesorectal fascia (based on magnetic resonance imaging [MRI]), and risk classification on the appropriateness of radiation and/or chemotherapy. Intermediate risk was defined as T1-2N1 or T3N0. Moderately high risk included T1-2N2, T3N1, or T4N0 tumors. High risk encompassed T3N2 or T4N1-2. These classifications were adapted from Gunderson et al.\textsuperscript{12} The use of distance to the edge of the mesorectal
fascia on MRI (see Figure 1 for example) reflects the trend in the United States for MRI to replace endoscopic ultrasonography as the standard for staging. It also aligns with the National Comprehensive Cancer Network (NCCN) guideline on rectal cancer, which likewise considers MRI part of the staging workup. For patients in the high risk category, the distance from the tumor to the mesorectal fascia was not included in the scenarios.

**Figure 1.** Rectal MRI axial T2 image

Five treatments were rated: short-course radiation, endorectal brachytherapy, chemoradiation, chemotherapy alone, and no neoadjuvant therapy. Short-course radiation was assumed to be 25 Gy in 5 fractions based on the Dutch TME study^{39,40} and endorectal brachytherapy was based on a Canadian regimen of high-dose rate intraluminal delivery of a dose of 26 Gy in 4 fractions.^41 Standard chemoradiation was considered to be 45 Gy to the whole pelvis with a conedown to exclude small bowel to 50.4 Gy with concurrent infusional 5-FU or capecitabine. Neoadjuvant chemotherapy alone was assumed to be FOLFOX.^15
For the initial round, 26.7% (28 scenarios) were rated Appropriate, 16.2% (17 scenarios) were rated May Be Appropriate, and 57.1% (60 scenarios) were rated Rarely Appropriate. Disagreement was present on 8.6% (9 scenarios). At the meeting, 27.6% (29 scenarios) were rated Appropriate, 24.8% (26 scenarios) were rated May Be Appropriate, and 47.6% (50 scenarios) were rated Rarely Appropriate. There were no scenarios with disagreement. In the third round, one scenario was changed to Rarely Appropriate from May Be Appropriate and another became May Be Appropriate from Rarely Appropriate.

The expert panel always rated conventionally fractionated chemoradiation Appropriate for patients with stage II and III rectal cancer with a median rating of 9 (Figure 5). While the ratings were not as high (medians 5 to 7) as for long-course chemoradiation, the panel also rated neoadjuvant short-course radiation May Be Appropriate to Appropriate depending on risk and tumor location (Figure 2). There were no situations where short-course radiation was rated Rarely Appropriate. The panel rated neoadjuvant chemotherapy alone May Be Appropriate for certain patients, particularly those with large margins from the mesorectal fascia in intermediate and moderately high risk disease. Panelists mostly rated this approach Rarely Appropriate in patients with closer mesorectal fascia margins as well as high risk disease (Figure 3). The expert panel rated endorectal brachytherapy alone as Rarely Appropriate for all patients (Figure 4) although it was noted that this could be considered in the setting of a clinical trial. Finally, regarding panelists’ views on omitting neoadjuvant therapy in stage II and III rectal cancer, they rated it May Be Appropriate in patients with intermediate risk disease ≥5 cm from the anal verge with non-threatened mesorectal fascia, and moderately high risk disease that was >10 cm from the anal verge and had no threatened mesorectal fascia (Figure 6). In other situations, the expert panel rated it Rarely Appropriate to not offer neoadjuvant therapy.
Figure 2. Appropriateness of neoadjuvant short-course RT

Risk classification*

Intermediate risk disease

Moderately high risk disease

High risk disease

Stage II and III rectal cancer

Distance from anal verge

≤10 cm

>10 cm

Distance from tumor edge to edge of mesorectal fascia^

<2 mm

≥2 mm

<2 mm

≥5 cm

≥2 mm

M

A

M

A

M

A

M

* Intermediate risk = T1-2N1, T3N0, Moderately high risk = T1-2N2, T3N1, High risk = T3N2, T4N1-2

^ Based on MRI

A = Appropriate (median 7-9 without disagreement), M = May Be Appropriate (median 4-6 or disagreement)
Figure 3. Appropriateness of neoadjuvant chemotherapy alone

Risk classification*

Distance from anal verge

Intermediate risk disease

- <5 cm
- 5-10 cm
- >10 cm

Moderately high risk disease

- <5 cm
- 5-10 cm
- >10 cm

High risk disease

Distance from tumor edge to edge of mesorectal fascia^

High risk disease

- ≤5 mm
- >5 mm
- ≤2 mm
- ≥2 mm

Intermediate risk disease

- ≤5 mm
- >5 mm
- <2 mm
- ≥2 mm

Moderately high risk disease

- ≤5 mm
- >5 mm
- <2 mm
- ≥2 mm

* Intermediate risk = T1-2N1, T3N0, Moderately high risk = T1-2N2, T3N1, High risk = T3N2, T4N1-2

^ Based on MRI

M = May Be Appropriate (median 4-6 or disagreement), R = Rarely Appropriate (median 1-3 without disagreement)
Figure 4. Appropriateness of neoadjuvant endorectal brachytherapy

Stage II and III rectal cancer

All patient groups

R

Figure 5. Appropriateness of neoadjuvant chemoradiation

Stage II and III rectal cancer

All patient groups

A

A = Appropriate (median 7-9 without disagreement), R = Rarely Appropriate (median 1-3 without disagreement)
Figure 6. Appropriateness of no neoadjuvant therapy

Risk classification*

Distance from anal verge

<5 cm

5-10 cm

>10 cm

Distance from tumor edge to edge of mesorectal fascia^}

≤5 mm

>5 mm

<2 mm

≥2 mm

≤10 cm

>10 cm

M = May Be Appropriate (median 4-6 or disagreement), R = Rarely Appropriate (median 1-3 without disagreement)

* Intermediate risk = T1-2N1, T3N0, Moderately high risk = T1-2N2, T3N1, High risk = T3N2, T4N1-2

^ Based on MRI
Adjuvant therapy

There were 38 scenarios in the second section addressing the options for adjuvant therapy in stage II and III rectal cancer. Only patients with no gross residual disease after curative surgery were included. The scenarios looked at the impact of circumferential resection margin (CRM), risk classification, distance from the anal verge, and total nodal count on the appropriateness of adjuvant chemoradiation (plus four months or more of chemotherapy) and chemotherapy alone. The first round resulted in 52.6% (20 scenarios) rated May Be Appropriate, and 47.4% (18 scenarios) rated Appropriate. There was disagreement on 5.3% (2 scenarios). For the second round, 50.0% (19 scenarios) were rated Appropriate and 50.0% (19 scenarios) were rated May Be Appropriate. Disagreement was seen on 2.6% (1 scenario). No scenarios were rated Rarely Appropriate in either round.

The expert panel was asked to consider the benefit of chemoradiation in addition to ≥4 months of chemotherapy and of chemotherapy alone in the adjuvant setting in the setting of a patient resected with a positive CRM. Chemoradiation was assumed to be standard, long-course pelvic radiotherapy with concurrent infusional 5-FU or capecitabine and chemotherapy could be adjuvant 5-FU and leucovorin, FOLFOX, capecitabine, or CapeOx. Panel members identified the occurrence of a positive margin in a patient who did not undergo pre-operative chemoradiation as “inadvertent” and potentially suggestive of poor quality surgery in the era of TME, more accurate pre-operative staging and imaging, and the established role of pre-operative pelvic radiotherapy. The panel rating of 9 (the maximum in the Appropriate category) indicated a strong agreement for chemoradiation in addition to ≥4 months of chemotherapy (Figure 7). The panel rating of 4 for chemotherapy alone just met criteria for May Be Appropriate, reflecting some uncertainty to this approach in the setting of positive margins, although it may be suitable in some scenarios (Figure 8).

The reporting of pathologic assessment of the quality of TME surgery was identified as not being routinely and consistently available. Given that the quality of surgery is a well-established determinant
of locoregional recurrence risk, the number of lymph nodes dissected was used as a surrogate of optimal surgery. Panel experts were provided a cut off of <12 or ≥12 nodes dissected as a surrogate of the quality of TME surgery. In the setting of negative margins and intermediate risk, the expert panel did not alter the recommendation for post-operative chemoradiation plus adjuvant chemotherapy based on the number of nodes dissected. The primary cancer location as measured by distance from the anal verge was a determinant of score for post-operative chemoradiation plus adjuvant chemotherapy. The expert panel rating changed from Appropriate to May Be Appropriate for tumors >10 cm from the anal verge indicating less certainty about pelvic chemoradiation for more proximal rectal tumors. Chemotherapy alone was rated May Be Appropriate for all scenarios.

In the setting of negative margins and moderately high risk, the number of nodes dissected also did not alter the expert panel’s recommendation for post-operative chemoradiation plus adjuvant chemotherapy. The panel provided a slightly lower rating within the Appropriate category for post-operative chemoradiation plus adjuvant chemotherapy as the distance from the anal verge increased. Chemotherapy alone was also rated Appropriate for tumors >10 cm above the anal verge and May Be Appropriate for more proximal tumors. In the setting of negative margins and high risk, the expert panel felt that post-operative chemoradiation plus adjuvant chemotherapy was Appropriate, regardless of the number of nodes dissected or distance from the anal verge. Chemotherapy alone was rated May Be Appropriate in the negative margin, high risk group, also regardless of number of nodes dissected or distance from the anal verge.
Figure 7. Appropriateness of adjuvant chemoradiation (plus ≥4 months of chemo)

* Intermediate risk = T1-2N1, T3N0, Moderately high risk = T1-2N2, T3N1, High risk = T3N2, T4N1-2

A = Appropriate (median 7-9 without disagreement), M = May Be Appropriate (median 4-6 or disagreement)
Figure 8. Appropriateness of adjuvant chemotherapy alone

- Intermediate risk = T1-2N1, T3N0, Moderately high risk = T1-2N2, T3N1, High risk = T3N2, T4N1-2
- A = Appropriate (median 7-9 without disagreement), M = May Be Appropriate (median 4-6 or disagreement)

Risk classification*

Distance from anal verge

Circumferential margin

Stage II and III rectal cancer

Positive margin

Negative margin

Intermediate risk disease

Moderately high risk disease

High risk disease

≤10 cm

>10 cm

M

M

M

A

M

M

M
Medically inoperable patients

The third section contained 60 scenarios. The factors considered in this section were performance status, presence of local symptoms, and distance from the anal verge. Good performance status was defined as Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1 and poor performance status as ECOG performance status 2 or greater. The appropriateness of five treatments was rated: external beam radiation alone, endorectal brachytherapy, chemoradiation alone, chemoradiation plus endorectal brachytherapy, and chemotherapy alone. In the first round, 18.3% (11 scenarios) were rated Rarely Appropriate, 71.7% (43 scenarios) were rated May Be Appropriate, and 10% (6 scenarios) were rated Appropriate. Only 1.7% (1 scenario) had disagreement. In the second round, 10.0% (6 scenarios) were rated Appropriate, 73.3% (44 scenarios) rated May Be Appropriate, and 16.7% (10 scenarios) rated Rarely Appropriate. There were no scenarios with disagreement.

Although data regarding best treatment for medically inoperable rectal cancer are limited, there was general agreement from the expert panel across all scenarios. Chemoradiation alone was consistently rated Appropriate for good performance status patients and May Be Appropriate for poor performance status patients (Figure 12). External beam radiation alone was rated May Be Appropriate for all medically inoperable scenarios (Figure 11). Chemotherapy alone was also rated May Be Appropriate, although supporting data are limited (Figure 13). Endorectal brachytherapy alone was not rated Appropriate for any scenario, but rather was largely rated May Be Appropriate for tumors less than 10 cm from the anal verge (Figure 9). The combination of chemoradiation and endorectal brachytherapy was rated May Be Appropriate for scenarios with tumor <10 cm from the anal verge with the exception of poor performance status patients with tumors 5-10 cm from the anal verge, which was rated Rarely Appropriate (Figure 10).

Location from the anal verge was only a factor for endorectal brachytherapy and the presence or absence of symptoms had minimal impact on ratings. It is important to note that, if definitive doses of
endorectal brachytherapy are delivered (6.5 Gy x 4), patients may have increased rectal symptoms if they do not undergo resection. The only effect of performance status was on the use of chemotherapy in combination with radiation, which was rated Appropriate in good performance status patients. These were the only scenarios rated Appropriate by the panel. Patients with medically inoperable rectal cancer were rated May Be Appropriate for external beam radiation alone or chemotherapy alone, most endorectal brachytherapy alone and chemoradiation plus endorectal brachytherapy scenarios if < 10 cm from verge, or chemoradiation with poor performance status.
Figure 9. Appropriateness of **definitive endorectal brachytherapy**

Medically inoperable stage II and III rectal cancer

Performance status

Good performance status (ECOG 0-1)

Poor performance status (ECOG ≥2)

Local Symptoms

Present

Absent

Distance from anal verge

≤10 cm

>10 cm

<5 cm

≥5 cm

M = May Be Appropriate (median 4-6 or disagreement), R = Rarely Appropriate (median 1-3 without disagreement)
Figure 10. Appropriateness of **definitive chemoradiation plus endorectal brachytherapy**

Medically inoperable stage II and III rectal cancer

- **Performance status**
  - Good performance status
  - Poor performance status

- **Local Symptoms**
  - Present
  - Absent

- **Distance from anal verge**
  - ≤10 cm
  - >10 cm

- **M** = May Be Appropriate (median 4-6 or disagreement)
- **R** = Rarely Appropriate (median 1-3 without disagreement)
**Figure 11. Appropriateness of definitive EBRT**

Medically inoperable stage II and III rectal cancer

All patient groups

M

**Figure 12. Appropriateness of definitive chemoradiation**

Medically inoperable stage II and III rectal cancer

Good performance status

A

Poor performance status

M

**Figure 13. Appropriateness of definitive chemotherapy alone**

Medically inoperable stage II and III rectal cancer

All patient groups

M

A = Appropriate (median 7-9 without disagreement), M = May Be Appropriate (median 4-6 or disagreement)
Patients seeking to avoid/refusing APR

The fourth section was comprised of 32 scenarios in the initial round. All patients covered had low-lying tumors (<5 cm from the anal verge) and were otherwise operative candidates but were attempting to achieve response to chemoradiation and avoid permanent colostomy. It was specified that patients who progressed or did not respond to chemoradiation (based on physician assessment) should receive an APR. The scenarios include incorporated three factors: nodal status, T-stage, and whether a full thickness transanal excision had been performed. Patients who had T1 or T2 tumors and were node negative were excluded since they have stage I disease and are outside the scope of this Best Practice Statement. The treatments evaluated were endorectal brachytherapy, chemoradiation, chemoradiation together with endorectal brachytherapy, and APR.

After extensive discussion during the in-person meeting, the expert panel, which was composed of a multidisciplinary group including several colorectal surgeons, decided not to rate the individual scenarios since the overall question was whether there is any alternative to an APR in patients who refuse surgery. The surgeons also made the argument that, although the original scenarios made a distinction between whether a patient had a full thickness transanal excision or not, if a full-thickness transanal excision were possible then a low anterior resection with a coloanal anastomosis could be performed and an APR is not needed. The panel was also concerned that by rating the radiation options, they would be recommending use of a non-standard therapy rather than having another surgeon potentially perform a radical resection without an APR. Therefore, the panel opted to replace the section with a single new question regarding patients with stage II or III very low lying tumors refusing the standard treatment, APR, and emphasized the fact that this was in the setting of patient refusal and therefore outside of the standard approach. Panelists were asked to then rate chemoradiation (standard dose), chemoradiation (standard dose) plus endorectal brachytherapy boost, and chemoradiation with external beam radiation boost.
In the first round, using the original questions, 25% (8 scenarios) were rated Rarely Appropriate, 28.1% (9 scenarios) were rated May Be Appropriate, and 46.9% (15 scenarios) were rated Appropriate. Disagreement was found for 12.5% (4 scenarios). In the second round, with the new question, all three scenarios were rated Appropriate with no disagreement. The panel felt that in the scenario of patient refusal of an APR, any of the radiation approaches could be justified (Figures 14 to 16).
Figure 14. Appropriateness of definitive chemoradiation (standard dose)

Stage II and III rectal cancer

Patient with very low lying tumor refusing abdominoperineal resection

A = Appropriate (median 7-9 without disagreement)

Figure 15. Appropriateness of definitive chemoradiation (standard dose) plus endorectal brachytherapy

Stage II and III rectal cancer

Patient with very low lying tumor refusing abdominoperineal resection

A

Figure 16. Appropriateness of definitive chemoradiation (standard dose) with EBRT boost

Stage II and III rectal cancer

Patient with very low lying tumor refusing abdominoperineal resection

A
IMRT

In addition to the four sections, one supplemental question was also included, which asked the Expert Panel to rate the appropriateness of using IMRT to deliver neoadjuvant and adjuvant treatment. IMRT was rated May Be Appropriate in both settings during the first round, with disagreement seen for neoadjuvant therapy. For the second round of rating, neoadjuvant therapy was separated into short-course RT and chemoradiation at the request of the expert panel. All three options were subsequently rated May Be Appropriate, with no disagreement.

While the question addressed the use of IMRT in three different scenarios, neoadjuvant short-course pelvic radiotherapy, neoadjuvant long-course chemoradiation, and adjuvant chemoradiation, the ratings were primarily May Be Appropriate (Figures 17 to 19). Further distinction between the situations was not possible due to the lack of familiarity with the technical aspects of IMRT versus 3D-CRT among the non-radiation oncologists on the panel. Thus, the multidisciplinary expert panelists deferred for this question to the radiation oncologists who generally felt that the use of IMRT would be a case-by-case decision and there might be extenuating circumstances when it would add substantial benefit.
Figure 17. Appropriateness of neoadjuvant short-course RT delivered with IMRT

Stage II and III rectal cancer

M

Figure 18. Appropriateness of neoadjuvant chemoradiation delivered with IMRT

Stage II and III rectal cancer

M

Figure 19. Appropriateness of adjuvant therapy delivered with IMRT

Stage II and III rectal cancer

M

M = May Be Appropriate (median 4-6 or disagreement)
Discussion

The analysis of the ratings of the many clinical scenarios that were evaluated by the expert panel demonstrate that, while a standard treatment approach exists in stage II and III rectal cancer, further studies are necessary to refine the treatment recommendations. The expert panelists had very good agreement (only one final scenario had disagreement) for the appropriateness of the various treatment options presented, which reflects the excellent multidisciplinary approach that has been applied to the management of rectal cancer. Emerging options such as short-course radiotherapy, neoadjuvant chemotherapy alone, and non-operative management in the setting of patient refusal of an APR were included in this Best Practice Statement, despite the lack of widespread use or limited high level evidence regarding these options in the United States, to provide practicing radiation oncologists with the current assessment of the appropriateness of these options.

Neoadjuvant therapy

Patients presenting for neoadjuvant therapy before to definitive surgery make the bulk of referrals for rectal cancer to the radiation oncologist. Following the seminal German cancer rectal trial, it was established that neoadjuvant chemoradiation improves local control with decreased toxicity as compared with adjuvant chemoradiation. The approach offered in this trial, conventionally fractionated radiation therapy with concurrent 5-FU based chemotherapy, was considered appropriate by all of the expert panel members for stage II and stage III rectal cancer. This is also reflected in other clinical guidelines, such as the NCCN and Cancer Care Ontario.

More interestingly, panelists rated neoadjuvant short-course radiation therapy Appropriate in many patients with non-threatened mesorectal fascia margins and May Be Appropriate in other patients. This is consistent with the fact that short-course is not intended for downstaging as usually surgery is performed within a couple of weeks of finishing radiation therapy. The ratings have also been supported
by randomized studies comparing short course with conventional chemoradiation,\textsuperscript{43,44} selective adjuvant therapy,\textsuperscript{45} and no therapy.\textsuperscript{40} There are also ongoing randomized studies looking to incorporate short-course radiation with neoadjuvant chemotherapy.\textsuperscript{46,47} The use of short-course radiation has been relatively uncommon in North America and is not present in the current NCCN guideline.\textsuperscript{48}

Another emerging area is the use of neoadjuvant chemotherapy alone for selected patients with stage II or III rectal cancer. While the accrual of a large, phase III randomized trial is ongoing,\textsuperscript{16} the expert panel rated this approach May Be Appropriate for selected patients in intermediate and moderately high risk disease with non-threatened mesorectal fascia. There was no patient group that neoadjuvant chemotherapy alone was rated Appropriate for and this regimen is not offered in the NCCN guidelines currently.

Neoadjuvant brachytherapy alone was rated Rarely Appropriate across the scenarios. This has been performed by select centers.\textsuperscript{49} This remains an area of active investigation and may be more relevant in patients who are not surgical candidates, as described in the medically inoperable section, or as a boost in well-selected patients.\textsuperscript{50} Finally, the expert panel rated forgoing neoadjuvant therapy altogether for certain patients with stage II or III rectal cancer May Be Appropriate. These included patients with mid to high rectal cancers with a non-threatened mesorectal fascia, undergoing TME. This acknowledges that potential patient benefit from neoadjuvant therapy may be diminished by treatment-related toxicity, and that these patients may be evaluated for adjuvant therapy based on pathologic findings.

\textit{Adjuvant therapy}

Since modern practice has established the role of neoadjuvant radiation regimens as the standard treatment for locally advanced rectal tumors,\textsuperscript{6} a positive CRM should be an uncommon clinical scenario and may reflect inadequate TME technique or very poor tumor biology. Understaging or lack of
identification of a threatened mesorectal margin pre-operatively may also increase the risk of a post-operative positive CRM. When a positive margin does occur, especially in the setting of high-quality surgery, it is associated with poor outcomes and the question of how to address the potentially residual disease in the post-operative setting is always a difficult one. There is no level 1 evidence to guide the management of a positive CRM but data from clinical trials highlight the increased risk of local recurrence.\(^{40,51}\) High rates of long term local failure, 48.6% R1 vs. 7.7% R0, were observed on the adjuvant chemoradiation arm of the pre-operative vs. post-operative randomized German rectal cancer trial.\(^7\) A randomized trial (MRC CR07 + NCIC CTG C016) of selective chemoradiation for patients with a positive CRM demonstrated inferior local control compared to pre-operative short-course pelvic radiation therapy.\(^{52}\) However, there is no clinical trial comparing adjuvant pelvic chemradiotherapy to chemotherapy or observation alone on the setting of positive margins. In the absence of clinical trials, post-operative chemoradiotherapy plus adjuvant chemotherapy remains the standard treatment regimen in the setting of a positive CRM.

However, the alternative strategy of adjuvant chemotherapy alone in the setting of positive CRM was also rated May Be Appropriate to Appropriate. This may be an option for patients who are not eligible for post-operative therapy due to comorbid conditions, known contraindications to radiation therapy, or patient refusal. Adjuvant chemotherapy alone might also be appropriate for patients with a very high risk of systemic relapse, with the caution that chemotherapy alone may be associated with a higher rate of locoregional recurrence, which is associated with significant morbidity both from the pelvic recurrence and from any surgical salvage approach.

For adjuvant radiation and chemotherapy in the setting of negative CRM, the data are largely derived from studies performed in the pre-TME era, when transmural or node positive cancers had a local recurrence risk as high as 50%,\(^{53}\) which led to the NCI consensus statement in 1990\(^5\) that adjuvant chemoradiation was the new standard regimen. The expert panel was asked to consider the role of
adjuvant chemoradiation in the TME era, considering the individualized local control benefit and the potential for normal tissue toxicity when pelvic radiotherapy is delivered in the post-operative setting. For most scenarios, adjuvant chemoradiation plus chemotherapy was rated Appropriate (Figure 7). Adjuvant chemotherapy alone was rated May Be Appropriate or Appropriate (Figure 8), indicating that the expert panel supported the approach that, with pathologic information demonstrating that for intermediate risk disease (T3N0, T1-2N1), adjuvant chemotherapy results in similar outcomes as adjuvant chemoradiation, based on pooled analyses of prospective data comparing adjuvant therapy options after surgery.

The panel was also provided the number of lymph nodes reported in the pathology report as a surrogate to estimate the adequacy of the surgical resection since this may often be the only quality indicator available. However, node count may be a marker of the quality of pathology as well as surgery and may also reflect disease biology. While the optimal lymph node yield for rectal cancer without neoadjuvant therapy is still controversial, the <12 vs. ≥12 nodes dissected was used in each risk based scenario. Interestingly, the lymph node count did not alter the expert panel’s ratings for most scenarios, thus reflecting the relative lack of utility of nodal count as a measure of quality of rectal cancer surgery.

The relationship between the location of the primary rectal cancer as measured by distance from the anal verge and the benefit of pelvic radiotherapy also remains the subject of differing opinions. In the pre-operative setting with TME surgery, secondary subset analyses have evaluated the benefit of pelvic radiotherapy based on primary tumor location. The long term report of the Dutch TME trial demonstrated that the benefit of short-course pre-operative pelvic radiotherapy was greater for greater distance from the anal verge (p=0.03). If patients with a positive CRM were excluded from the analysis, the relationship between the distance from the anal verge and radiotherapy disappeared and irradiated patients had higher cancer-specific survival independent of distance from the anal verge.

The Trans-Tasman Radiation Oncology Group (TROG) compared pre-operative short-course pelvic
radiotherapy to long-course chemo-radiotherapy in T3 rectal cancers. There was a non-significant
(p=0.21) trend toward decreased local recurrence for long-course treatment and tumors <5 cm from the
anal verge.\textsuperscript{44} In the adjuvant setting, 11 year data from the pre-operative vs. post-operative German
Rectal Cancer Trial, showed that at 10 years, post-operative chemoradiation was associated with a LR
risk of 9.3\% vs. 18.7\% if no post-operative treatment was delivered if the tumor was at 5 to <10 cm and
2.7\% vs. 10.4\% if the tumor was at 10-16 cm. On multivariate analysis, not receiving chemoradiation
was significantly associated with a higher local recurrence risk.\textsuperscript{7} Overall, there was general agreement
among the expert panel that increasing distance from the anal verge was associated with lower risk of
local recurrence.

For low lying rectal cancers <5cm from the anal verge, there was strong agreement in rating
adjuvant chemoradiation Appropriate for all patients regardless of risk category or number of nodes
dissected. Long-term data from the Swedish Rectal Cancer Trial in the pre-TME era shows that the
local recurrence rate was 27\% for tumors \leq 5cm from anal verge, 26\% for tumors 6-10 cm, and 12\% for
tumors \geq 11 cm.\textsuperscript{55} Moreover, the type of surgery performed may be considered as well, since data from
the Dutch CKVO trial have shown that, even with a good TME and a negative CRM, APR was
associated with presacral local recurrences.\textsuperscript{56} Post-operative chemoradiation was also associated with a
higher risk of local recurrence on multivariate analysis from updated data from the German Rectal
Cancer Trial in patients who had surgery that included intersphincteric resection or APR compared with
pre-operative radiation (P=0.03).\textsuperscript{56}

The panelists rated adjuvant chemotherapy alone May Be Appropriate for patients with low-
lying rectal cancers, including those where there is concern about an increased risk of toxicity to the
anastomosis depending on the type of surgery that has been performed (i.e. a hand-sewn coloanal
anastomosis). With post-operative chemoradiation, grade 3-4 anastomotic toxicity seen in 12\% of
patients in the German study.\textsuperscript{6}
For R0 resected tumors at 5-10 cm from the anal verge, there was again strong consensus that adjuvant regimens containing pelvic radiotherapy are appropriate. The surgeons on the panel noted that more proximal anastomoses would be anticipated to better tolerate pelvic radiation. Strategies to consider chemotherapy alone were also felt to be reasonable.

As the distance of the tumor from the anal verge increased to >10 cm, the strength of the recommendation for adjuvant regimens containing radiation decreased. Intermediate risk tumors in this category were rated as May Be Appropriate. Within the intermediate risk category, data from Gunderson et al. have noted a 7% local failure for T1-2/N1 tumors vs. a 9% local failure for T3N0 tumors.\(^\text{12}\) Thus by risk category as well as distance from the anal verge, this category of patients would be expected to have a relatively low rate of local failure, particularly in the more modern era with the use of TME. For high risk tumors >10 cm from the anal verge, panelists rated the adjuvant radiation regimens Appropriate but at the lowest end of this category (median of 7). However, it should be noted that the location of the peritoneal reflection can vary in relation to the distance from the anal verge. Therefore tumors at >10 cm from the anal verge may or may not be intraperitoneal. Adjuvant chemotherapy only regimens were rated May Be Appropriate for intermediate and high risk tumors regardless of nodes dissected and Appropriate for tumors of moderate risk.

**Medically inoperable**

Medically inoperable patients are rare and there are limited data to guide choice of therapy. In addition, this group of patients is heterogeneous with regard to reasons for inoperability. Factors other than performance status and presence of symptoms likely impact choice of therapy. Uncontrolled pelvic malignancy is known to be associated with significant symptoms in most patients. Thus, there was clear consensus by the expert panel that local therapy, including some form of chemoradiation, is appropriate in good performance status patients.
With the emerging data from the operable patients showing non-operative management may be curative for selected patients with a clinical complete response after pre-operative chemoradiation, there was general consensus that chemoradiation was rated Appropriate. External beam radiation combined with endorectal brachytherapy without surgery has been associated with excellent outcomes in patients with favorable rectal cancers (<12 cm from anal verge, <3 cm diameter, mobile without ulceration, T1-2, grade 1-2) and may be used for unfavorable patients who are medically inoperable. Local control in more advanced T2-3 distal rectal cancers has been reported in >70% of patients treated with a combination of endorectal brachytherapy, external radiation and interstitial brachytherapy with 5-year survival in excess of 60%. Given the excellent local control rates reported in selected patients and potential for long-term survival, all medically inoperable patients should be evaluated for potentially curative intent radiation therapy.

Endorectal brachytherapy alone has been demonstrated to be effective curative treatment for grade 1-2, T1N0, < 3 cm diameter rectal cancers located < 10 cm from the anal verge. Extrapolating from these data, the expert panel rated endorectal brachytherapy alone as May Be Appropriate for medically inoperable patients with distal tumors. It should be noted that endorectal brachytherapy is generally contraindicated in patients with invasion of the anal sphincters given potential effects on sphincter function.

The panel also felt that some patients in this section, particularly those with poor performance status and an absence of local symptoms, should receive palliative treatment. However, this option was not included in the rating.

Patient refusal of an APR

There is also growing interest in non-operative management for operable patients with low-lying rectal cancers who have achieved a pCR to pre-operative chemoradiation to improve quality of life.
following treatment for rectal cancer. While sphincter preservation can be achieved in some patients by performing a low anterior resection with a coloanal anastomosis, these procedures are associated with impaired bowel function.\textsuperscript{20} In addition, patients face the morbidity and mortality attendant with major abdominal surgery and the need for temporary diversion if restoration of intestinal continuity is possible. Finally, rectal cancer surgery also impacts sexual functioning. Several prospective studies have evaluated patient-reported quality of life after treatment for rectal cancer and have demonstrated low scores, particularly in patients with stomas or low rectal anastomoses.\textsuperscript{21-23}

However, since non-operative management for stage II or III disease is still considered a non-standard approach, the panel did not want to rate its use for various clinical scenarios. The decision was to address the situation in which a patient refuses standard therapy and consensus of the panel was that local therapy with chemoradiation with or without endorectal brachytherapy was an inferior but acceptable alternative to radical surgery. As more studies evaluate the non-operative approach with intensive follow-up for patients with complete response to chemoradiation there may be future Best Practices Statements that will have sufficient supporting literature to rate more specific clinical scenarios and address additional considerations such as how to assess treatment response after chemoradiation.

\textit{IMRT}

Further improvements in outcomes for rectal cancer patients may also come with incorporating newer radiotherapy techniques to deliver more focal dose to the tumor and lymph node regions while sparing the radiosensitive structures of the pelvis. By minimizing the toxicity to the normal tissues, acute and long-term toxicities of pelvic radiotherapy may be reduced, thus improving the therapeutic ratio of this approach. IMRT allows for more conformal delivery of radiotherapy by using computed-tomography (CT) based planning and sophisticated computational software to generate treatment plans. However, the increased cost and lack of reimbursement for IMRT in many gastrointestinal cancers has
also impacted on its use. For this reason, the question was framed to identify specific situations where IMRT might be more useful, for instance with higher dose-per-fraction, such as with neoadjuvant short-course RT where late effects have been shown to be significantly elevated versus surgery alone, as well as in the post-operative setting, which is associated with more toxicity compared to neo-adjuvant therapy.

The use of IMRT for long-course neoadjuvant chemoradiation has been controversial in rectal cancer given the lack of data addressing the benefit of a more conformal approach over standard 3-dimensional conformal radiotherapy. The only prospective study evaluating the use of IMRT in rectal cancer was a yet-to-be published, single-arm Phase II trial, RTOG 0822. This study evaluated the use of concurrent capecitabine and oxaliplatin with pelvic radiotherapy using IMRT planning. The primary endpoint was an improvement in Grade 2 or higher gastrointestinal toxicity in this study as compared to the RTOG 0247 trial, which used the same chemotherapy regimen with non-IMRT pelvic radiotherapy. RTOG 0822 failed to demonstrate a significant benefit to the use of IMRT. However, interpretation of this study is limited by the use of concurrent oxaliplatin with 5-FU based chemoradiation given there have been four large, phase III randomized trials demonstrating increased GI toxicity when oxaliplatin is added to pre-operative chemoradiation. IMRT planning may not have been able to overcome the effect of the oxaliplatin on GI toxicity. Several retrospective studies have demonstrated a reduction in GI toxicity using IMRT over 3D-CRT for rectal cancer.

**Conclusion/Future Directions**

Radiotherapy remains a standard component of management of rectal cancer; however, there is still the need to further refine its role as part of neoadjuvant, adjuvant and definitive therapy in order to better tailor therapy for patients with rectal cancer. This Best Practices Statement provides a comprehensive overview of the therapeutic options for patients with locally advanced (Stage II/III)
rectal cancer and further classifies this larger group into subgroups based on known risk factors that were described in the clinical scenarios. By utilizing a multi-disciplinary panel of experts, and including both GI-specialized and non-GI-specialized radiation oncologists, the Best Practice process effectively removes biases which could result from a tendency to recommend treatments that are delivered by the panelists. Thus, the appropriateness ratings were not only individualized and risk-stratified, but also representative of the overall community of practitioners treating rectal cancer. Nonetheless, the ratings should not be taken as absolutes, as there may be unique circumstances that require clinicians and patients to use best clinical judgment in optimal decision making. The use of novel techniques such as IMRT was considered in this Best Practices Statement and was felt to be potentially appropriate because it may lead to less toxicity. However, further study to assess the impact of this approach on treatment outcomes is warranted to ensure the appropriate technology utilization and this questions may be better answered in future Best Practices Statements.

In the future, results of ongoing trials may help clarify areas of uncertainty, particularly with regard to the use of neoadjuvant FOLFOX as an alternative to chemoradiation and the possibility of pursuing non-operative management in patients who have a complete clinical response after chemoradiation. On-going studies of both molecular and imaging biomarkers may also improve risk stratification and allow for more tailored therapies for rectal cancer patients. Meanwhile, this Best Practices Statement will serve as an overview of options to help guide physicians as we move toward more individualized approaches for our patients.


## Appendix 1: Complete rating tables

### Section 1: Neoadjuvant therapy

#### Neoadjuvant therapy, intermediate risk, <5 cm from anal verge

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<th>Chemoradiation</th>
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Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement), red = Rarely Appropriate (median 1-3 without disagreement)

#### Neoadjuvant therapy, intermediate risk, 5-10 cm from anal verge

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Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement), red = Rarely Appropriate (median 1-3 without disagreement)

#### Neoadjuvant therapy, intermediate risk, >10 cm from anal verge

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Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement), red = Rarely Appropriate (median 1-3 without disagreement)
### Neoadjuvant therapy, moderately high risk, <5 cm from anal verge

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</tbody>
</table>

Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement), red = Rarely Appropriate (median 1-3 without disagreement)

### Neoadjuvant therapy, moderately high risk, 5-10 cm from anal verge

<table>
<thead>
<tr>
<th>Tumor edge</th>
<th>Short-course RT</th>
<th>Endorectal brachytherapy</th>
<th>Chemoradiation</th>
<th>Chemotherapy alone</th>
<th>No neoadjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 mm</td>
<td>5</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>2-5 mm</td>
<td>7</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>&gt;5 mm</td>
<td>5</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

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### Neoadjuvant therapy, moderately high risk, >10 cm from anal verge

<table>
<thead>
<tr>
<th>Tumor edge</th>
<th>Short-course RT</th>
<th>Endorectal brachytherapy</th>
<th>Chemoradiation</th>
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<tr>
<td>&lt; 2 mm</td>
<td>5</td>
<td>2</td>
<td>9</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2-5 mm</td>
<td>7</td>
<td>1</td>
<td>8</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>&gt;5 mm</td>
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</tr>
</tbody>
</table>

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### Neoadjuvant therapy, high risk

<table>
<thead>
<tr>
<th>Tumor edge</th>
<th>Short-course RT</th>
<th>Endorectal brachytherapy</th>
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</tr>
</thead>
</table>
### Section 2: Adjuvant therapy

#### Adjuvant therapy, positive circumferential margin

<table>
<thead>
<tr>
<th>Chemoradiation (plus ≥4 months of chemo)</th>
<th>Chemotherapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

#### Adjuvant therapy, negative circumferential margin, intermediate risk, <5 cm from anal verge

| <12 nodes dissected | 9 | 5 |
| ≥12 nodes dissected | 7 |  |

#### Adjuvant therapy, negative circumferential margin, intermediate risk, 5-10 cm from anal verge

| <12 nodes dissected | 8 | 5 |
| ≥12 nodes dissected | 6 |  |

#### Adjuvant therapy, negative circumferential margin, intermediate risk, >10 cm from the anal verge

| <12 nodes dissected | 6 | 6 |
| ≥12 nodes dissected | 5 |  |

#### Adjuvant therapy, negative circumferential margin, moderately high risk, <5 cm from the anal verge

---

Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement), red = Rarely Appropriate (median 1-3 without disagreement)
<table>
<thead>
<tr>
<th></th>
<th>Chemoradiation (plus ≥4 months of chemo)</th>
<th>Chemotherapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 nodes dissected</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>≥12 nodes dissected</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement)

**Adjuvant therapy, negative circumferential margin, moderately high risk, 5-10 cm from the anal verge**

<table>
<thead>
<tr>
<th></th>
<th>Chemoradiation (plus ≥4 months of chemo)</th>
<th>Chemotherapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 nodes dissected</td>
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<td>6</td>
</tr>
<tr>
<td>≥12 nodes dissected</td>
<td>6</td>
<td>6</td>
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Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement)

**Adjuvant therapy, negative circumferential margin, moderately high risk, >10 cm from the anal verge**

<table>
<thead>
<tr>
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<th>Chemoradiation (plus ≥4 months of chemo)</th>
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<tbody>
<tr>
<td>&lt;12 nodes dissected</td>
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<td>7</td>
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<tr>
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<td>7</td>
<td>7</td>
</tr>
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</table>

Green = Appropriate (median 7-9 without disagreement)

**Adjuvant therapy, negative circumferential margin, high risk, <5 cm from the anal verge**

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</tbody>
</table>

Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement)

**Adjuvant therapy, negative circumferential margin, high risk, 5-10 cm from the anal verge**

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<td>5</td>
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</tbody>
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Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement), grey = May Be Appropriate due to disagreement
Adjuvant therapy, negative circumferential margin, high risk, >10 cm from the anal verge

<table>
<thead>
<tr>
<th></th>
<th>Chemoradiation (plus ≥4 months of chemo)</th>
<th>Chemo alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;12 nodes dissected</td>
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<td>6</td>
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<td></td>
<td></td>
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</tbody>
</table>

Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement)

Section 3: Medically inoperable patients

Medically inoperable, good performance status (ECOG 0-1), local symptoms present

<table>
<thead>
<tr>
<th></th>
<th>External beam RT alone</th>
<th>Endorectal brachytherapy</th>
<th>Chemoradiation</th>
<th>Chemoradiation plus endorectal brachytherapy</th>
<th>Chemo alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 cm from anal verge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10 cm from anal verge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 cm from anal verge</td>
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<td></td>
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<td></td>
<td></td>
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</tbody>
</table>

Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement), red = Rarely Appropriate (median 1-3 without disagreement)

Medically inoperable, good performance status (ECOG 0-1), local symptoms absent

<table>
<thead>
<tr>
<th></th>
<th>External beam RT alone</th>
<th>Endorectal brachytherapy</th>
<th>Chemoradiation</th>
<th>Chemoradiation plus endorectal brachytherapy</th>
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<tbody>
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</tr>
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<td>5-10 cm from anal verge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 cm from anal verge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Green = Appropriate (median 7-9 without disagreement), yellow = May Be Appropriate (median 4-6 without disagreement), red = Rarely Appropriate (median 1-3 without disagreement)

Medically inoperable, poor performance status (ECOG ≥2), local symptoms present

<table>
<thead>
<tr>
<th></th>
<th>External beam RT alone</th>
<th>Endorectal brachytherapy</th>
<th>Chemoradiation</th>
<th>Chemoradiation plus endorectal brachytherapy</th>
<th>Chemo alone</th>
</tr>
</thead>
<tbody>
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<td>&lt;5 cm from anal verge</td>
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</tr>
<tr>
<td>5-10 cm from anal verge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 cm from anal verge</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Medically inoperable, poor performance status (ECOG ≥2), local symptoms absent**

<table>
<thead>
<tr>
<th></th>
<th>External beam RT alone</th>
<th>Endorectal brachytherapy</th>
<th>Chemoradiation</th>
<th>Chemoradiation plus endorectal brachytherapy</th>
<th>Chemotherapy alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 cm from anal verge</td>
<td>6</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5-10 cm from anal verge</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>&gt;10 cm from anal verge</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Yellow = May Be Appropriate (median 4-6 without disagreement), red = Rarely Appropriate (median 1-3 without disagreement)

**Section 4: Patients with very low lying tumor refusing APR**

**Patient with very low lying tumor refusing abdominoperineal resection**

<table>
<thead>
<tr>
<th></th>
<th>Chemoradiation (standard dose)</th>
<th>Chemoradiation (standard dose) plus endorectal brachytherapy</th>
<th>Chemoradiation with EBRT boost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Green = Appropriate (median 7–9 without disagreement)

**Intensity-modulated radiation therapy**

**Please rate the appropriateness of using IMRT to deliver:**

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant short-course RT</th>
<th>Neoadjuvant chemoradiation</th>
<th>Adjuvant therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Yellow = May Be Appropriate (median 4-6 without disagreement)
### Appendix 2: Expert Panel members who were leads of rectal cancer clinical trials – January to June 2014

<table>
<thead>
<tr>
<th>Panelist (specialty)</th>
<th>Trial Name</th>
<th>Role in Trial</th>
<th>Phase of trial at time of Expert Panel Participation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salma Jabbour (radiation oncology)</td>
<td>None</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Harvey Mamon (radiation oncology)</td>
<td>None</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Patrick Francke (radiation oncology)</td>
<td>None</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Richard Goldberg (medical oncology)</td>
<td>None</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Bruce Lin (medical oncology)</td>
<td>Bayer 15983 (NCT01939223) - A Randomized, Double-blind, Placebo-controlled Phase-III Study of Adjuvant Regorafenib Versus Placebo for Patients With Stage IV Colorectal Cancer After Curative Treatment of Liver Metastases (COAST)</td>
<td>Site principal investigator</td>
<td>Patient accrual</td>
</tr>
<tr>
<td></td>
<td>PledPharma PP095 (NCT01619423) - A Double Blinded Randomised Three Armed Phase II Trial of PledOx in Two Different Doses in Combination With FOLFOX6 Compared to Placebo + FOLFOX6 in Patients With Advanced Metastatic Colorectal (Stage IV) Cancer (PLIANT)</td>
<td>Site principal investigator</td>
<td>Patient accrual</td>
</tr>
<tr>
<td></td>
<td>Pfizer B2151005 (NCT01925274) - A Randomized Phase 2 Study Of PF-05212384 Plus Irinotecan Versus Cetuximab Plus Irinotecan In Patients With KRAS Wild Type Metastatic Colorectal Cancer</td>
<td>Site principal investigator</td>
<td>Patient accrual</td>
</tr>
<tr>
<td></td>
<td>Pfizer B2151007 (NCT01937715) - An Open-Label, Multi-Center, Randomized Phase 1b/2 Study Of PF-05212384 Plus 5-Fluorouracil-Leucovorin-Irinotecan (FOLFIRI) Versus Bevacizumab Plus FOLFIRI In Metastatic Colorectal Cancer</td>
<td>Site principal investigator</td>
<td>Patient accrual</td>
</tr>
<tr>
<td>Julio Garcia-Aguilar (surgery)</td>
<td>Trial Evaluating 3-year Disease Free Survival in Patients With Locally Advanced Rectal Cancer Treated With Chemoradiation Plus Induction or Consolidation Chemotherapy and Total Mesorectal Excision or Non-operative Management</td>
<td>Principal investigator</td>
<td>Preparation for accrual/patient accrual</td>
</tr>
<tr>
<td>George Chang (surgery)</td>
<td>ACOSOG Z6051: A Phase III Prospective Randomized Trial Comparing Laparoscopic-assisted Resection Versus Open Resection for Rectal Cancer</td>
<td>Principal investigator</td>
<td>Patient accrual</td>
</tr>
<tr>
<td>Study Title</td>
<td>Principal investigator</td>
<td>Patient accrual</td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>------------------------</td>
<td>-----------------</td>
<td></td>
</tr>
<tr>
<td><strong>NCCTG N1048:</strong> A Phase II/III Trial of Neoadjuvant FOLFOX, with Selective Use Of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision</td>
<td>Principal investigator</td>
<td>Patient accrual</td>
<td></td>
</tr>
<tr>
<td>A single blind, randomized, controlled study to evaluate the safety and effectiveness of EVICE</td>
<td>Principal investigator</td>
<td>Patient accrual</td>
<td></td>
</tr>
<tr>
<td></td>
<td>l as an adjunct to GI anastomosis techniques, 2012-0235</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>David Dietz</strong> (surgery)</td>
<td>Timing of rectal cancer response to chemoradiation</td>
<td>Site principal investigator</td>
<td>Data analysis</td>
</tr>
<tr>
<td><strong>Jeffrey Tokar</strong> (gastro)</td>
<td>CGI-066: Assessing Intratumoral Heterogeneity and Chemoradiation Response In Locally Advanced Rectal Cancer Utilizing Sequencing and PET/CT</td>
<td>Sub-investigator</td>
<td>Patient accrual</td>
</tr>
<tr>
<td><strong>(CIRB) N1048:</strong> A Phase II/III trial of Neoadjuvant FOLFOX, with Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Low Anterior Resection with Total Mesorectal Excision</td>
<td>Sub-investigator</td>
<td>Patient accrual</td>
<td></td>
</tr>
<tr>
<td><strong>Marilyn Schapira</strong> (internal med)</td>
<td>None</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>