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Rectal Cancer, Version 2.2018

Clinical Practice Guidelines in Oncology

Al B. Benson III, MD; Alan P. Venook, MD; Mahmoud M. Al-Hawary, MD; Lynette Cederquist, MD; Yi-Jen Chen, MD, PhD; Kristen K. Ciombor, MD; Stacey Cohen, MD; Harry S. Cooper, MD; Dustin Deming, MD; Paul F. Engstrom, MD; Jean L. Grem, MD; Axel Grothey, MD; Howard S. Hochster, MD; Sarah Hoffe, MD; Steven Hunt, MD; Ahmed Kamel, MD; Natalie Kirilcuk, MD; Smitha Krishnamurthi, MD; Wells A. Messersmith, MD; Jeffrey Meyerhardt, MD, MPH; Mary F. Mulcahy, MD; James D. Murphy, MD, MS; Steven Nurkin, MD, MS; Leonard Saltz, MD; Sunil Sharma, MD; David Shibata, MD; John M. Skibber, MD; Constantinos T. Sofocleous, MD, PhD, FSIR, FCIRSE; Elena M. Stoffel, MD, MPH; Eden Stotsky-Himelfarb, BSN, RN; Christopher G. Willett, MD; Evan Wuthrick, MD; Kristina M. Gregory, RN, MSN, OCN; Lisa Gurski, PhD; and Deborah A. Freedman-Cass, PhD

Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer address diagnosis, staging, surgical management, perioperative treatment, management of recurrent and metastatic disease, disease surveillance, and survivorship in patients with rectal cancer. This portion of the guidelines focuses on the management of localized disease, which involves careful patient selection for curative-intent treatment options that sequence multimodality therapy usually comprised of chemotherapy, radiation, and surgical resection.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2018, an estimated 43,030 new cases of rectal cancer will occur in the United States (25,920 cases in men; 17,110 cases in women), and an estimated 50,630 people will die from rectal and colon cancer combined.[1] Despite

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Rectal Cancer are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the NCCN Rectal Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Rectal Cancer Panel members can be found on page 901. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

these statistics, the incidence per 100,000 population of CRC decreased from 60.5 in 1976 to 46.4 in 2005.[2] In fact, the incidence of CRC decreased at a rate of approximately 2.9% per year or greater between 2005 and 2014.[1] The incidence rate of CRC reported by the CDC for 2011 was 40.0 per 100,000 persons.[3] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[4] and is currently down by approximately 50% from peak mortality rates.[1] These improvements in incidence of and mortality from CRC are thought to be a result of better treatment modalities and cancer prevention and earlier diagnoses through screening.

Despite the observed improvements in the overall CRC incidence rate, a retrospective cohort study of the SEER CRC registry found that the incidence of CRC in patients aged <50 years has been increasing.[5] The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients aged 20 to 34 years by 2030. The cause of this trend is currently unknown.

This discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, management of recurrent and metastatic disease, patient surveillance, and survivorship. These guidelines overlap considerably with the NCCN Guidelines for Colon Cancer, especially in the treatment of metastatic disease. Recommendations in these guidelines are classified as category 2A except

Text cont. on page 881.

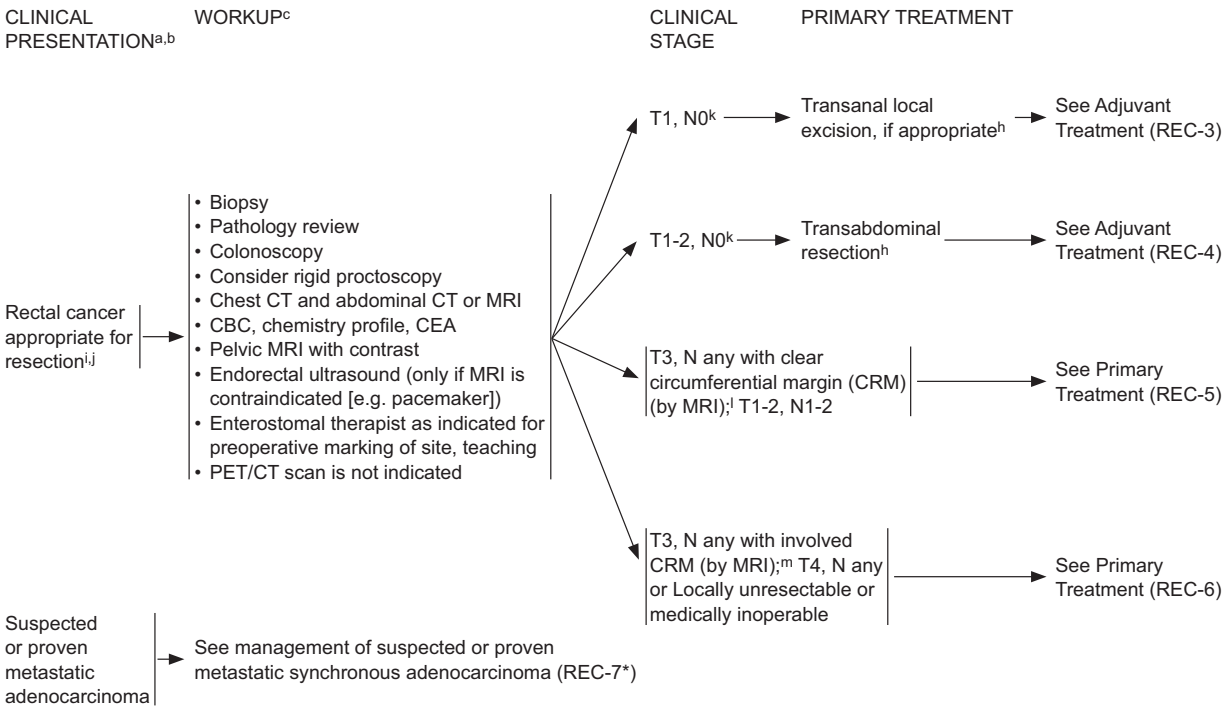
NCCN Rectal Cancer Panel Members

*Al B. Benson III, MD/Chair†
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
*Alan P. Venook, MD/Vice-Chair†‡
UCSF Helen Diller Family Comprehensive Cancer Center
Mahmoud M. Al-Hawary, MDϕ
University of Michigan Rogel Cancer Center
Lynette Cederquist, MDÞ
UC San Diego Moores Cancer Center
Yi-Jen Chen, MD, PhD§
City of Hope Comprehensive Cancer Center
Kristen K. Ciombor, MD†
Vanderbilt-Ingram Cancer Center
Stacey Cohen, MD†
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance
Harry S. Cooper, MD≠
Fox Chase Cancer Center
Dustin Deming, MD†
University of Wisconsin Carbone Cancer Center
Paul F. Engstrom, MD†
Fox Chase Cancer Center
Jean L. Grem, MD†
Fred & Pamela Buffett Cancer Center
Axel Grothey, MD†
Mayo Clinic Cancer Center
Howard S. Hochster, MD†
Yale Cancer Center/Smilow Cancer Hospital
Sarah Hoffe, MD§
Moffitt Cancer Center
Steven Hunt, MD¶
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine
Ahmed Kamel, MDϕ
University of Alabama at Birmingham Comprehensive Cancer Center
Natalie Kirilcuk, MD¶
Stanford Cancer Institute
Smitha Krishnamurthi, MD†Þ
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute
Wells A. Messersmith, MD†
University of Colorado Cancer Center
Jeffrey Meyerhardt, MD, MPH†
Dana-Farber Cancer Institute
Mary F. Mulcahy, MD‡†
Robert H. Lurie Comprehensive Cancer Center of Northwestern University
James D. Murphy, MD, MS§
UC San Diego Moores Cancer Center
Steven Nurkin, MD, MS¶
Roswell Park Comprehensive Cancer Center
Leonard Saltz, MD†‡Þ
Memorial Sloan Kettering Cancer Center
Sunil Sharma, MD†
Huntsman Cancer Institute at the University of Utah
David Shibata, MD¶
St. Jude Children's Research Hospital/ The University of Tennessee Health Science Center
John M. Skibber, MD¶
The University of Texas MD Anderson Cancer Center
Constantinos T. Sofocleous, MD, PhD, FSIR, FCIRSEϕ
Memorial Sloan Kettering Cancer Center
Elena M. Stoffel, MD, MPH¤
University of Michigan Rogel Cancer Center
Eden Stotsky-Himelfarb, BSN, RN¥
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins
Christopher G. Willett, MD§
Duke Cancer Institute
Evan Wuthrick, MD§
The Ohio State University Comprehensive Cancer Center – James Cancer Hospital and Solove Research Institute

NCCN Staff: Deborah A. Freedman-Cass, PhD; Kristina M. Gregory, RN, MSN, OCN; and Lisa Gurski, PhD

*Discussion Section Writing Committee

Specialties: †Medical Oncology; §Radiotherapy/Radiation Oncology; ¶Surgery/Surgical Oncology; ≠Pathology; ‡Hematology/Hematology Oncology; ÞInternal Medicine; ϕDiagnostic/Interventional Radiology; ¤Gastroenterology; ¥Patient Advocate



*Available online, in these guidelines, at NCCN.org.
†To view the most recent version of these guidelines, visit NCCN.org.

[a]All patients with rectal cancer should be counseled for family history. Patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal†.
[b]For melanoma histology, see the NCCN Guidelines for Melanoma†.
[c]See Principles of Imaging (REC-A*).
[h]See Principles of Surgery (REC-C*).
[i]For optimizing care of older adult patients with cancer, see the NCCN Guidelines for Older Adult Oncology†.
[j]The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.
[k]T1-2, N0 should be based on assessment of pelvic MRI (preferred) or endorectal ultrasound.
[l]CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia, levator muscles and not invading into the intersphincteric plane.
[m]CRM measured at the closest distance of the tumor to the mesorectal fascia. Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.

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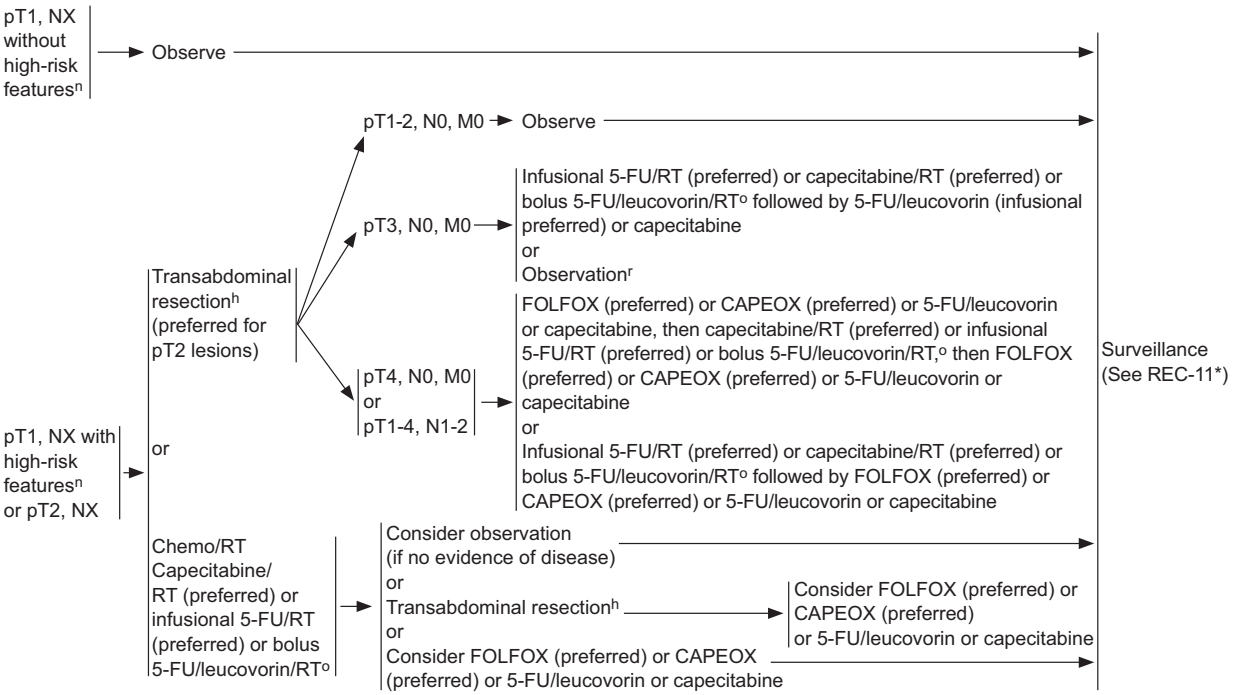
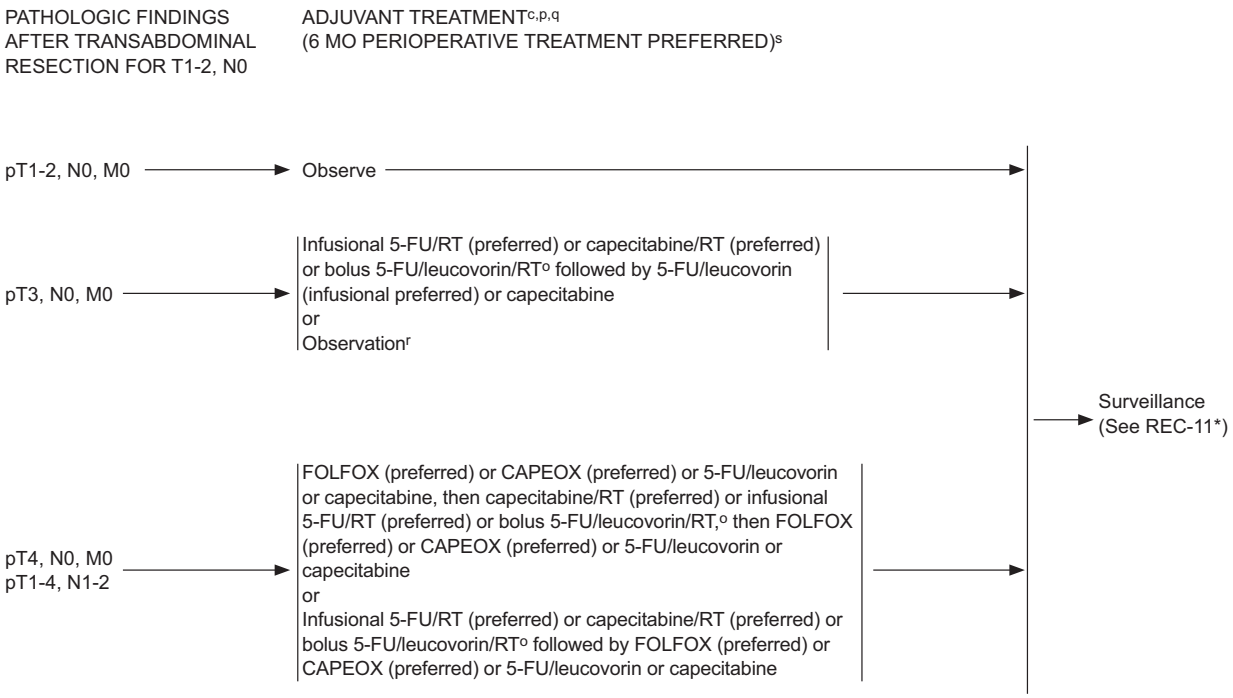
PATHOLOGIC FINDINGS AFTER TRANSANAL LOCAL EXCISION FOR T1, N0

ADJUVANT TREATMENT[c,p,q] (6 MO PERIOPERATIVE TREATMENT PREFERRED)[s]



*Available online, in these guidelines, at NCCN.org.

[c]See Principles of Imaging (REC-A*).
[h]See Principles of Surgery (REC-C*).
[n]High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion (submucosal invasion to the lower third of the submucosal level).
[o]Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p]See Principles of Adjuvant Therapy (REC-D*).
[q]See Principles of Radiation Therapy (REC-E*).
[r]Observation following transabdominal resection can be considered in patients with pT3N0 rectal cancer if the tumor was well-differentiated or moderately well-differentiated carcinoma invading less than 2 mm into the mesorectum, without lymphatic or venous vessel involvement and was located in upper rectum. Willett CG, Badizadegan K, Ancukiewicz M, Shellito PC. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999;42:167-173.
[s]A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.



*Available online, in these guidelines, at NCCN.org.

[c]See Principles of Imaging (REC-A*).
[o]Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p]See Principles of Adjuvant Therapy (REC-D*).
[q]See Principles of Radiation Therapy (REC-E*).
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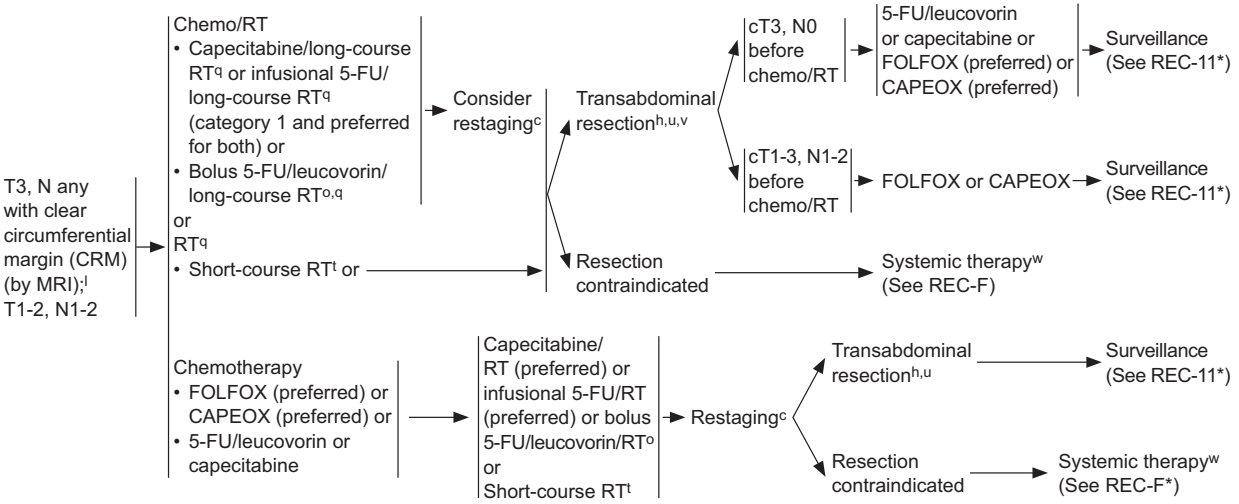

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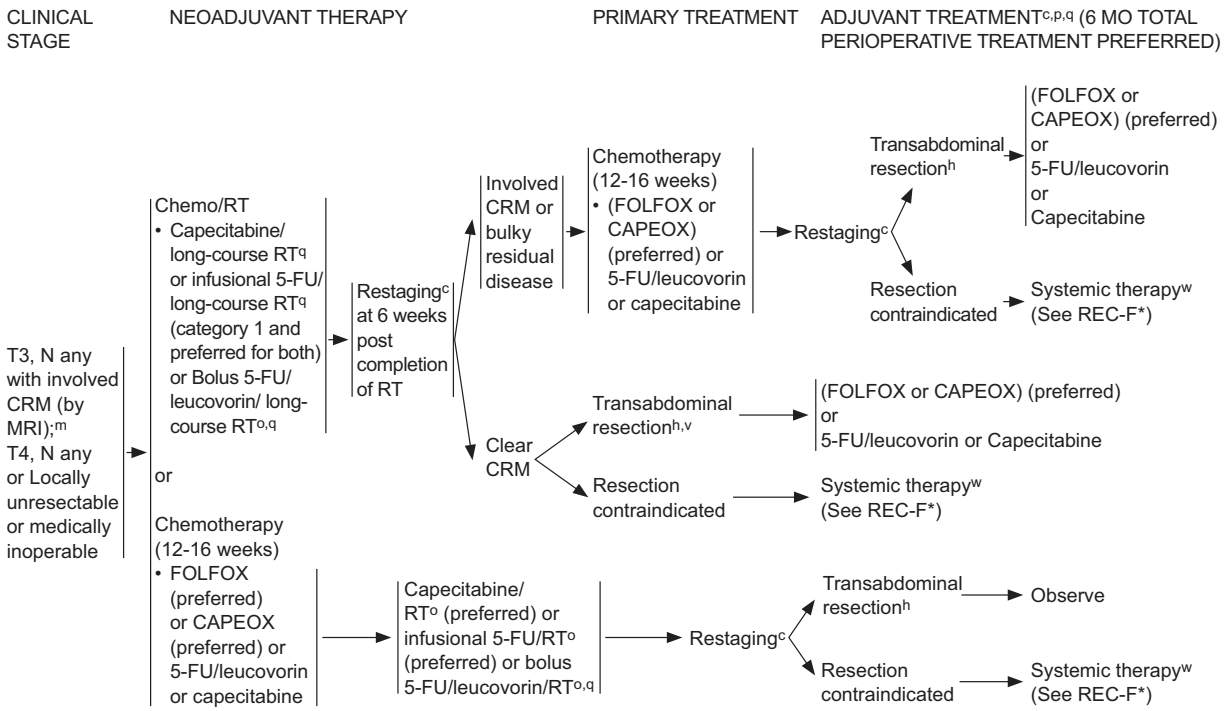
[c]See Principles of Imaging (REC-A*).
[h]See Principles of Surgery (REC-C*).
[l]CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia, levator muscles and not invading into the intersphincteric plane.
[o]Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p]See Principles of Adjuvant Therapy (REC-D*).
[q]See Principles of Radiation Therapy (REC-E*).
[t]Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.
[u]If patient treated with short course RT, surgery should be within 1 week or delayed 6-8 weeks.
[v]In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for non-operative management should involve a careful discussion with the patient of his/her risk tolerance.
[w]FOLFOXIRI is not recommended in this setting.



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[c]See Principles of Imaging (REC-A*).
[h]See Principles of Surgery (REC-C*).
[m]CRM measured at the closest distance of the tumor to the mesorectal fascia. Involved CRM: within 1mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane
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[w]FOLFOXIRI is not recommended in this setting.

Cont. from page 875.

where noted. The panel unanimously endorses patient participation in a clinical trial over standard or accepted therapy, especially for cases of advanced disease and for patients with locally aggressive CRC receiving combined modality treatment.

Management of Localized Rectal Cancer

Rectal cancer is a cancerous lesion in the rectum, which lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI (see Figure 1, online, in these guidelines, at NCCN.org). The rectum ends at the superior border of the functional anal canal, defined as the palpable upper border of the anal sphincter and puborectalis muscles of the anorectal ring.

Determination of an optimal treatment plan for patients with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative or palliative), consideration must also be given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence and preserving genitourinary functions. For patients with distal rectal cancer, in particular, the simultaneous achievement of the goals of cure and minimal impact on quality of life can be challenging.[6] Furthermore, risk of pelvic recurrence is higher in patients with rectal cancer compared with colon cancer, and locally recurrent rectal cancer is associated with a poor prognosis.[7–9] Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoradiotherapy (chemoRT), chemotherapy, and operative treatment for most patients is recommended.[10]

Clinical Evaluation/Staging

The initial clinical workup of patients with rectal cancer provides important preoperative information on the clinical stage of disease. Because the clinical stage is used to direct decisions regarding choice of primary treatment, including surgical intent (eg, curative or palliative) and whether to recommend preoperative chemoRT, implications of either clinically understaging or overstaging rectal cancer can be substantial.

Patients who present with rectal cancer appropriate for resection require a complete staging evaluation, which includes total colonoscopy to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum; rigid proctoscopy can also be considered. Additionally, a complete physical examination, including carcinoembryonic antigen determination and assessment of performance status to determine operative risk, is required.

Clinical staging is also based on histopathologic examination of the specimen obtained via biopsy or local excision (eg, excised polyps). Endoscopic biopsy specimens of the lesion should undergo careful pathology review for evidence of invasion into the muscularis mucosa. If removal of the rectum is contemplated, early consultation with an enterostomal therapist is recommended for preoperative marking of the site and patient teaching purposes.

Imaging also plays a critical role in preoperative evaluation, both for evaluation of the primary tumor and to assess for the presence of distant metastases. Preoperative imaging for rectal cancer includes chest/abdominal CT and pelvic MRI, or chest CT and abdominal/pelvic MRI, as described in the following sections.

Preoperative Pelvic Imaging in Rectal Cancer: The accessibility of rectal cancer to evaluation by pelvic MRI with contrast makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.[11,12] Pelvic MRI has the ability to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia so as to provide information useful in the prediction of the clear circumferential margin (CRM) before radical surgery.[13–18] The CRM by MRI is measured at the closest distance of the tumor to the mesorectal fascia. The panel defines a clear CRM as >1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane; whereas an involved CRM is within 1 mm of mesorectal fascia or, for lower third rectal tumors, within 1 mm from levator muscle. Results of 5-year follow-up from the MERCURY Study show that high-resolution MRI can accurately assess the CRM preoperatively, differentiating patients with low- and high-risk disease.[19] Patients with MRI-clear CRM had a 5-year overall survival (OS) of 62.2% compared with 42.2% for MRI-involved CRM (hazard ratio [HR], 1.97; 95% CI, 1.27–3.04; $P<.01$). Preoperative MRI imaging also predicted disease-free survival (DFS; HR, 1.65; 95% CI, 1.01–2.69; $P<.05$)

and local recurrence (HR, 3.50; 95% CI, 1.53–8.00; *P*<.05). MRI has also been shown to be accurate for the prediction of T and N stage.[20] A group of experts developed consensus guidelines for standardized imaging of rectal cancer by MRI.[21]

Only a limited number of studies using CT for the purpose of T staging have been performed, and it is not currently considered to be an optimal method for staging the extent of tumor penetration.[13,16,22] In addition, CT has poor sensitivity for the prediction of CRM status.[23] Furthermore, CT has lower sensitivity and specificity for the prediction of lymph node involvement than MRI (CT, 55% and 74%; MRI, 66% and 76%, respectively).[22] Therefore, pelvic CT is not recommended for rectal staging.

A 2004 meta-analysis showed that endoscopic ultrasound (EUS) and MRI have similar sensitivities and specificities for the evaluation of lymph nodes (EUS, 67% and 78%; MRI, 66% and 76%, respectively).[22] However, newer data suggest that EUS is not very accurate for rectal cancer staging.[24] Furthermore, EUS cannot fully image high or bulky rectal tumors nor regions beyond the immediate area of the primary tumor (eg, tumor deposits, vascular invasion).[13] Another disadvantage of EUS is a high degree of operator dependence.[22] At this time, the panel believes that EUS should only be used to evaluate the pelvis if MRI is contraindicated (eg, due to a pacemaker).

Preoperative Imaging for Distant Metastases: Additional information for the occurrence of distant metastases should be determined preoperatively through chest and abdominal imaging with CT scan and CT or MRI, respectively. Lung metastases occur in approximately 4% to 9% of patients with CRC,[25–27] and studies have shown that 20% to 34% of patients with CRC present with synchronous liver metastases.[28,29]

The panel consensus is that a PET scan is not indicated for preoperative staging of rectal cancer. If done, PET/CT does not supplant a contrast-enhanced diagnostic CT scan. PET/CT should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or in patients with a strong contraindication to intravenous contrast.

Restaging/Assessing Treatment Response: Restaging after neoadjuvant treatment is performed to detect distant metastases that would change the treatment strategy, plan the surgical approach, and, increasingly, determine if additional therapy or resection can be avoided for select patients (see "Watch-and-Wait Approach for Clinical Complete Responders" and "Preoperative Chemotherapy Without ChemoRT," pages 891 and 889, respectively). MRI, CT, and EUS have been used for restaging after neoadjuvant treatment but the accuracy of these techniques for determining T stage and lymph node involvement is limited.[30–38] As with initial staging, the panel recommends pelvic MRI for restaging with chest and abdominal imaging to assess for distant disease. Abdominal/pelvic CT has been shown to identify resectable liver metastases in 2.2% of patients (95% CI, 0.8%–5.1%) during restaging, with false-positives that could cause unnecessary treatment in 1.3% (95% CI, 0.3%–3.9%).[39] In this study, the use of restaging abdominal/pelvic CT was at physician discretion, and no difference was seen in recurrence-free survival (RFS) for those who had an abdominal/pelvic CT before resection compared with those who did not.

Advanced functional MRI techniques (eg, dynamic contrast-enhanced MRI, diffusion-weighted MRI) allow for the measurement of microcirculation, vascular permeability, and tissue cellularity, and thus may be useful for determining response to neoadjuvant treatment and restaging patients with rectal cancer.[37,40–42] FDG-PET/CT is also being investigated for its ability to accurately determine response to neoadjuvant treatment.[41,43]

At this time, the panel recommends chest CT, abdominal CT or MRI, and pelvic MRI for restaging.

Surgical Approaches

A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions.[44,45] These methods include local procedures, such as polypectomy, transanal local excision, and transanal endoscopic microsurgery (TEM), and more invasive procedures involving a transabdominal resection (eg, low anterior resection [LAR], proctectomy with total mesorectal excision [TME] and coloanal anastomosis, abdominoperineal resection [APR]).[44,45]

Transanal Local Excision: Transanal local excision is only appropriate for selected T1,N0 early-stage cancers. Small (<3 cm), well- to moderately differentiated tumors that are within 8 cm of the anal

verge and limited to <30% of the rectal circumference, and for which there is no evidence of nodal involvement can be approached with transanal local excision with negative margins.[46] In addition, full thickness excision must be feasible.

TEM can facilitate excision of small tumors through the anus when lesions can be adequately identified in the rectum. TEM may be technically feasible for more proximal lesions. Although data are limited, a 2015 meta-analysis found that TEM may achieve superior oncologic outcomes compared with transanal local excision.[47] A small prospective, single-blinded, randomized trial compared laparoscopic surgery with laparoscopy combined with TEM in 60 patients with rectal cancer.[48] The TEM group had shorter operation times and hospital stays, and no local nor distant recurrences were seen in either group after a median follow-up of 28 months.

Both transanal local excision and TEM involve a full-thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (>3 mm) deep and mucosal margins are required, and tumor fragmentation should be avoided.

The locally excised specimen should be oriented and pinned before fixation and brought to the pathologist by the surgeon to facilitate an oriented histopathologic evaluation of the specimen. If pathologic examination reveals adverse features such as positive margins, lymphovascular invasion, poor differentiation, or invasion into the lower third of the submucosa (sm3 level),[49,50] a more radical resection is recommended.

Data are limited on long-term patient outcomes, including risk of local recurrence, for patients undergoing local excision for T2 tumors.[51] Results of a multi-institutional, single-arm, open-label, nonrandomized, phase II trial suggest that chemoRT with CAPEOX followed by local excision may be a safe alternative to transabdominal resection in patients with T2,N0 distal rectal cancer.[52] A meta-analysis also suggests that this approach of neoadjuvant chemoRT followed by local excision may be a safe and effective alternative for patients with any T and any N stage of rectal cancer who refuse or are unfit for transabdominal resection.[53] Further studies in this area are needed.

Advantages of a local procedure include minimal morbidity (eg, a sphincter-sparing procedure) and mortality and rapid postoperative recovery.[6,51] Limitations of a local excision include the absence of pathologic staging of nodal involvement. Further, evidence indicates that lymph node micrometastases are common in early rectal lesions and unlikely to be identified by endorectal ultrasound.[54] These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.[51,55,56] A retrospective study of 282 patients undergoing either transanal local excision or radical resection for T1 rectal cancer from 1985 to 2004 showed local recurrence rates of 13.2% and 2.7% (P=.001), respectively.[56] A similar retrospective study of 2,124 patients showed local recurrence rates of 12.5% and 6.9% for those undergoing local excision versus standard resection, respectively (P=.003).[51] More recently, an analysis of >164,000 individuals from the National Cancer Database (NCDB) with resected, invasive, nonmetastatic rectal cancer diagnosed from 1998 to 2010 found that positive margins were more likely after local excision compared with transabdominal excision in both the T1 and T2 populations (95% vs 76% in T1/T2 combined; P<.001).[57] In the T1,N0 population, a small but significant decrease in OS was also noted in the local excision group. Interestingly, limited data suggest that TEM might have superior oncologic outcomes in patients with stage I rectal cancer compared with radical resection,[55,58] although not all studies have seen such results.[59]

Thus, careful patient selection for local excision of T1,N0 rectal cancer is important, as well as the careful examination of the resection specimen with subsequent transabdominal resection in patients found to have T2 disease or high-risk features, as described previously.

Transabdominal Resection: Patients with rectal cancer who do not meet requirements for local surgery should be treated with a transabdominal resection. Organ-preserving procedures that maintain sphincter function are preferable, but not possible in all cases. Preoperative chemoRT may result in tumor downsizing and a decrease in tumor bulk (see "Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease," page 885); sphincter preservation may become possible in cases where initial tumor bulk prevented consideration of such surgery and exposure to the tumor is improved by neoadjuvant treatment.

In transabdominal resections, TME is recommended. A TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a "tumor package" through sharp dissection, and is designed to spare the autonomic nerves.[6,45,60] The lymphatic drainage regions of rectal tumors are influenced by their position in the rectum. More distal tumors are more likely to be characterized by both upward and lateral lymphatic drainage, whereas the likelihood of only upward mesorectal drainage is much higher for more proximal tumors.[61] The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.[62] The NCCN panel does not recommend extension of nodal dissection beyond the field of resection (eg, into the distribution of iliac lymph nodes) unless these nodes are clinically suspicious. In cases where anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis.

For lesions in the mid to upper rectum, an LAR extended to 4 to 5 cm below the distal edge of the tumor using TME, followed by creation of a colorectal anastomosis, is the treatment of choice. Where creation of an anastomosis is not possible, colostomy is required. Wide TME is recommended to facilitate adequate lymphadenectomy and improve the probability of achieving negative circumferential margins.

An APR with TME should be performed when the tumor directly involves the anal sphincter or levator muscles. An APR is also necessary in cases where a margin-negative resection of the tumor would result in loss of anal sphincter function and incontinence. An APR involves en bloc resection of the rectosigmoid, rectum, and anus, as well as the surrounding mesentery, mesorectum (TME), and perianal soft tissue, and it necessitates creation of a colostomy.[63] In the NSABP R-04 trial, patients who had an APR reported worse body image, worse micturition symptoms, and less sexual enjoyment at 1-year after surgery than those who had sphincter-sparing surgery.[64] An extralevator APR may have benefits over a conventional APR approach, including lower rates of intraoperative perforation, CRM involvement, and local recurrence, although inconsistencies are seen between studies.[65,66]

Pathologists play a key role in evaluating the surgical specimen, including a macroscopic assessment of both its external appearance/completeness and the CRM.[67,68] The panel defines a positive CRM as tumor within 1 mm from the transected margin (see "Pathology," available online, in the complete guidelines, at NCCN.org).[69–71] Detailed descriptions of how the quality of the mesorectal specimens should be scored were provided in the Dutch Rectal Cancer TME Trial, and these guidelines are endorsed by the NCCN panel.[70]

Recent retrospective comparisons of outcomes in patients undergoing an APR versus an LAR for the treatment of rectal cancer have shown that those treated with an APR have worse local control and OS.[72,73] Whether these differences can be attributed to the APR alone, to patient- and tumor-related characteristics, or some combination of these factors is presently unclear. However, results from a recent retrospective study of 3,633 patients with T3–4 rectal cancer tumors included in 5 large European trials suggest that there is an association between the APR procedure itself and the increased risks of recurrence and death.[72] Importantly, quality of life between patients with or without a permanent colostomy appears to be fairly comparable.[74,75]

Laparoscopic Resection: Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer have been maturing in recent years.[76–79] One large, prospective, multicentre study, which included 4,405 patients with rectal cancer but was not randomized, found no differences in recurrence or survival, although complications and other measures of quality indicated a benefit to the laparoscopic approach.[80] The phase III COLOR II trial, powered for noninferiority, randomized patients with localized rectal cancer to laparoscopic or open surgery. Short-term secondary end points were met, with patients in the laparoscopic arm losing less blood, having shorter hospital stays, and having a quicker return of bowel function, but with longer operation times.[81] No differences were seen in completeness of resection, percentage of patients with a positive CRM, morbidity, or mortality between the arms. The primary end point of locoregional recurrence at 3 years was identical in the 2 groups (5.0%), and no statistically significant differences were seen in DFS or OS.[76]

In the CLASICC trial, which compared laparoscopically assisted resection to open resection, nearly half of the 794 patients were diagnosed with

rectal cancer.[82] No significant differences in local recurrence, DFS, or OS were observed between the 2 groups of patients with colon or rectal cancer based on surgical approach. A 5-year follow-up of the CLASICC trial showed that this lack of difference in local recurrence, DFS, or OS was maintained for patients with rectal cancer, despite a trend towards improved 5-year OS after laparoscopic surgery (52.9% and 60.3% for open and laparoscopic surgery, respectively; *P*=.132).[83]

The COREAN trial randomized patients with stage II–III low- to mid-rectal cancer to an open or laparoscopic resection, and short-term benefits were seen with the laparoscopic approach.[84] The primary end point, 3-year DFS, did not differ between the 2 groups at 72.5% (95% CI, 65.0%–78.6%) for open surgery and 79.2% (95% CI, 72.3%–84.6%) for the laparoscopic group.[77] Factors that may confound conclusions drawn from randomized studies comparing open surgery with laparoscopically assisted surgery for CRC have been described,[85] and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Two other trials, ACOSOG Z6051 and ALaCaRT, have reported pathologic outcomes.[78,79] In Z6051, the primary end point was a composite of CRM >1 mm, negative distal margin, and TME completeness.[78] No significant differences were observed between the arms in these 3 measures or in the composite of successful resection. For example, complete or nearly complete TME was achieved in 92.1% (95% CI, 88.7%–95.5%) in the laparoscopic resection arm and 95.1% (95% CI, 92.2%–97.9%) in the open resection arm, for a difference of −3.0 (95% CI, −7.4 to 1.5; *P*=.20). However, criteria for noninferiority of the laparoscopic approach were not met. In ALaCaRT, the primary end point was also a composite of resection quality measures.[79] Successful resections were achieved in 82% of the laparoscopic resection arm and 89% of the open resection arm, for a difference of –7.0% (95% CI, –12.4% to infinity). A negative CRM was achieved in 93% and 97%, respectively (risk difference, –3.7%; 95% CI, –7.6% to 0.1%; *P*=.06). Similar to Z6051, the criteria for noninferiority of the laparoscopic approach were not met in ALaCaRT. Longer follow up with oncologic outcomes from these trials is needed.

An analysis of results from >18,000 patients in the NCDB undergoing LAR for rectal cancer found short-term oncologic outcomes to be similar between the open and laparoscopic approaches.[86] In addition, older reviews and meta-analyses consistently found the laparoscopic approach to be safe and feasible,[77,87–100] even though a 2017 meta-analysis found that the risk for a non–complete mesorectal excision is significantly higher in patients receiving a laparoscopic resection compared with those receiving an open resection.[101]

Several studies have also compared outcomes of robotic-assisted resection to conventional laparoscopic resection.[102–106] Comparable results are generally seen between the approaches in conversion to open resection, TME quality, postoperative complications, and quality of life.

In conclusion, some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared with open surgery,[76,77] whereas other studies have shown the laparoscopic approach to be associated with higher rates of CRM positivity and incomplete TME.[78,79] The NCCN Guidelines Panel defined principles by which minimally invasive resection of rectal cancer can be considered: the procedure can be considered by an experienced surgeon, should include thorough abdominal exploration, and should be limited to lower-risk tumors, as outlined in the guidelines. An international group of experts has defined standards for the technical details of laparoscopic TME.[107]

Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease

Neoadjuvant/adjuvant therapy of stage II (T3–4, node-negative disease with tumor penetration through the muscle wall) or stage III (node-positive disease without distant metastasis) rectal cancer usually includes locoregional treatment due to the relatively high risk of locoregional recurrence. This risk is associated with the close proximity of the rectum to pelvic structures and organs, the absence of a serosa surrounding the rectum, and technical difficulties associated with obtaining wide surgical margins at resection. In contrast, adjuvant treatment of colon cancer is more focused on preventing distant metastases because this disease is characterized by lower rates of local recurrence.

Although radiation therapy (RT) has been associated with decreased rates of local recurrence of rectal cancer, it is also associated with increased toxicity

(eg, radiation-induced injury, hematologic toxicities) relative to surgery alone.[108–110] It has been suggested that some patients with disease at lower risk of local recurrence (eg, proximal rectal cancer staged as T3,N0,M0, characterized by clear margins and favorable prognostic features) may be adequately treated with surgery and adjuvant chemotherapy.[108,111,112] According to the results of a retrospective multicenter study,[113] 22% of 188 patients clinically staged with T3,N0 rectal cancer by either EUS or MRI and who subsequently received preoperative chemoRT had positive lymph nodes following pathologic review of the surgical specimens, thus suggesting that many patients are understaged and would benefit from chemoRT. Therefore, the NCCN Guidelines recommend preoperative chemoRT for patients with T3,N0 disease.

Combined-modality therapy consisting of surgery, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis (chemoRT), and chemotherapy is recommended for most patients with stage II or III rectal cancer. Use of perioperative pelvic RT for patients with stage II/III rectal cancer continues to evolve. The current NCCN Guidelines recommend several possible sequences of therapy, depending on predicted CRM status and response to initial therapy. The total duration of perioperative therapy, including chemoRT and chemotherapy, should not exceed 6 months.

Preoperative Versus Postoperative RT: Several studies have compared the administration of RT preoperatively versus postoperatively for stage II/III rectal cancer.[114,115] A large prospective, randomized trial from the German Rectal Cancer Study Group (the CAO/ARO/AIO-94 trial) compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer.[114] Study results indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs 13%; *P*=.006) and treatment-associated toxicity (27% vs 40%; *P*=.001), although OS was similar in the 2 groups. Long-term follow-up of this trial was later published.[116] The improvement in local control persisted, with the 10-year cumulative incidence of local recurrence at 7.1% and 10.1% in the preoperative and postoperative treatment arms, respectively (*P*=.048). OS at 10 years was also similar between the groups (59.6% and 59.9%, respectively; *P*=.85), in addition to DFS and occurrence of distant metastases.

Interestingly, a recent SEER database analysis of 4,724 patients with T3,N0 rectal cancer found that RT given after resection was associated with a significant decrease in risk for cancer death compared with surgery without any RT (HR, 0.69; 95% CI, 0.58–0.82; *P*<.001) and RT given before resection was not (HR, 0.86; 95% CI, 0.72–1.04; *P*=.13).[117]

Putative advantages to preoperative RT, versus postoperatively, are related to both tumor response and preservation of normal tissue.[114,115,118] First, reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Although some studies have indicated that preoperative RT or chemoRT is associated with increased rates of sphincter preservation in patients with rectal cancer,[114,115] this conclusion is not supported by 2 meta-analyses of randomized trials involving preoperative chemoRT in this patient population.[119,120] Second, irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative RT can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by postsurgical adhesions. Finally, preoperative RT that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected).

One disadvantage of using preoperative RT is the possibility of overtreating early-stage tumors that do not require adjuvant RT.[114,121] Improvements in preoperative staging with pelvic MRI have allowed for more accurate staging, but the risk of overstaging disease has not been eliminated.[113] Weighing these advantages and disadvantages, the NCCN panel recommends preoperative chemoRT for patients with stage II/III rectal cancer. Postoperative chemoRT is recommended when stage I rectal cancer is upstaged to stage II/III after pathologic review of the surgical specimen.

Concurrent Chemotherapy With RT: A number of randomized trials have evaluated the effectiveness of the addition of concurrent chemotherapy to RT administered either preoperatively after clinical evaluation/staging (eg, T3–4 by EUS) or postoperatively after pathologic staging of rectal cancer as pT3 and/or N1–2.[122] Putative benefits of the addition of chemotherapy concurrent with either preoperative or postoperative RT include local RT sensitization

and systemic control of disease (ie, eradication of micrometastases). Preoperative chemoRT also has the potential to increase rates of pathologic complete response (pCR) and sphincter preservation.

In a study of patients with T3–4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative RT alone or preoperative concurrent chemoRT with 5-FU/LV, no difference in OS or sphincter preservation was observed in the 2 groups, although patients receiving chemoRT were significantly more likely to exhibit a pCR (11.4% vs 3.6%; $P<.05$) and grade 3/4 toxicity (14.6% vs 2.7%; $P<.05$) and were less likely to exhibit local recurrence of disease (8.1% vs 16.5%; $P<.05$).[122]

Preliminary results of a phase III trial that included an evaluation of the addition of chemotherapy to preoperative RT in patients with T3–4 resectable rectal cancer demonstrated that use of 5-FU/LV chemotherapy enhanced the tumoricidal effect of RT when the 2 approaches were used concurrently.[123] Significant reductions in tumor size, pTN stage, and lymphatic invasion, vascular invasion, and perineural invasion rates were observed with use of combined-modality therapy compared with use of RT and surgery without chemotherapy.[123] More mature results from this trial, which included 4 treatment groups (preoperative RT; preoperative chemoRT; preoperative RT + postoperative chemotherapy; and preoperative chemoRT + postoperative chemotherapy), indicated that no significant differences in OS were associated with adding 5-FU–based chemotherapy preoperatively or postoperatively.[124]

The conclusions from these trials were supported in a 2009 systematic review that included 4 randomized controlled trials.[125] In addition, a recent Cochrane review of 6 randomized controlled trials found that chemotherapy added to preoperative RT in patients with locally advanced stage III rectal cancer reduced the risk of local recurrence, but had no effect on OS, 30-day mortality, sphincter preservation, and late toxicity.[126] Similarly, a separate Cochrane review of stage II and III resectable disease found that the addition of chemotherapy to preoperative RT enhanced pathologic response and improved local control, but had no effect on DFS or OS.[127] Another recent meta-analysis of 5 randomized controlled trials compared neoadjuvant chemoRT with neoadjuvant RT and had similar conclusions.[110]

Regarding the type of chemotherapy administered concurrently with RT,[112] the equivalence of bolus 5-FU/LV and infusional 5-FU in concurrent chemoRT for rectal cancer is supported by the results of a phase III trial (median follow-up, 5.7 years). This study reported similar outcomes, with respect to OS and relapse-free survival, when an infusion of 5-FU or bolus 5-FU/LV was administered concurrently with postoperative RT, although hematologic toxicity was greater in those who received bolus 5-FU.[128] On the other hand, results from an earlier trial from the North Central Cancer Treatment Group (NCCTG) showed that postoperative administration of infusional 5-FU during pelvic irradiation was associated with longer OS when compared with bolus 5-FU.[129] Most of the patients in this study had node-positive disease. The NCCN panel considers bolus 5-FU/LV/RT as an option for patients not able to tolerate capecitabine or infusional 5-FU (both preferred in the chemoRT setting).

Recent studies have shown that capecitabine is equivalent to 5-FU in perioperative chemoRT therapy.[130,131] The randomized NSABP R-04 trial examined the preoperative use of infusional 5-FU ± oxaliplatin versus capecitabine ± oxaliplatin in 1,608 patients with stage II or III rectal cancer.[131,132] No differences in locoregional events, DFS, OS, complete pathologic response, sphincter-saving surgery, or surgical downstaging were seen between the regimens, although toxicity was increased with the inclusion of oxaliplatin.

Similarly, a phase III randomized trial in which 401 patients with stage II or III rectal cancer received capecitabine-based or 5-FU–based chemoRT either preoperatively or postoperatively showed that capecitabine was noninferior to 5-FU with regard to 5-year OS (75.7% vs 66.6%, respectively; $P=.0004$), with capecitabine showing borderline significance for superiority ($P=.053$).[130] Furthermore, in this trial capecitabine demonstrated a significant improvement in 3-year DFS (75.2% vs 66.6%; $P=.034$).[130] Because of these studies, capecitabine given concurrently with RT is listed in the NCCN Guidelines as an acceptable alternative to infusional 5-FU for patients who are able to manage the responsibilities inherent in self-administered, oral chemotherapy.

Addition of Oxaliplatin: In attempts to improve on the outcomes achieved with neoadjuvant 5-FU/RT

or capecitabine/RT, several large randomized phase III trials (ACCORD 12, STAR-01, NSABP R-04, CAO/ARO/AIO-04, and FOWARC) addressed the addition of oxaliplatin to these regimens. In a planned interim report of primary tumor response in the STAR-01 trial, grade 3 and 4 adverse events occurred more frequently in patients receiving infusional 5-FU/oxaliplatin/RT than in those receiving infusional 5-FU/RT (24% vs 8%; *P*<.001), although there was no difference in pathologic response between the study arms (16% pCR in both arms).[133] Recently reported results of the NSABP R-04 trial also showed that the addition of oxaliplatin did not improve clinical outcomes including the end points of locoregional events, DFS, OS, pCR, sphincter-saving surgery, and surgical downstaging, although it increased toxicity.[131,132] Further follow-up of these trials is necessary to determine if there is a difference in local recurrence rates and progression-free survival over time. The primary end points of OS for the STAR-01 trial will be reported in the future.

Similar results were seen in the ACCORD 12/0405-Prodige 2 trial, which compared capecitabine/RT (45 Gy) with CAPEOX/RT (50 Gy), with the primary end point of pCR.[134] pCR rates were similar at 19.2% and 13.9% (*P*=.09) for the oxaliplatin-containing arm and the control arm, respectively. Although patients treated with oxaliplatin and the higher radiation dose in the ACCORD 12 trial had an increased rate of minimal residual disease at time of surgery (39.4% vs 28.9%; *P*=.008), this did not translate to improved local recurrence rates, DFS, or OS at 3 years. The results did not change after longer follow-up.[135]

Results of the German CAO/ARO/AIO-04 trial have been published.[136,137] This trial also assessed the addition of oxaliplatin to a fluorouracil RT regimen. In contrast to STAR-01, NSABP R-04, and ACCORD 12, higher rates of pCR were seen in the oxaliplatin arm (17% vs 13%; *P*=.038),[137] but this could be due to differences in the fluorouracil schedule between the arms.[138] The primary end point of this trial, the 3-year DFS rate, was 75.9% (95% CI, 72.4%–79.5%) in the oxaliplatin arm versus 71.2% (95% CI, 67.6%–74.9%) in the control group (*P*=.03).[136] Importantly, oxaliplatin was also added to the adjuvant therapy in the AIO-04 trial but not in the other trials, so cross-trial comparisons are limited.

In line with CAO/ARO/AIO-04, the Chinese FOWARC phase III open-label multicenter trial, which randomized patients with locally advanced rectal cancer to neoadjuvant treatment consisting of infusional 5-FU/LV/RT, FOLFOX/RT, or FOLFOX, found that FOLFOX/RT resulted in higher rates of pCR and downstaging than the other regimens.[139]

Another randomized multicenter phase III trial examined the addition of oxaliplatin during concurrent capecitabine chemoRT in the adjuvant setting for pathologic stage II/III disease.[140] Interim analysis showed no significant difference in 3-year DFS, OS, local recurrences, or distant metastases, with an increase in grade 3/4 acute toxicity in the CAPEOX/RT group.

Based on the results available to date, the addition of oxaliplatin to neoadjuvant chemoRT is not recommended at this time.

Addition of Targeted Agents: The randomized phase II EXPERT-C trial assessed the CR rate with the addition of cetuximab to RT in 165 patients.[141] Patients in the control arm received CAPEOX followed by capecitabine/RT, then surgery followed by CAPEOX; those randomized to the cetuximab arm received the same therapy with weekly cetuximab throughout all phases. A significant improvement in OS was seen in patients with *KRAS* exon 2/3 wild-type tumors treated with cetuximab (HR, 0.27; 95% CI, 0.07–0.99; *P*=.034). However, the primary end point of CR rate was not met, and other phase II trials have not shown a clear benefit to the addition of cetuximab in this setting.[142,143] Further evaluation of this regimen is warranted.

The randomized, multicenter, phase II SAKK 41/07 trial evaluated the addition of panitumumab to preoperative capecitabine-based chemoRT in patients with locally advanced *KRAS* wild-type rectal cancer.[144] The primary end point was pathologic near-complete plus complete tumor response, which occurred in 53% of patients (95% CI, 36%–69%) in the panitumumab arm versus 32% (95% CI, 16%–52%) in the control arm. Patients receiving panitumumab experienced increased rates of grade ≥3 toxicity.

Another phase II study, RaP/STAR-03, also assessed the potential role of panitumumab in neoadjuvant chemoRT in patients with *KRAS* wild-type, cT3,N0 or cT2–3,N1–2, mid to low rectal cancer with a predicted negative CRM.[145] All patients were

treated with panitumumab/chemoRT followed by resection and adjuvant FOLFOX. The primary end point of pCR was observed in 10.9% (95% CI, 4.7–17.1), not meeting the prespecified level of 16%.

A phase II study of 57 patients with resectable T3–4 rectal cancer evaluated preoperative treatment with capecitabine, oxaliplatin, bevacizumab, and RT followed by surgery 8 weeks later and adjuvant FOLFOX/bevacizumab.[146] The 5-year OS rate was 80%, and the 5-year relapse-free survival rate was 81%. However, the primary end point of pCR was not met, significant toxicities were observed, and compliance with adjuvant therapy was low.

Additional phase II trials assessing the effects of adding irinotecan or bevacizumab to neoadjuvant or adjuvant regimens have begun.[147–149] However, at this time, the panel does not endorse the use of bevacizumab, cetuximab, panitumumab, irinotecan, or oxaliplatin with concurrent RT for rectal cancer.

Induction Chemotherapy and the Total Neoadjuvant Therapy Approach: Several small trials have tested the utility of a course of neoadjuvant chemotherapy preceding chemoRT and resection,[150–155] which is referred to as a total neoadjuvant therapy (TNT) approach. In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CAPEOX either before chemoRT or after surgery.[152,156] Similar pCR rates were seen between arms, and induction chemotherapy appeared to be less toxic and better tolerated. Another phase II trial randomized patients to chemoRT and surgery with or without FOLFOX induction therapy.[154] There were no differences between the clinical outcomes, but those receiving induction therapy experienced higher toxicity. The phase II AVACROSS study assessed the safety and efficacy of adding bevacizumab to induction therapy with CAPEOX prior to capecitabine/bevacizumab-chemoRT and surgery.[155] The regimen was well tolerated with a pCR rate of 36%.

A single-institution retrospective cohort analysis of patients with T3–4 or node-positive rectal cancer compared outcomes after either a (1) traditional approach of neoadjuvant chemoRT then resection with planned adjuvant chemotherapy (n=320) or (2) TNT approach of induction chemotherapy then chemoRT before resection (n=308). Patients in the TNT group received a greater percentage of the planned chemotherapy dose than those in the adjuvant chemotherapy group. CR rates were 36% and 21% in the TNT and adjuvant chemotherapy groups, respectively.

Possible benefits of using chemotherapy first include the early prevention or eradication of micrometastases, higher rates of pCR, minimizing the time patients need an ileostomy, facilitating resection, and improving the tolerance and completion rates of chemotherapy. This approach was added to the 2015 version of these guidelines as an acceptable option.

Preoperative Chemotherapy Without ChemoRT: A small, single-center, phase II pilot trial treated patients with stage II or III rectal cancer with induction FOLFOX/bevacizumab chemotherapy followed by chemoRT only in those with stable or progressive disease and resection in all patients.[157] All 32 of the participants had an R0 resection, and the 4-year DFS was 84% (95% CI, 67%–94%). Another phase II trial, which included 60 patients with stage II/III rectal cancer (excluding cT4b) from 8 institutions, assessed the R0 resection rate after FOLFOX + bevacizumab or cetuximab.[158] An R0 resection was achieved in 98.3% of the patients, and the pCR rate was 16.7%.

The phase III FOWARC trial, discussed previously, compared neoadjuvant therapy with and without RT (without additional therapy for those with stable or progressive disease), and found that neoadjuvant FOLFOX without RT resulted in lower rates of pCR than regimens that included RT (6.6% vs 14.0% for 5-FU/RT, and 27.5% for FOLFOX/RT).[139] The rate of downstaging in the FOLFOX group was similar to the 5-FU/RT group but lower than the FOLFOX/RT group (35.5% vs 37.1% for 5-FU/RT and 56.4% for FOLFOX/RT).

A 2015 systematic review identified 1 randomized phase III trial, 6 single-arm phase II trials, and 1 retrospective case series study that addressed the effectiveness of neoadjuvant chemotherapy (without chemoRT) and surgery in patients with locally advanced rectal cancer.[159] The ranges of R0 resection and pCR rates were 90% to 100% and 4% to 33%, respectively.

The ongoing N1048/C81001/Z6092 PROSPECT trial by the Alliance for Clinical Trials in Oncology is also asking whether chemotherapy alone is effective in treating stage II or III rectal cancer in patients with at least 20% tumor regression following neoadjuvant treatment (ClinicalTrials.gov identifier: NCT01515787). This approach could spare

patients the morbidities associated with RT, but the panel has considered it investigational at this time.

Technical Aspects of RT: Multiple RT fields should include the tumor or tumor bed with a 2- to 5-cm margin, presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures; inclusion of the inguinal nodes for tumors invading into the distal anal canal can also be considered. Recommended doses of RT are typically 45 to 50 Gy in 25 to 28 fractions to the pelvis using 3 or 4 fields. Positioning and other techniques to minimize radiation to the small bowel are encouraged. RTOG has established normal pelvic contouring atlases for women and men (available at https://www.rtog.org/CoreLab/ContouringAtlases.aspx).[160] Intensity-modulated RT should only be used in the setting of a clinical trial or in unique clinical situations such as re-irradiation of previously treated recurrent disease or unique anatomical situations.

Coordination of preoperative chemoRT and surgery is important. Although longer intervals from completion of chemoRT to surgery have been shown to be associated with an increase in pCR rates,[161–166] it is unclear whether such longer intervals are associated with clinical benefit. Results of one NCDB analysis suggest that an interval of >8 weeks was associated with increased odds of pCR,[167] whereas other similar analyses concluded that an interval >56 or 60 days (8–8.5 weeks) is associated with higher rates of positive margins, lower rates of sphincter preservation, and/or shorter survival.[168,169]

The GRECCAR6 phase III, multicenter, randomized, open-label, parallel-group controlled trial randomized patients with stage II/III rectal cancer treated with chemoRT to a 7-week or 11-week interval before surgery.[170] The pCR rate was not different between the groups (15.0% vs 17.4%; *P*=.60), but morbidity (44.5% vs 32%; *P*=.04), medical complications (32.8% vs 19.2%; *P*=.01), and rate of complete mesorectal resection (78.7% vs 90%; *P*=.02) were worse in the 11-week group. The rate of anastomotic leaks and the mean length of hospital stay were similar between the groups.

Based on these data, the NCCN panel recommends an interval of 5 to 12 weeks following completion of full-dose 5.5-week chemoRT prior to surgical resection for patients treated with preoperative chemoRT to allow patient recuperation from chemoRT-associated toxicities.

Short-Course RT: Several European studies have examined the efficacy of a shorter course of preoperative RT (25 Gy over 5 days), not combined with chemotherapy, for the treatment of rectal cancer. Results of the Swedish Rectal Cancer Trial evaluating the use of short-course RT administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence with this approach compared with surgery alone.[171] However, a follow-up study published in 2005 showed that the patients with short-course preoperative RT had an increased relative risk for postoperative hospitalization due to bowel obstructions and other gastrointestinal complications.[172] A number of other studies also investigating the effectiveness of preoperative short-course RT in patients with rectal cancer staged as T1–3 demonstrated that OS was not significantly affected despite improvements in local control of disease.[173–175] A more recent multicenter randomized study of 1,350 patients with rectal cancer compared short-course preoperative RT and no postoperative treatment with no preoperative RT and a postoperative approach that included chemoRT in selected patients (ie, those with a positive CRM following resection) and no RT in patients without evidence of residual disease following surgery.[176] Results indicated that patients in the preoperative RT arm had significantly lower local recurrence rates and a 6% absolute improvement in 3-year DFS (*P*=.03), although no difference in OS was observed between the study arms.[176,177]

Long-term follow-up (12 years) of one of the short-course RT trials (Dutch TME trial[174]) was reported.[178] Analysis showed that 10-year survival was significantly improved in patients with stage III disease and a negative CRM in the RT plus surgery group versus surgery alone (50% vs 40%; *P*=.032).[178] However, this long follow-up showed that secondary malignancies and other non-rectal cancer causes of death were more frequent in the RT group than in the control group (14% vs 9% for secondary malignancies), negating any survival advantage in the node-negative subpopulation.

A few studies have compared short-course RT to long-course chemoRT. One randomized study of 312 patients in Poland directly compared preoperative short-course RT with more conventional preop-

erative long-course chemoRT, and found no differences in local recurrence or survival.[179] Similarly, an Australian/New Zealand trial (TROG 01.04) that randomized 326 patients to short-course RT or long-course chemoRT found no differences in local recurrence and OS rates.[180] In addition, rates of late toxicity, distant recurrence, and relapse-free survival were not significantly different between the arms. Patients in the long-course arm were more likely to experience serious adverse events (eg, radiation dermatitis rates, 0% vs 5.6%; *P*=.003), whereas those in the short-course arm were more likely to have a permanent stoma (38.0% vs 29.8%; *P*=.13).[181] However, no overall difference was seen in health-related quality of life between the groups.[182] Finally, a trial compared short-course RT with long-course chemoRT with delayed surgery in both groups.[183] Although the long-course arm experienced greater tumor downsizing and downstaging compared with short-course treatment, no differences were seen in the R0 resection rates or postoperative morbidity. The 3-year DFS was better in the long-course arm than in the short-course arm (75% vs 59%; *P*=.022), with no difference in OS.[184]

A 2014 systematic review identified 16 studies (randomized controlled trials, phase II trials, and retrospective studies) that addressed the interval between short-course RT and resection of rectal cancer.[185] Lower rates of severe acute post-RT toxicity but higher rates of minor postoperative complications were seen in the immediate surgery group (1- to 2-week interval) compared with the delayed surgery group (5- to 13-week interval). pCR rates were significantly higher in the delayed surgery group, with no differences in sphincter preservation and R0 resection rates.

Overall, it appears that short-course RT gives effective local control and the same OS as more conventional RT schedules, and therefore is considered as an appropriate option for patients with T3,N0 or T1–3,N1–2 rectal cancer. A multidisciplinary evaluation, including a discussion of the need for downstaging and the possibility of long-term toxicity, is recommended when considering short-course RT. Short-course RT is not recommended for T4 disease at this time. The ongoing randomized RAPIDO trial (ClinicalTrials.gov identifier: NCT01558921) is assessing DFS at 3 years with the use of preoperative short-course RT followed by 6 cycles of CAPEOX before resection in patients with clinical stage T3–4 rectal cancer.[186]

Response to Neoadjuvant Treatment: Following neoadjuvant therapy, 50% to 60% of patients are downstaged, with approximately 20% of patients showing a pCR.[187–193] Recent studies have suggested that the response to neoadjuvant treatment correlates with long-term outcomes in patients with rectal cancer. In the MERCURY prospective cohort trial, 111 patients were assessed by MRI and pathologic staging.[194] On multivariate analysis, MRI-assessed tumor regression grade was significantly associated with OS and DFS. Patients with a poor tumor regression grade had 5-year survival rates of 27% versus 72% for those with a good tumor regression grade (*P*=.001), and DFS rates were 31% versus 64% (*P*=.007). Similarly, in the CAO/ARO/AIO-94 trial, patients with pathologic complete regression had 10-year cumulative incidence of distant metastasis and DFS of 10.5% and 89.5%, respectively, while those with poor regression had corresponding incidences of 39.6% and 63%.[195] A recent retrospective review of 725 patients with rectal cancer found similar results.[191] In this study, pathologically determined response to neoadjuvant treatment correlated with long-term outcomes, with 5-year RFS rates of 90.5%, 78.7%, and 58.5% for patients with complete, intermediate, and poor responses, respectively (*P*<.001). Distant metastases and local recurrences also correlated with level of response. Other studies have also shown a prognostic effect of response to neoadjuvant treatment.[196,197]

In addition to its prognostic value, there is some initial evidence of predictive value to neoadjuvant treatment response. Subgroup analysis of the EORTC 22921 trial showed that patients downstaged to ypT0–2 were more likely to benefit from adjuvant chemotherapy than those with ypT3–4 staging.[187] Similar results were seen from another retrospective review.[198] Although no prospective data to predict the benefit of adjuvant therapy in patients with tumor downstaging or a pCR exist, the NCCN panel believes that such patients should be strongly considered for adjuvant chemotherapy.

Watch-and-Wait Approach for Clinical Complete Responders: As preoperative treatment and imaging modalities have improved, some have suggested that patients with a clinical CR to chemoRT may

be able to be spared the morbidities of surgery. In 2004, Habr-Gama et al[199] retrospectively compared the outcomes of 71 patients who were observed without surgery after complete clinical response (27% of patients) with the outcome of 22 patients (8%) who had incomplete clinical responses but complete pathologic responses post-TME. OS and DFS rates at 5 years were 100% and 92%, respectively, in the nonoperative group compared with 88% and 83%, respectively, in the resected group. However, other studies did not achieve as impressive results, and many clinicians were skeptical of the approach.[200]

A more recent prospective study included a more thorough assessment of treatment response and used very strict criteria to select 21 of 192 patients (11%) with clinical CRs who were then observed with careful follow-up and compared with 20 patients with a complete pathologic response after resection.[201] Only 1 patient in the nonoperative group developed a local recurrence after a mean follow-up of 25 months; that patient underwent successful surgery. No statistical differences in long-term outcomes were seen between groups. Cumulative probabilities for 2-year DFS and OS were 89% (95% CI, 43%–98%) and 100%, respectively, in the watch-and-wait group and 93% (95% CI, 59%–99%) and 91% (95% CI, 59%–99%), respectively, in the resected group. Short-term functional outcomes, however, were better in the watch-and-wait group, with better bowel function scores, less incontinence, and 10 patients avoiding permanent colostomy.

Other nonrandomized, prospective studies have added to the growing evidence that the nonoperative approach may warrant further study.[202–205] For example, one study showed that 49% of patients experienced a complete clinical response after 5-FU–based chemoRT, and found that strict surveillance in these patients, with resection of recurrences when possible, resulted in a 5-year RFS of 69%, which rose to 94% after resections were performed.[203]

Several systematic reviews have been published on the nonoperative approach.[206–208] All the reviews show that the approach is likely safe with the use of resection in patients with tumor regrowth, but that the data are very limited.

Despite the impressive results of prospective trials, many still believe that longer follow-up, larger sample sizes, and additional careful observational studies are needed before patients with a clinical CR are routinely managed by a watch-and-wait approach.[209] Furthermore, recent studies have found that neither FDG-PET nor MRI nor CT can accurately determine a pCR, complicating the selection of appropriate patients for a nonoperative approach.[30–38,210] In addition, lymph node metastases are still seen in a subset of patients with pCR.[211] Keeping these caveats in mind, the NCCN panel believes that a nonoperative management approach may be considered in centers with experienced multidisciplinary teams after a careful discussion with the patient of their risk tolerance.

The use of nonoperative management in rectal cancer has been increasing in the United States, likely representing both some early adoption of the approach described herein as well as disparities in the receipt of appropriate rectal cancer resection.[212] An analysis of the NCDB from 2004 through 2008 looked at all patients with clinical stage II/III rectal cancer who received neoadjuvant chemoRT only (for whom surgery was "not part of the planned first course of treatment") or neoadjuvant chemoRT plus resection.[213] No data were available regarding the clinical response to neoadjuvant therapy. Although the patients in this study represent a very different population than the trials discussed previously, it is important to note that those with the nonoperative approach had a worse OS (HR, 1.90; 95% CI, 1.75–2.04). These results underscore the importance of careful patient selection, vigilant surveillance, and resection of recurrences for those choosing a watch-and-wait approach.

Adjuvant Chemotherapy: Adjuvant chemotherapy is recommended for all patients with stage II/III rectal cancer after neoadjuvant chemoRT and surgery if they did not receive neoadjuvant chemotherapy regardless of the surgical pathology results, although few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well-defined.[214,215] The addition of 5-FU adjuvant chemotherapy to preoperative chemoRT provided no benefit to the rate of local recurrence in the EORTC Radiotherapy Group trial 22921.[124] However, this study did show an improvement in DFS (HR, 0.87; 95% CI, 0.72–1.04; *P*=.13) of patients receiving adjuvant chemotherapy (±RT) following preoperative RT (±5-FU–based chemotherapy).[124] Long-term results of the EORTC 22921 trial confirmed that adjuvant 5-FU chemotherapy did not

improve OS, and the difference in DFS was less pronounced than following the previous analysis (HR, 0.91; 95% CI, 0.77–1.08; *P*=.29).[216] Limitations of this trial include the fact that only 43% of participants received the full course of adjuvant chemotherapy. Other trials have failed to show an improvement in OS or DFS with adjuvant therapy with a fluoropyrimidine alone in this setting.[217,218]

Other trials have investigated the use of more modern agents in the adjuvant setting. The phase III ECOG E3201 trial was designed to investigate the effect of adding either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) to 5-FU/LV–based adjuvant chemotherapy administered to patients with stage II/III rectal cancer after either preoperative or postoperative chemoRT. This study was replaced with an alternative trial with bevacizumab, but results from an initial 165 patients indicated that adjuvant FOLFOX can be safely used in this patient population.[219] The open-label phase II ADORE trial randomized 321 patients with resected rectal cancer and neoadjuvant therapy to adjuvant 5-FU/LV or FOLFOX.[220] The FOLFOX arm had higher 3-year DFS at 71.6% versus 62.9% (HR, 0.66; 95% CI, 0.43–0.99; *P*=.047). The CAO/ARO/AIO-04 trial found an improvement in 3-year DFS when oxaliplatin was added to 5-FU in both neoadjuvant and adjuvant treatment (75.9% vs 71.2%; *P*=.03).[136]

A study in which patients who received neoadjuvant chemoRT and experienced a pCR were observed without additional adjuvant chemotherapy found 5-year DFS and OS rates of 96% and 100%, respectively.[221] In addition, a meta-analysis of 4 randomized trials (1,196 patients) concluded that adjuvant fluorouracil-based chemotherapy (5-FU/LV, capecitabine, or CAPEOX) after preoperative therapy and surgery did not improve OS, DFS, or the rate of distant recurrences in patients with stage II or III rectal cancer.[222] However, more recent trials that found a DFS benefit for the addition of adjuvant oxaliplatin-based adjuvant therapy were not included in this study, and other meta-analyses have come to the opposite conclusion.[223,224] A systematic review published in 2017 identified 8 phase III trials and 1 randomized phase II trial comparing adjuvant chemotherapy with observation in patients with nonmetastatic rectal cancer treated with neoadjuvant chemoRT.[225] The authors reported that the data are not robust enough to warrant routine use of adjuvant therapy in this population.

Most database studies have also failed to see much of a benefit to adjuvant chemotherapy in this setting.[226–228] However, 2 similar analyses that used the NCDB from 2006–2013 or from 2006–2012 and that looked only at patients achieving a pCR after neoadjuvant chemoRT (n=2,891; n=2,764) found a significant improvement in OS with the use of adjuvant chemotherapy.[229,230]

An analysis of the NCCN Outcomes Database for CRC found that, of 2,073 patients with stage II/III rectal cancer who received neoadjuvant chemoRT treatment, 203 patients (9.8%) did not receive any adjuvant chemotherapy as recommended by these guidelines.[231] Multivariate analysis found that complete pathologic response, infection, no closure of ileostomy/colostomy, age, poor performance status, and being on Medicaid or indigent were associated with not receiving adjuvant chemotherapy. Results from the SEER database indicated that even fewer patients in the general population are receiving adjuvant therapy (61.5%) in this setting.[232] Pathologic stage, age, and postoperative readmissions were associated with a decreased likelihood of receiving adjuvant treatment. Other database analyses show that adjuvant chemotherapy is used in 74% to 92% of patients in this setting.[226,227]

Although conclusive data on the benefits of adjuvant therapy in patients with stage II/III rectal cancer are lacking, the panel recommends its use. Choice of regimen depends on initial clinical staging and predicted CRM status, with FOLFOX or CAPEOX as preferred or only options for higher risk patients and 5-FU/LV or capecitabine as additional options in some cases. For example, these less intensive adjuvant chemotherapy options might be especially appropriate for patients who responded to neoadjuvant treatment with 5-FU or capecitabine.

Timing and Duration of Adjuvant Therapy: A 2011 systematic review and meta-analysis of 10 studies involving >15,000 patients with colon or rectal cancer looked at the effect of timing of adjuvant therapy following primary tumor resection.[233] Results of this analysis showed that each 4-week delay in chemotherapy resulted in a 14% decrease in OS, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses.[234] The op-

timal duration of adjuvant treatment in rectal cancer is still unclear.[235,236] In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.[237] The use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) is justified when preoperative chemoRT is administered.

Multigene Assays: Several multigene assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer (see NCCN Guidelines for Colon Cancer, available at NCCN.org).[238]

Among the multigene assays used in colon cancer is the Oncotype DX colon cancer assay, which quantifies the expression of 7 recurrence-risk genes and 5 reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.[239] Clinical validation in patients with stage II and III colon cancer from the QUASAR and NSABP C-07 trials showed that recurrence scores are prognostic for recurrence, DFS, and OS in stage II and III colon cancer, but are not predictive of benefit to adjuvant therapy.[240] For the low, intermediate, and high recurrence risk groups, recurrence at 3 years was 12%, 18%, and 22%, respectively. Similar results were found in other prospectively designed studies.[241,242]

A recent prospectively designed validation study assessed this assay for predicting recurrence risk in patients with stage II and III rectal cancer.[243] For patients who underwent surgery without neoadjuvant therapy in the Dutch TME trial, recurrence score was predictive of recurrence, distant recurrence, and rectal cancer–specific survival. In patients with stage II rectal cancer, recurrence at 5 years was 11%, 27%, and 43% for the low, intermediate, and high recurrence risk groups, respectively.

The panel believes the information from this test can further inform the risk of recurrence over other risk factors, but they question the value added. Furthermore, there is no evidence of predictive value in terms of the potential benefit of chemotherapy in patients with colon or rectal cancer with any of the available multigene assays. The panel believes that there are insufficient data to recommend the use of multigene assays to determine adjuvant therapy for patients with CRC.

Leucovorin Shortage: A leucovorin shortage recently existed in the United States. No specific data guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with leucovorin shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levo-leucovorin is equivalent to 400 mg/m^2 of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients because the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175-mg leucovorin gave similar survival and 3-year recurrence rates as 25-mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for CRC.[244] Another study showed no difference in response rate or survival in patients with metastatic CRC receiving bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) leucovorin.[245] Also, the Mayo Clinic and NCCTG determined that there was no therapeutic difference between the use of high- (200 mg/m^2) or low-dose (20 mg/m^2) leucovorin with bolus 5-FU in the treatment of advanced CRC, although 5-FU doses were different in the 2 arms.[246] Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade ≥II toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

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Individual Disclosures for Rectal Cancer Panel

Panel Member	Clinical Research Support/ Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Mahmoud M. Al-Hawary, MD	None	None	None	4/13/18
Al B. Benson III, MD	None	Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Celgene Corporation; Eli Lilly and Company; EMD Serono, Inc.; Exelixis Inc.; Genentech, Inc.; Genomic Health, Inc.; ImClone Systems Incorporated; Merck & Co., Inc.; Oncosil Medical; sanofi-aventis U.S. LLC; Spectrum Pharmaceuticals, Inc.; and Taiho Parmaceuticals Co., Ltd.	None	2/20/18
Lynette Cederquist, MD	None	None	None	12/4/17
Yi-Jen Chen, MD, PhD	None	None	None	6/6/18
Kristen K. Ciombor, MD	AbbVie, Inc.; Amgen Inc.; Array Biopharma Inc.; Bayer HealthCare; Boston Biomedical, Inc.; Bristol-Myers Squibb Company; Daiichi Sankyo Co.; Incyte Corporation; MedImmune Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; NuCana; Pfizer Inc.; and sanofi-aventis U.S. LLC	None	None	5/16/18
Stacey Cohen, MD	None	None	None	6/11/18
Harry S. Cooper, MD	None	None	None	7/4/17
Dustin Deming, MD	Abbott Laboratories; and Merck & Co., Inc.	Bristol-Myers Squibb Company; and Novocure Ltd	None	8/1/17
Paul F. Engstrom, MD	None	None	None	6/4/18
Jean L. Grem, MD	Elion Oncology; and ICON	None	None	5/25/18
Axel Grothey, MD	None	Bayer HealthCare; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Genentech, Inc.; and Guardant Health Inc.	None	9/15/17
Howard S. Hochster, MD	None	Amgen Inc.; Bayer HealthCare; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Eleison Pharma; Eli Lilly and Company; Genentech, Inc.; Merck & Co., Inc.; and Taiho Parmaceuticals Co., Ltd.	None	8/3/17
Sarah Hoffe, MD	None	None	None	7/27/17
Steven Hunt, MD	None	None	None	6/1/18
Ahmed Kamel, MD	Boston Scientific Corporation	Boston Scientific Corporation; and Sirtex Medical	Bard Peripheral Vascular; and Boston Scientific Corporation	3/12/18
Natalie Kirilcuk, MD	None	None	None	3/21/18
Smitha Krishnamurthi, MD	CytomX Therapeutics, Inc.; and Regeneron Pharmaceuticals, Inc.	None	None	4/30/18
Wells A. Messersmith, MD	Alexo Therapeutics, Inc.; D3 Pharma Limited; Genentech, Inc.; Gilead Sciences, Inc.; Immunomedics, Inc.; Incyte Corporation; Millennium Pharmaceuticals, Inc.; OncoMed Pharmaceuticals, Inc.; Pfizer Inc.; Purdue Pharma LP; and Roche Laboratories, Inc.	Purdue Pharma LP	None	8/29/17
Jeffrey Meyerhardt, MD, MPH	Ignyta, Inc.	Chugai Pharmaceutical Co., Ltd	None	3/16/18
Mary F. Mulcahy, MD	None	None	None	4/26/18
James D. Murphy, MD, MS	None	None	None	4/23/18
Steven Nurkin, MD, MS	None	None	None	6/3/18
Leonard Saltz, MD	Taiho Pharmaceutical Co., Ltd.	None	None	4/4/18
Sunil Sharma, MD	None	Arrien Pharmaceuticals; and Novartis Pharmaceuticals Corporation	ARIAD Pharmaceuticals, Inc.; Blend Therapeutics; Clovis Oncology; Exelixis Inc.; Guardant Health Inc.; and LSK Biopharma	10/18/17
David Shibata, MD	None	None	None	10/19/17
John M. Skibber, MD	None	None	None	4/13/18
Constantinos T. Sofocleous, MD, PhD, FSIR, FCIRSE[a]	None	Sirtex Medical Inc.	Sirtex Medical Inc.	8/1/17
Elena M. Stoffel, MD, MPH	Cancer Prevention Pharmaceuticals	None	None	11/22/17
Eden Stotsky-Himelfarb, BSN, RN	None	None	None	6/11/18
Alan P. Venook, MD	Halozyme, Inc.	AstraZeneca Pharmaceuticals LP; Eisai Inc.; Genentech, Inc.; Roche Laboratories, Inc.; and Taiho Parmaceuticals Co., Ltd.	None	6/4/18
Christopher G. Willett, MD	Extrinsic Health	Extrinsic Health	None	9/22/17
Evan Wuthrick, MD	None	None	None	6/22/17

The NCCN Guidelines Staff have no conflicts to disclose.

[a]The following individuals have disclosed that they have an Employment/Governing Board, Patent, Equity, or Royalty:
Constantinos T. Sofocleous, MD, PhD, FSIR, FCIRSE: Ethicon, Inc.