Rectal Cancer, Version 2.2022

ABSTRACT

This selection from the NCCN Guidelines for Rectal Cancer focuses on management of malignant polyps and resectable nonmetastatic rectal cancer because important updates have been made to these guidelines. These recent updates include redrawing the algorithms for stage II and III disease to reflect new data supporting the increasingly prominent role of total neoadjuvant therapy, expanded recommendations for short-course radiation therapy techniques, and new recommendations for a “watch-and-wait” nonoperative management technique for patients with cancer that shows a complete response to neoadjuvant therapy. The complete version of the NCCN Guidelines for Rectal Cancer, available online at NCCN.org, covers additional topics including risk assessment, pathology and staging, management of metastatic disease, posttreatment surveillance, treatment of recurrent disease, and survivorship.

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NCCN GUIDELINES FOR RECTAL CANCER

All recommendations are category 2A unless otherwise noted.

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

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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.

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The complete NCCN Guidelines for Rectal Cancer are not printed in this issue of JNCCN but can be accessed online at NCCN.org.

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Disclosures for the NCCN Rectal Cancer Panel

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The complete and most recent version of these guidelines is available free of charge at NCCN.org.

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Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2022, an estimated 44,850 new cases of rectal cancer will occur in the United States (26,650 cases in males; 18,200 cases in females). During the same year, it is estimated that 52,580 people will die of rectal and colon cancer combined. Despite these high numbers, the incidence of colorectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005 and, more recently, 38.7 in 2016. In addition, mortality from CRC has been decreasing for decades (since 1947 in women and since 1980 in men) and is currently down by more than 50% from peak mortality rates. These improvements in incidence and mortality from CRC are thought to be a result of cancer prevention and earlier diagnoses through screening and of better treatment modalities. Recent data show continued rapid declines in incidence among those aged 65 years or older, with a decrease of 3.3% annually between 2011 and 2016. CRC incidence and mortality rates vary by race and ethnicity with the highest rates in non-Hispanic Black individuals and lowest in Asian Americans/Pacific Islanders. The magnitude of disparity in mortality rates is double that of incidence rates. Reasons for these racial disparities include differences in risk factor prevalence; access to healthcare and other social determinants of health; comorbidities; and tumor characteristics.

Conversely, incidence has increased among those younger than 65 years, with a 1% annual increase in those aged 50 to 64 years and 2% annual increase in those younger than 50 years. CRC death rates also showed age-dependent trends, declining by 3% annually for those 65 years and older, compared with a 0.6% annual decline for individuals aged 50 to 64 years and a 1.3% annual increase for individuals younger than 50 years. A retrospective cohort study of the SEER CRC registry also found that the incidence of CRC in patients younger than 50 years has been increasing. The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients 20 to 34 years by 2030. The cause of this trend is currently unknown. One review suggests that CRC that occurs in young adult patients may be clinicopathologically and genetically different from CRC in older adults, although this has not been confirmed broadly. If cancer in this population is different, there would be a need to develop specific treatment strategies for this population.
Clinical Presentation and Treatment of Nonmetastatic Disease

Management of Malignant Polyps

A malignant rectal polyp is defined as an adenoma that harbors a focus of cancer invading through the muscularis mucosae and into the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis. Before making a decision about formal surgical resection for an endoscopically resected pedunculated or sessile malignant polyp, physicians should review the pathology and consult with the patient. The panel recommends marking the malignant polyp site at the time of colonoscopy or within 2 weeks if deemed necessary by the surgeon. All patients with a malignant polyp should undergo mismatch repair (MMR) or microsatellite instability (MSI) testing at diagnosis (see REC-1, page 1140).

In patients with pedunculated polyps (adenomas), no additional surgery is required if the polyp has been completely removed endoscopically with favorable histologic features. Favorable histologic features include lesions of grade 1 or 2 without angiolymphatic invasion and with a negative resection margin. There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated using endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than do pedunculated malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable for adverse outcome, and endoscopically removed malignant sessile polyps with grade I or II histology, negative margins, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy alone. Also see the section on “Principles of Pathologic Review” in the full version of the guidelines available online at NCCN.org. Rectal surgery is also an option for these patients.

Rectal surgery is also recommended for patients with malignant polyps with unfavorable histologic features or when the specimen is fragmented or margins cannot be assessed. A complete workup is recommended before surgery for patients with malignant polyps showing these characteristics because more extensive disease is more likely in this situation (see “Clinical Evaluation/Staging,” page 1143). Unfavorable histologic features for adenomas are grade 3 or 4, angiolymphatic invasion, or a positive/
nonassessable margin of resection. In such cases, risk of nodal involvement is higher. It should be noted that no consensus currently exists as to the definition of what constitutes a positive margin of resection. A positive margin for an endoscopically removed polyp has been defined as the presence of tumor within 1 to 2 mm from the transected margin or by the presence of tumor cells within the diathermy of the transected margin.8-12 In addition, several studies have shown that tumor budding is an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.13-16

Rectal surgery consists of either a transanal local excision, if appropriate, or a transabdominal resection. In patients with unfavorable pathologic features, transabdominal resection should be considered to include lymphadenectomy. All patients who have malignant polyps removed by transanal local excision or transabdominal resection should undergo total colonoscopy to rule out other synchronous polyps and should undergo surveillance as described in the guidelines.

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 (Figure 1). 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.

The determination of an optimal treatment plan for an individual patient 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 of minimal impact on quality of life can be challenging.17 Furthermore, the risk of pelvic recurrence is higher in patients with rectal cancer compared with those with colon cancer, and locally recurrent rectal cancer is associated with a poor prognosis.18-20 Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoradiation (chemoRT), chemotherapy, and operative treatment of most patients is recommended.21
Clinical Evaluation/Staging
The initial clinical workup of patients with rectal cancer provides important preoperative information on the clinical stage of disease (see REC-2, page 1141). 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 total neoadjuvant therapy (TNT), the implications of either clinically understaging or overstaging rectal cancer can be substantial. Based on this, a multidisciplinary team evaluation is recommended, including a formal surgical evaluation. A discussion of infertility risks and counseling on fertility preservation, if appropriate, should be performed before the start of treatment.

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. Proctoscopy can be useful in determining the distance of the cancer from the anal verge and length and, therefore, is a consideration. Patients with rectal cancer also require a complete physical examination, including CEA determination and assessment of performance status to determine operative risk.

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. All patients with rectal cancer should undergo MMR or MSI testing at diagnosis to aid in the diagnosis of Lynch syndrome and for clinical trial availability, especially related to checkpoint inhibitors as neoadjuvant therapy (see section on dostarlimab-gxly in “Preoperative Systemic Therapy Without ChemoRT,” page 1153). Those with loss of MMR proteins and/or MSI should be referred for genetic counseling and testing.

Imaging also plays a critical role in preoperative evaluation, for evaluation of the primary tumor, regional adenopathy, 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 subsequent section.

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.\textsuperscript{22,23} 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 circumferential resection margin (CRM) before radical surgery.\textsuperscript{24-26} 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. An involved or threatened CRM, in contrast, is within 1 mm of mesorectal fascia and levator muscles and not invading into the intersphincteric plane.

Published 5-year follow-up results of the MERCURY trial show that high-resolution MRI can accurately assess the CRM preoperatively, differentiating patients with low-risk and high-risk disease.\textsuperscript{31} Patients with MRI-clear CRM had a 5-year overall survival (OS) of 62.2% compared with 42.2% in patients with MRI-involved CRM (hazard ratio [HR], 1.97; 95% CI, 1.27–3.04; \textit{P}<.01). The preoperative MRI imaging also predicted disease-free survival (DFS; HR, 1.65; 95% CI, 1.01–2.69; \textit{P}<.05) and local recurrence (HR, 3.50; 95% CI, 1.53–8.00; \textit{P}<.05). MRI has also been shown to be accurate for the prediction of T and N stage.\textsuperscript{32} ESGAR has developed consensus guidelines for standardized imaging of rectal cancer by MRI.\textsuperscript{33}

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.\textsuperscript{24,27,34} In addition, CT has poor sensitivity for the prediction of CRM status.\textsuperscript{35} Furthermore, CT has lower sensitivity and specificity for the prediction of lymph node involvement than MRI (CT, 55% and 74%; MRI, 66% and 76%).\textsuperscript{34} 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 evaluation of lymph nodes (EUS, 67% and 78%; MRI, 66% and 76%).\textsuperscript{34} However, newer data suggest that EUS is not very accurate for rectal cancer staging.\textsuperscript{36} Furthermore, EUS cannot fully image high or bulky rectal tumors or regions beyond the immediate area of the primary tumor (eg, tumor deposits, vascular invasion).\textsuperscript{24} Another disadvantage of EUS is a high degree of operator dependency.\textsuperscript{34} At this time, the panel recommends that EUS may be used to evaluate the pelvis if MRI is contraindicated (eg, because of a pacemaker), or it may be considered as an alternative for superficial lesions.
### Rectal Cancer, Version 2.2022

#### CLINICAL STAGE

<table>
<thead>
<tr>
<th>T3, N any with involved or threatened CRM (by MRI)</th>
<th>T4, N any or Locally unresectable or medically inoperable</th>
</tr>
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<tbody>
<tr>
<td><strong>TOTAL NEOADJUVANT THERAPY</strong></td>
<td><strong>PRIMARY TREATMENT</strong></td>
</tr>
<tr>
<td>Long-course chemo/RT&lt;sup&gt;6&lt;/sup&gt; or infusional 5-FU&lt;sup&gt;7&lt;/sup&gt; or Short-course RT&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Chemotherapy (12–16 wk) or FOLFOX or CAPEOX &lt;br&gt;Consider FOLFIRINOX (for T4, N+)</td>
</tr>
<tr>
<td></td>
<td>Restaging&lt;sup&gt;9&lt;/sup&gt;</td>
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<td></td>
<td>Transabdominal resection&lt;sup&gt;10,11&lt;/sup&gt; or Surveillance (REC-11*)</td>
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<td></td>
<td>Transabdominal resection&lt;sup&gt;10,11&lt;/sup&gt; or Surveillance (REC-11*)</td>
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**Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.**

**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 (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams.**

### Restaging/Assessing Treatment Response

**Restaging after neoadjuvant treatment is done to detect distant metastases that would change the treatment strategy, to plan the surgical approach, and, increasingly, to determine if additional therapy or resection can be avoided for select patients (see “Watch-and-Wait” Nonoperative Approach for Clinical Complete Responders,” page 1156, and “Preoperative Systemic Therapy Without ChemoRT,” page 1153). 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.**

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% (95% CI, 0.8%–5.1%) of patients during restaging, with false-positive findings that could cause unnecessary treatment in 1.3% (95% CI, 0.3%–3.9%) of patients. In this study, the use of restaging abdominal/pelvic CT was at the physician’s discretion, and no difference was seen in relapse-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. FDG PET/CT
is also being investigated for its ability to accurately determine response to neoadjuvant treatment.\textsuperscript{53,55}

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.\textsuperscript{56,57} 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]).\textsuperscript{56,57}

**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 less than 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.\textsuperscript{58} 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.\textsuperscript{59} A small prospective, single-blind, randomized trial compared laparoscopic surgery with laparoscopy combined with TEM in 60 patients with rectal cancer.\textsuperscript{60} 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 (LVI), poor differentiation, or invasion into the lower third of the submucosa (sm3 level),\textsuperscript{61,62} 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 high-risk T1 or T2 tumors.\textsuperscript{63} A meta-analysis reported a substantial risk of local recurrence in patients with high-risk pT1 and pT2 rectal cancer who receive no additional therapy after local excision.\textsuperscript{64} Completion TME or adjuvant chemoRT (for pT1) were found to mitigate that risk. Results of a multi-institutional, single-arm, open-label, nonrandomized, phase II trial suggest that chemoradiotherapy with CAPEOX (capecitabine, oxaliplatin) followed by local excision may be a safe alternative to transabdominal resection in patients with T2N0 distal rectal cancer.\textsuperscript{65} 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.\textsuperscript{66} 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.\textsuperscript{17,63} Limitations of a local excision include the absence of pathologic staging of nodal involvement. Further, evidence indicates that lymph node micrometastases are both common in early rectal lesions and unlikely to be identified by endorectal ultrasound.\textsuperscript{67} These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.\textsuperscript{63,68,69} A retrospective study of 282 patients undergoing either transanal local excision or radical resection for T1 rectal cancer from 1985 to 2004 showed respective local recurrence
rates of 13.2% and 2.7% for these 2 groups ($P=.001$). A similar retrospective study of 2,124 patients showed local recurrence rates of 12.5% and 6.9% for patients undergoing local excision versus standard resection, respectively ($P=.003$). 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; $P<.001$). 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, although not all studies have seen such results.

Thus, careful patient selection for local excision of T1, N0 rectal cancer is important, as is 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 or TNT may result in tumor downsizing and a decrease in tumor bulk (see “Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease,” page 1148); 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. 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. The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles. The panel does not recommend extension of nodal dissection beyond the field of resection (e.g., into the distribution of iliac lymph nodes) unless these nodes are clinically suspicious. In cases in which 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 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 the 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, the rectum, and the anus, as well as the surrounding mesentery, mesorectum (TME), and perianal soft tissue, and it necessitates creation of a colostomy. In the NSABP R-04 trial, patients who underwent APR reported worse body image, worse micaturation symptoms, and less sexual enjoyment at 1-year post surgery than those who had sphincter-sparing surgery. 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.

Pathologists play a key role in evaluating the surgical specimen, including a macroscopic assessment of both its external appearance/completeness and the CRM. The panel defines an involved or threatened CRM as tumor within 1 mm from the resected margin (see “Pathology” in the full version of the guidelines available online at NCCN.org). Detailed descriptions of how the quality of the mesorectal specimens should be scored were provided in the Dutch Rectal Cancer Trial, and these guidelines are endorsed by the NCCN Panel.

Recent retrospective comparisons of the outcomes of patients undergoing an APR versus an LAR in the treatment of rectal cancer have shown that those treated with an APR have worse local control and OS. Whether these differences can be attributed to the surgical procedure 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 an association between the APR procedure itself and the increased risks of recurrence and death. Importantly, quality of life for patients with or without a permanent colostomy appears to be fairly comparable.

**Laparoscopic Resection**

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer have matured in recent years. One large prospective multicenter 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. The phase III COLOR II trial, powered for non-inferiority, randomized patients with localized rectal cancer to laparoscopic or open surgery. Short-term secondary endpoints 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 surgical times. No differences were seen in completeness of resection, percentage of patients with a positive CRM, morbidity, or mortality between the arms. The primary endpoint 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.

In the CLASICC trial comparing laparoscopically assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer. 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 toward better 5-year OS after laparoscopic surgery (52.9% and 60.3% for open and laparoscopic surgery, respectively; \( P = .132 \)).

The COREAN trial randomized patients with stage II or III low- to midrectal cancer to an open or laparoscopic resection, with short-term benefits seen with the laparoscopic approach. The primary endpoint, 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. Factors that may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically assisted surgery for CRC have been described, and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Two other trials, ACOSOG Z6051 and ALaCaRT, have reported pathologic outcomes. In Z6051, the primary endpoint was a composite of CRM \( \geq 1 \) mm, negative distal margin, and TME completeness. 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, the criteria for noninferiority of the laparoscopic approach were not met in these initial results. Follow-up results of Z6051 reported similar 2-year DFS rates between laparoscopic (79.5%) and open resection (83.2%). Locoregional and distant recurrence rates were also found to be similar between laparoscopic and open resection (4.6% vs 4.5% for locoregional recurrences and 14.6% vs 16.7% for distant recurrences). In ALaCaRT, the primary endpoint was also a composite of resection quality measures. 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%; \( P = .06 \)). Follow-up results for ALaCaRT showed similar recurrence, DFS, and OS rates for laparoscopic versus open resection after 2 years. Two-year locoregional recurrence rates were 5.4% and 3.1%, 2-year DFS rates were 80% and 82%, and 2-year OS rates were 94% and 93% for laparoscopic resection and open resection, respectively. As in Z6051, the criteria for noninferiority of the laparoscopic approach were not met in the initial ALaCaRT report, but the techniques were found to not differ significantly after longer follow-up with oncologic outcomes.

An analysis of results from > 18,000 individuals in the NCDB undergoing LAR for rectal cancer found short-term oncologic outcomes to be similar between the open and laparoscopic approaches. In addition, older reviews and meta-analyses consistently found the laparoscopic approach to be safe and feasible, even though a meta-analysis published in 2017 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. Several studies have also compared outcomes of robotic-assisted resection to conventional laparoscopic resection. 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, whereas other studies have shown the laparoscopic approach to be associated with higher rates of CRM positivity and incomplete TME. The 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.

**Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease**

Neoadjuvant/adjuvant therapy for 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 since 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.123–125 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.123,126,127 However, 22% of 188 patients clinically staged with T3, N0 rectal cancer using either EUS or MRI who subsequently received preoperative chemoRT had positive lymph nodes after pathologic review of the surgical specimen according to results of a retrospective multicenter study.128 These results suggest that many patients are understaged and would benefit from chemoRT. Therefore, the guidelines recommend preoperative treatment of 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 stage III rectal cancer. Use of perioperative pelvic RT in the treatment of patients with stage II/III rectal cancer continues to evolve. The current guidelines recommend several possible sequences of therapy, depending on predicted CRM status and response to initial therapy.

Total Neoadjuvant Therapy Approach
A treatment approach for stage II or III rectal cancer, including courses of both chemoRT and chemotherapy given as neoadjuvant therapy before transabdominal resection, has been gaining prominence. This approach, called total neoadjuvant therapy, was first tested in several small, phase II trials, but more recently has been supported by phase III trial data.129–134

In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CAPEOX either before chemoRT or after surgery.131,135 Similar pathologic complete response rates and 5-year DFS and OS were seen, and induction chemotherapy appeared to be less toxic and better tolerated. The GCR-3 trial provided the rationale for RAPIDO and demonstrated that the TNT approach increased compliance, lowered acute toxicity, and yielded similar outcomes compared with the traditional approach. A pooled analysis of 2 phase II trials, EXPERT and EXPERT-C, assessed the safety and efficacy of neoadjuvant chemotherapy followed by chemoRT and surgery.136 Of the 269 patients who were included, 91.1% completed chemotherapy, 88.1% completed chemoRT, and 89.2% underwent curative surgery. Five-year PFS and OS rates were 66.4% and 73.3%, respectively. Another phase II trial comparing response rates in patients with stage II–III rectal cancer treated with chemoRT alone or chemoRT followed by increasing durations of FOLFOX (5-FU, leucovorin [LV], oxaliplatin) before resection found that delivery of FOLFOX was independently associated with higher rates of pathologic complete response, with the highest complete response rate (38%) after 6 cycles of neoadjuvant FOLFOX and the lowest (18%) in the group that received chemoRT alone.137 However, it is difficult to determine if the higher pathologic complete response rate with FOLFOX was due to the increased duration of FOLFOX, the longer duration of time between chemoRT and surgery, or some combination of the 2.

More recently, the TNT approach has been tested in phase III trials. RAPIDO, a randomized phase III trial, compared a standard treatment approach (chemoRT, followed by TME, then optional adjuvant chemotherapy with CAPEOX or FOLFOX) to an experimental TNT approach (short-course RT, followed by chemotherapy before TME) in 912 patients with locally advanced rectal cancer.138 At 3 years after randomization, the rate of disease-related treatment failure was 23.7% with TNT compared with 30.4% with standard treatment (HR, 0.75; 95% CI, 0.60–0.95; P=.019). No differences were found in the secondary endpoint of OS. Serious adverse events occurred in 38% of the TNT group and 34% in the standard treatment group. Another randomized phase III trial, UNICANCER-PRODIGE 23, compared a neoadjuvant therapy approach including both FOLFIRINOX (5-FU, LV, irinotecan, oxaliplatin) and chemoRT prior to TME to a standard approach of neoadjuvant chemoRT alone followed by TME for 461 patients with locally advanced rectal cancer.139 Both arms followed TME by adjuvant FOLFOX, although the duration of adjuvant treatment was shorter in the group that had received neoadjuvant chemotherapy. After a median follow-up of 46.5 months, 3-year DFS was 76% in the group that received neoadjuvant chemotherapy, compared with 69% in the standard treatment group (HR, 0.69; 95% CI, 0.49–0.97; P=.034). During the whole treatment period, serious adverse events occurred in 11% of patients in the neoadjuvant chemotherapy group and 23% in the standard-of-care group (P=.0049). No postoperative deaths occurred within 30 days in the neoadjuvant group, whereas 5 deaths occurred in the standard treatment group (4 from cardiac or vascular events, 1 from suicide).

These results have also been supported by systemic review and meta-analyses showing a higher pathologic complete response rate with TNT.140–141 In a single-institution retrospective cohort analysis of patients with T3–4 or
node-positive rectal cancer, patients in the TNT group received a greater percentage of the planned chemotherapy dose than those in the adjuvant chemotherapy group.\(^{142}\) The complete response rates were 36% and 21% in the TNT and adjuvant chemotherapy groups, respectively.

Whether it is better to start with chemotherapy, then follow with chemoRT, or vice versa when following a TNT approach has not been established. Results from the phase II Organ Preservation in Rectal Adenocarcinoma (OPRA) trial suggest that initiating treatment with chemoRT may improve TME-free survival.\(^{143,144}\) The randomized phase II CAO/ARO/AIO-12 study also looked at this question, comparing TNT approaches using either induction chemotherapy with FOLFIRINOX followed by 5-FU/oxaliplatin chemoRT or chemoRT followed by consolidation chemotherapy.\(^{145}\) This trial reported that upfront chemoRT led to higher completion rates for chemoRT, but lower completion rates for chemotherapy compared with upfront chemotherapy. Pathologic complete response was seen in 17% of those who received upfront chemotherapy and 25% of those who received upfront chemoRT. A secondary analysis reporting long-term (median, 43 months) results from the CAO/ARO/AIO-12 study showed similar long-term outcomes between the 2 groups, including 3-year DFS (73% for both groups; HR, 0.95; 95% CI, 0.63–1.45), 3-year incidence of local recurrence (6% vs 5%), and distant metastases (18% vs 16%).\(^{146}\) Chronic toxicity of grade 3 or higher occurred in 11.8% of patients who received chemotherapy first compared with 9.9% who received chemoRT first. Collectively, these data suggest that the TNT approach of chemoRT followed by chemotherapy results in a higher rate of pathologic complete response while showing no significant differences in DFS, locoregional recurrence, distant metastases, or toxicities.

A few trials have investigated the use of FOLFIRINOX or FOLFOXIRI (LV, 5-FU, oxaliplatin, irinotecan) as neoadjuvant chemotherapy for locally advanced rectal cancer. One of these trials was the randomized, phase III UNICANCER-PRODIGE 23 study, which was described previously.\(^{139}\) The prospective, single-arm phase II FORTUNE study investigated the use of FOLFOXIRI as initial therapy for patients with stage II or III rectal cancer.\(^{147}\) After initial chemotherapy, patients were either treated with surgery or RT/chemoRT followed by surgery, depending on the response to initial FOLFOXIRI. In 103 patients who completed neoadjuvant therapy, pathologic complete response and tumor downstaging rates were seen in 20.4% and 42.7%, respectively. Another phase II trial involving patients with node-positive, cT4, or high-risk T3 rectal cancer investigated the use of induction FOLFOXIRI plus bevacizumab followed by capectabine-based chemoRT with bevacizumab.\(^{148}\) Surgery was performed 8 weeks after completion of the chemoRT. Of 49 enrolled patients, 44 completed surgery and 2-year DFS was 80%. Although the NCCN Panel recommends induction chemotherapy with FOLFIRINOX as an option for T4, node-positive rectal cancer, the addition of targeted agents (such as bevacizumab) is not currently recommended in this setting. UNICANCER-PRODIGE 23 enrolled patients with cT3 and cT4, node-negative tumors,\(^{139}\) but the NCCN Panel only recommends the use of FOLFIRINOX for the cT4, N+ tumors due to the higher toxicity of FOLFIRINOX compared with FOLFOX or CAPEOX and the results observed with CAPEOX or FOLFOX in RAPIDO, which enrolled patients at higher risk of recurrence.\(^{138}\) It is important to note that the trials evaluating TNT with FOLFIRINOX or FOLFOXIRI compared the TNT regimen to a standard preoperative chemoRT approach, not to a TNT strategy using FOLFOX; therefore, adequate data to compare FOLFOX to FOLFIRINOX in this setting are not available.

The TNT approach has shown benefits including the early prevention or eradication of micrometastases, higher rates of pathologic complete response and longer PFS,\(^{137,142}\) minimizing the length of time patients need an ileostomy,\(^{142}\) facilitating resection, and improving the tolerance and completion rates of chemotherapy.\(^{131,137–139}\) For some patients, surgery may be avoided if a complete response is achieved as a result of neoadjuvant therapy (see “Watch-and-Wait Nonoperative Approach for Clinical Complete Responders,” page 1156). Based on this, the NCCN Panel recommends TNT as the preferred approach for stage II–III rectal cancer.

**Preoperative ChemoRT**

When not using a TNT approach, preoperative chemoRT is recommended for patients with stage II–III rectal cancer. Postoperative chemoRT is recommended when stage I rectal cancer is upstaged to stage II or III after pathologic review of the surgical specimen.

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.\(^{149}\) Results of this study 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.\(^{150}\) 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 again similar between the groups (59.6% and 59.9%, respectively; \(P=.85\)), as was DFS and the occurrence of distant metastases.

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue. First of all, reducing tumor volume may facilitate resection...
and increase the likelihood of a sphincter-sparing procedure. Although some studies have indicated that preoperative radiation or chemorT is associated with increased rates of sphincter preservation in patients with rectal cancer,149,151 this conclusion is not supported by 2 meta-analyses of randomized trials involving preoperative chemorT in the treatment of rectal cancer.152,153 Second, irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by postsurgical adhesions. Finally, preoperative radiation 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).

**Regimens for Concurrent ChemorT**

A number of randomized trials have established the benefit of adding chemotherapy (most often 5-FU/LV or capecitabine) to RT for treatment of localized rectal cancer. Putative benefits of the addition of chemotherapy concurrent with 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 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 pathologic complete response (11.4% vs 3.6%; \(P<.05\)) and grade 3/4 toxicity (14.6% vs 2.7%; \(P<.05\)) and less likely to exhibit local recurrence of disease (8.1% vs 16.5%; \(P<.05\)).154

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.155 Significant reductions in tumor size, pTN stage, lymphatic invasion, vascular invasion, and perineural invasion rates were observed.155 More mature results from this trial reported that no significant differences in OS were associated with adding 5-FU–based chemotherapy preoperatively or postoperatively.156

The conclusions of these trials were supported in a 2009 systematic review that included 4 RCTs.157 In addition, a recent Cochrane review of 6 RCTs found that chemotherapy added to preoperative radiation in patients with stage III, locally advanced rectal cancer reduced the risk of local recurrence, but had no effect on OS, 30-day mortality, sphincter preservation, and late toxicity.158 Similarly, a separate Cochrane review of stage II and III resectable disease found that the addition of chemotherapy to preoperative radiation enhances pathologic response and improves local control, but has no effect on DFS or OS.159 Another recent meta-analysis of five RCTs comparing neoadjuvant chemorT with neoadjuvant radiotherapy came to similar conclusions.125

With respect to the type of chemotherapy administered concurrently with RT,127 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 of 5.7 years) in which similar outcomes with respect to OS and RFS were observed when an infusion of 5-FU or bolus 5-FU plus LV was administered concurrently with postoperative RT, although hematologic toxicity was greater in the group of patients receiving bolus 5-FU.160 Conversely, results from an earlier trial from the North Central Cancer Treatment Group showed that postoperative administration of infusional 5-FU during pelvic irradiation was associated with longer OS when compared with bolus 5-FU.161 Most of the patients in this study had node-positive disease. The panel considers bolus 5-FU/LV/RT as an option for patients not able to tolerate capecitabine or infusional 5-FU.

Recent studies have shown that capecitabine is equivalent to 5-FU in perioperative chemorT therapy.162,163 The randomized NSABP R-04 trial compared the preoperative use of infusional 5-FU with or without oxaliplatin to capecitabine with or without oxaliplatin in 1,608 patients with stage II or III rectal cancer.163,164 No differences in locoregional events, DFS, OS, complete pathologic response, sphincter-sparing surgery, or surgical downstaging were seen between the regimens, while 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 or 5-FU–based chemorT either pre- or postoperatively showed that capecitabine was noninferior to 5-FU with regard to 5-year OS (capecitabine 75.7% vs 5-FU 66.6%; \(P=.0004\)), with capecitabine showing borderline significance for superiority (\(P=.053\)).162 Furthermore, in this trial capecitabine demonstrated a significant improvement in 3-year DFS (75.2% vs 66.6%; \(P=.034\)).162 Because of these studies, capecitabine given concurrently with RT is listed in the guidelines as an acceptable alternative to infusional 5-FU in those 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, R-04, CAO/ARO/AIO-04, FOWARC, and PETACC 6) addressed the addition of oxaliplatin to the...
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%, \( P < .001 \)), while there was no difference in pathologic response between the arms of the study (16% pathologic complete response in both arms). Results of the NSABP R-04 trial also showed that the addition of oxaliplatin did not improve clinical outcomes including the endpoints of locoregional events, DFS, OS, pathologic complete response, sphincter-saving surgery, and surgical downstaging, while it increased toxicity.\(^{163,164}\)

Similar results were seen in the ACCORD 12/0405-Prodige 2 trial, in which capcitabine/RT (45 Gy) was compared with CAPEOX/RT (50 Gy) and the primary endpoint was pathologic complete response.\(^{166} \) The pathologic complete response 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 the 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 term follow-up.\(^{167} \) The PETACC 6 trial also investigated whether the addition of oxaliplatin to pre- and postoperative capcitabine would improve DFS for locally advanced rectal cancer.\(^{168} \) Similar to other trials, oxaliplatin was found to impair tolerability without improving efficacy.

Results of the German CAO/ARO/AIO-04 trial have been published.\(^{169-170} \) This trial also assessed the addition of oxaliplatin to a fluorouracil RT regimen. In contrast to STAR-01, R-04, and ACCORD 12, higher rates of pathologic complete response were seen in the oxaliplatin arm (17% vs 13%, \( P = .038 \)),\(^{170} \) but this result could be because of differences in the fluorouracil schedule between the arms.\(^{171} \) The primary endpoint 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 (\( P = .03 \)).\(^{169} \) 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, early results from 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 FOLFIRI, found that FOLFOX-RT resulted in higher rates of pathologic complete response and downstaging than the other regimens.\(^{172} \) However, final results from FOWARC showed no significant improvement in 3-year DFS, local recurrence rates, or OS for FOLFOX with or without RT compared with 5-FU/LV-RT.\(^{173} \)

Another randomized, multicenter, phase III trial looked at the addition of oxaliplatin during concurrent capcitabine chemoRT in the adjuvant setting for pathologic stage II/III disease.\(^{174} \) 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 complete response rate with the addition of cetuximab to radiation treatment in 165 patients.\(^ {175} \) Patients in the control arm received CAPEOX followed by panitumumab/RT, then surgery followed by CAPEOX. Patients randomized to the cetuximab arm received the same therapy with weekly cetuximab through 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 endpoint of complete response rate was not met, and other phase II trials have not shown a clear benefit to the addition of cetuximab in this setting.\(^ {176,177} \) 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.\(^ {178} \) The primary endpoint was pathologic near-complete plus complete tumor response, which occurred in 53% (95% CI, 36%–69%) of patients in the panitumumab arm versus 32% (95% CI, 16%–52%) in the control arm. Patients receiving panitumumab experienced increased rates of grade 3 or greater toxicity.

Another phase II study, RaP Study/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.\(^ {179} \) All patients were treated with panitumumab-chemoRT followed by resection and adjuvant FOLFOX. The primary endpoint of pathologic complete response was observed in 10.9% (95% CI, 4.7–17.1) of participants, not meeting the prespecified level of 16%.

A phase II study of 57 patients with resectable T3/T4 rectal cancer evaluated preoperative treatment with capcitabine, oxaliplatin, bevacizumab, and RT, followed by surgery 8 weeks later and adjuvant FOLFOX/bevacizumab.\(^ {180} \) The 5-year OS rate was 80%, and the 5-year RFS rate was 81%. However, the primary endpoint of pathologic complete response was not met, significant toxicities were observed, and compliance with adjuvant therapy was low. Other randomized trials have also investigated the use of targeted therapies (eg, bevacizumab, ziv-afibercept) within neoadjuvant therapy for localized rectal cancer with mixed conclusions.\(^ {181,182,185} \)
At this time the panel does not endorse the use of bevacizumab, cetuximab, panitumumab, irinotecan, or oxaliplatin with concurrent radiotherapy for rectal cancer.

**Preoperative Systemic Therapy 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. 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 eight institutions, assessed the R0 resection rate after FOLFOX plus either bevacizumab or cetuximab. An R0 resection was achieved in 98.3% of the participants, and the pathologic complete response rate was 16.7%.

The phase III FOWARC trial, discussed previously, compared neoadjuvant therapy with and without radiation (without additional therapy for those with stable or progressive disease) and found that neoadjuvant FOLFOX without radiation gave lower rates of pathologic complete response than regimens that included radiation (6.6% vs 14.0% for 5-FU-RT and 27.5% for FOLFOX-RT). 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). However, final results from FOWARC showed no significant improvement in DFS, local recurrence rates, or OS for FOLFOX with or without RT compared with 5-FU/LV-RT. Three-year DFS was 72.9%, 77.2%, and 73.5% (P = .709); 3-year local recurrence rate after resection was 8.0%, 7.0%, and 8.3% (P = .873); and 3-year OS was 91.3%, 89.1%, and 90.7% (P = .971) for 5-FU/LV-RT, FOLFOX-RT, and FOLFOX without RT, respectively.

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 FOLFOX or CAPEOX alone as an option for pT3, N0, M0, margin-negative tumors high in the rectum or at the rectosigmoid junction. However, this approach is only appropriate in this small subset of tumors that behave more like colon tumors, and therefore may be treated as such.

The checkpoint inhibitor, dostarlimab-gxly, has also been investigated as neoadjuvant therapy in a small phase II study of patients with dMMR/MSI-H stage II or III rectal cancer. In this study, patients were initially treated with dostarlimab-gxly for 6 months, with chemoRT and surgery planned for those with residual disease. Remarkably, all 12 patients on this trial showed a complete clinical response to dostarlimab-gxly and no patients at the date of publication had required chemoRT or surgery. No cases of progression or recurrence were reported during follow-up (range 6 to 25 months). Although these data are encouraging, it has not yet been added as a recommended treatment approach in the guidelines.

**Technical Aspects of Radiation Therapy**

Multiple RT fields should include the tumor or tumor bed with a 2- to 5-cm margin, the mesorectum, the 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 radiation 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. The Radiation Therapy Oncology Group (RTOG) has established normal pelvic contouring atlases (available online at https://seor.es/wp-content/uploads/2014/03/RTOGanorectalContouringGuidelines-1.pdf). Intensity-modulated RT should be considered for clinical situations such as reirradiation of previously treated recurrent disease, patients treated postoperatively due to increased acute or late toxicity, T4 primary tumors given the more anterior field changes with coverage of the external iliac nodes which includes more small bowel, or unique anatomic situations where intensity-modulated RT facilitates the delivery of recommended target volumes while respecting accepted normal tissue dose-volume constraints. Ablative stereotactic body RT should only be used in the setting of a clinical trial or in the setting of oligometastasis to the lung, liver, or an abdominopelvic node when other modalities are not appropriate.

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 pathologic complete response rates, it is unclear whether such longer intervals are associated with clinical benefit. Results of 1 NCDB analysis suggest that an interval of >8 weeks is associated with increased odds of pathologic complete response, 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. A pooled analysis of 7 randomized trials concluded that the best time to achieve pathologic complete response was at 10 weeks after neoadjuvant chemoradiotherapy (CRT), with 95% of pathologic complete response events occurring within that time period.

The GRECCAR-6 phase III, multicenter, randomized, open-label, parallel-group controlled trial randomized patients with stage II/III rectal cancer treated with chemoradiotherapy to a 7-week or an 11-week interval before surgery. The pathologic complete response rate was not different between the groups (15.0% vs 17.4%; \( P = .60 \)), but the 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. Three-year survival results from the GRECCAR-6 trial showed no difference in 3-year OS (\( P = .8668 \)), DFS (\( P = .9409 \)), distant recurrence (\( P = .7432 \)), or local recurrence (\( P = .3944 \)) between the 7-week and 11-week interval groups.

**Short-Course Radiation**

Several European studies have looked at the efficacy of a shorter course of preoperative RT (25 Gy over 5 days), not combined with chemotherapy, for the treatment of rectal cancer. The 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. However, a follow-up study published in 2005 showed that the patients with short-course preoperative RT had increased relative risk for postoperative hospitalization due to bowel obstructions and other gastrointestinal complications. A number of other studies also investigating the effectiveness of preoperative short-course RT in patients with rectal cancer staged as T1–3 have demonstrated that OS was not significantly affected despite improvements in local control of disease. A more recent multicenter, randomized study of 1,350 patients with rectal cancer compared (1) short-course preoperative RT and no postoperative treatment with (2) no preoperative RT and a postoperative approach that included chemoradiation in selected patients (ie, those with a positive CRM after resection) and no RT in patients without evidence of residual disease following surgery. 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 arms of the study.

Long-term (12-year) follow-up of 1 of the short-course RT trials (the Dutch TME trial) was reported. The 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 compared with the group that received surgery alone (50% vs 40%; \( P = .032 \)). However, this long follow-up showed that secondary malignancies and other nonrectal 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 chemoradiotherapy. One randomized study of 312 patients in Poland directly compared preoperative short-course RT and more conventional preoperative long-course chemoradiotherapy and found no differences in local recurrence or survival. Similarly, an Australian/New Zealand trial (Trans-Tasman Radiation Oncology Group [TROG] trial 01.04) that randomized 326 patients to short-course RT or long-course chemoradiotherapy found no differences in local recurrence and OS rates. In addition, rates of late toxicity, distant recurrence, and RFS were not significantly different between the groups. 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 patients in the short-course arm were more likely to have a permanent stoma (38.0% vs 29.8%; \( P = .13 \)). However, no overall difference was seen in health-related quality of life between the groups. Finally, a trial compared short-course RT with long-course chemoradiotherapy with delayed surgery in both groups. 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.

The randomized phase III Polish II study randomized patients with cT3/cT4 rectal cancer to either preoperative short-course radiation followed by FOLFIRI or preoperative long-course chemoradiotherapy with bolus 5-FU/LV and oxaliplatin. Of 515 patients eligible for analysis, preoperative radiation acute treatment toxicity was lower with short-course RT (\( P = .006 \)). No differences in local efficacy or 3-year DFS were observed between the groups, although 3-year OS was higher for the short-course group (73% vs 65%, \( P = .046 \)). However, long-term results of this trial showed no difference in 8-year OS (49% for both groups). The rate of late complications was also similar between the 2 groups.

The randomized RAPIDO trial assessed the use of preoperative short-course (5 × 5 Gy) RT followed by 6 cycles of CAPEOX or 9 cycles of FOLFOX4 compared with long-course (25–28 × 2.0–1.8 Gy) capecitabine-based chemoradiotherapy before resection in patients with clinical stage T3 or T4 rectal cancer. Early results of 901 evaluable patients showed a high percentage of patients who completed at least 75% of their prescribed chemotherapy (84% for the short-course arm
compared with 57% in the long-course arm). Although considerable toxicity did occur during preoperative therapy, no significant differences were noted in the surgical procedures performed or postoperative complications between the 2 arms. A more mature analysis of the RAPIDO trial reported that in 920 randomized patients, pathologic complete response rates were 28% for the short-course arm compared with 14% for the long-course arm (odds ratio, 2.37; 95% CI, 1.67–3.37; \( P < .0001 \)). The primary outcome of 3-year disease-related treatment failure was lower in the short-course arm compared with the long-course arm (23.7% vs 30.4%; HR, 0.75 [0.60–0.95]; \( P = .019 \)). Probability of distant metastasis and locoregional failure were also lower for the short-course arm compared with the long-course RT arm. Overall, quality of life, and LAR syndrome score were comparable between the 2 treatment arms.

Stockholm III was another randomized, phase III study that compared short-course RT to long-course RT in 840 patients with resectable rectal cancer. This trial included 2 randomizations, a 2-arm randomization that compared short-course RT with immediate surgery to short-course RT with delayed surgery (described subsequently), and a 3-arm randomization that compared short-course RT with immediate surgery, short-course RT with delayed surgery, and long-course RT with delayed surgery. For the 385 patients in the 3-arm randomization, the incidence of local recurrence was 2.3% for short-course with immediate surgery, 3.1% for short-course with delayed surgery, and 5.4% for long-course RT with a median follow-up of 5.7 years. Median OS was 8.1, 10.3, and 10.5 years for short-course RT with immediate surgery, short-course RT with delayed surgery, and long-course RT, respectively. No comparisons showed statistically significant differences, and long-term health-related quality of life was also similar between the groups.

STELLAR is a randomized, phase III trial that compared short-course RT followed by CAPEOX to capecitabine-based long-course chemoradiotherapy as neoadjuvant therapy in 599 patients with stage II–III rectal cancer. Both groups received TME 6–8 weeks after preoperative treatment and adjuvant chemotherapy was given based on preoperative treatment. Three-year DFS was 64.5% for short-course RT and 62.3% for long-course chemoradiotherapy. There was also no significant difference in metastasis-free survival or locoregional recurrence between the 2 groups. Three-year OS was higher in the short-course RT group (86.5% vs 75.1%; \( P = .033 \)), but the prevalence of acute grade \( \geq 3 \) toxicities during preoperative treatment was higher with short-course RT (26.5% vs 12.6%; \( P < .001 \)).

A 2014 systematic review identified 16 studies (RCTs, phase II trials, and retrospective studies) that addressed the interval between short-course RT and resection of rectal cancer. Lower rates of severe acute postradiation 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). The pathologic complete response rates were significantly higher in the delayed-surgery group, with no differences in sphincter preservation and R0 resection rates. The Stockholm III trial also investigated the optimal interval between short-course radiotherapy and surgery in 455 patients within the 2-arm randomization. This trial showed similar oncologic outcomes and long-term health-related quality of life between the immediate surgery versus 4–8 weeks delay following short-course RT groups, but a lower rate of postoperative complications in the group that delayed surgery after short-course RT (53% vs 41%; odds ratio, 0.61; 95% CI, 0.45–0.83; \( P = .001 \)).

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 locally advanced 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.

**Response to Neoadjuvant Treatment**

Fifty percent to 60% of patients are downstaged after neoadjuvant therapy, with about 20% of patients showing a pathologic complete response. 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 using MRI and pathologic staging. On multivariate analysis, MRI-assessed tumor regression grade was significantly associated with OS and DFS. Patients with poor tumor regression grade had 5-year survival rates of 27% versus 72% for patients with 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%. A recent retrospective review of 725 patients with rectal cancer found similar results. In this study, pathologically determined response to neoadjuvant treatment correlated with long-term outcomes. Five-year RFS rates were 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 the level of response. Other studies have also shown a prognostic effect of response to neoadjuvant therapy.

In addition to its prognostic value, there is some initial evidence of predictive value for 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 patients with ypT3–4 staging.226 Similar results were seen from another retrospective review.237

Watch-and-Wait Nonoperative Approach for Clinical Complete Responders

As preoperative treatment and imaging modalities have improved, some have suggested that patients with a clinical complete response to chemorT may be able to be spared the morbidities of surgery. In 2004, Habr-Gama et al.238 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. The 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.239

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 complete responses who were then observed with careful follow-up and compared with 20 patients with a complete pathologic response after resection.240 Only one 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 the groups. The 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.241–243 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.242 A retrospective case series analysis compared patients who agreed to a watch-and-wait strategy after having a clinical complete response on neoadjuvant therapy with those who underwent surgery after neoadjuvant therapy and were found to have a pathologic complete response at resection.244 This study found that the watch-and-wait strategy resulted in excellent rectal preservation and pelvic tumor control. However, worse survival and a higher incidence of distant tumor progression were noted in patients in the watch-and-wait group with local regrowth versus those without. Several systematic reviews have been published on the nonoperative approach.245–247 They all show that the approach is likely safe with the use of resection in patients with tumor regrowth, but that the data are very limited.

The International Watch & Wait Database (IWWD) aims to collect data to expand knowledge on the benefits, risks, and safety of organ preservation in rectal cancer using a large-scale registry of pooled individual patient data from multiple institutions. A 2018 analysis included data from 880 patients in the IWWD with disease that had a complete clinical response after neoadjuvant therapy and were managed using watch-and-wait.248 In this analysis, the 2-year incidence of local recurrence was 25.2% and 88% of local recurrences occurred in the first 2 years. Distant metastases occurred in 8% of patients, 5-year OS was 85%, and 5-year disease-specific survival was 94%. A 2021 analysis of the IWWD showed similar results.249 This analysis included 793 patients with clinical complete response who were managed using the watch-and-wait strategy. With a median follow-up of 55.2 months, the probability of remaining free of local recurrence for an additional 2 years was 88.1% after 1 year of DFS, 97.3% after 3 years of DFS, and 98.6% after 5 years of DFS. These same measures for distant metastasis-free survival was 93.8% for 1 year, 97.8% for 3 years, and 96.6% for 5 years. Together, current data from the IWWD suggest that disease recurrence occurs most frequently in the first 2–3 years after complete response, and a more intense surveillance schedule is recommended for that time period.248,249

The OPRA trial is a randomized, phase II trial of the watch-and-wait approach.144 OPRA assessed the outcomes of 324 patients with stage II or III rectal cancer treated with TNT using either an induction chemotherapy followed by chemorT approach or an approach using chemorT followed by consolidation chemotherapy. After neoadjuvant treatment, patients received either TME or observation (watch-and-wait) based on tumor response. Organ preservation was achievable in about half of patients treated with TNT on OPRA with 3-year TME-free survival of 41% in the induction chemotherapy group and 53% in the consolidation chemotherapy group. The primary endpoint of DFS was 76% for both groups, which is in line with the 75% 3-year DFS rate observed historically. No differences were observed between the groups for RFS, distant metastasis-free survival, or OS.

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 complete response are routinely managed using a watch-and-wait approach.250 Furthermore, recent studies have found that neither FDG-PET nor MRI nor CT can accurately determine a pathologic complete response, complicating the selection of appropriate patients.
for a nonoperative approach.\textsuperscript{42,50,251} In addition, lymph node metastases are still seen in a subset of patients with pathologic complete response.\textsuperscript{252} Keeping these caveats in mind, the panel believes that a nonoperative management approach may be considered in centers with experienced multidisciplinary teams after a careful discussion with the patient about his or her risk tolerance.

Careful surveillance is essential for those considering a watch-and-wait approach to treat tumor regrowth in a timely manner. The OПРА trial included the following surveillance protocol for watch-and-wait: digital rectal examination, flexible sigmoidoscopy, and CEA every 4 months for the first 2 years, then every 6 months for years 3–5; MRI every 6 months for the first 2 years, then every 12 months for years 3–5; CT chest/abdomen/pelvis once a year for 5 years; and colonoscopy once at year 1 and again at year 5.\textsuperscript{144} Watch-and-wait surveillance protocols are an area of active investigation, and other protocols have been suggested.\textsuperscript{248,249,253} The watch-and-wait surveillance schedule recommended by the NCCN Panel based on clinical and institutional experiences is similar to the OПРА protocol and includes digital rectal examination and proctoscopy every 3–4 months for 2 years, then every 6 months for the next 3 years, and MRI of the rectum every 6 months for at least 3 years.

The use of nonoperative management of 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.\textsuperscript{254}

### Adjuvant Chemotherapy

Adjuvant chemotherapy is recommended for 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; however, few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well-defined.\textsuperscript{255,256} 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.\textsuperscript{156} 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 (plus/minus RT) following preoperative RT (plus/minus 5-FU–based chemotherapy).\textsuperscript{156} Long-term results of the 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; \(P = .29\)).\textsuperscript{257} 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.\textsuperscript{258,259}

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 indicate that adjuvant FOLFOX can be safely used in this patient population.\textsuperscript{260} The open-label phase II ADORE trial randomized 321 patients with resected rectal cancer and neoadjuvant therapy to adjuvant 5-FU/LV or FOLFOX.\textsuperscript{261} The FOLFOX arm had higher 3-year DFS, at 71.6% versus 62.9% (HR, 0.66; 95% CI, 0.43–0.99; \(P = .047\)). A long-term analysis confirmed these results with a 6-year DFS of 68.2% in the FOLFOX arm compared with 56.8% in the 5-FU/LV arm (HR, 0.63; 95% CI, 0.43–0.93; \(P = .018\)).\textsuperscript{262} 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%; \(P = .03\)).\textsuperscript{169}

A study in which patients who received neoadjuvant chemoRT and experienced a pathologic complete response were observed without additional adjuvant chemotherapy found 5-year DFS and OS rates of 96% and 100%, respectively.\textsuperscript{263} 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.\textsuperscript{264} However, more recent trials that found a DFS benefit to the addition of adjuvant oxaliplatin-based adjuvant therapy were not included in this study, and other meta-analyses have come to the opposite conclusion.\textsuperscript{265,266} 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.\textsuperscript{267} The authors report 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.\textsuperscript{268–270} However, 2 similar analyses that used the NCDB from 2006 to 2013 or from 2006 and 2012 and that looked only at patients experiencing a pathologic complete response after neoadjuvant chemoRT (n = 2891; n = 2764) found a significant improvement in OS with the use of adjuvant chemotherapy.\textsuperscript{271,272} Another analysis of the NCDB from the same time period reported that while oxaliplatin-based adjuvant therapy was associated with improved OS in patients with pathologic stage III disease, this association was not seen in patients with pathologic stage 0 or 1 disease.\textsuperscript{273} Therefore, the authors of this study conclude that oxaliplatin may be omitted from adjuvant therapy for tumors that exhibit a pathologic complete response.
A randomized, phase III study of the ECOG-ACRIN Research Group (E5204) compared FOLFOX alone to FOLFOX in combination with bevacizumab as adjuvant treatment of patients with stage II or III rectal cancer who had already undergone neoadjuvant chemoradiation and complete resection.\textsuperscript{274} Although the trial was terminated due to poor accrual, in the 355 registered patients, no difference was seen in 5-year OS or 5-year DFS between the 2 arms. However, the bevacizumab-containing arm had higher rates of early therapy discontinuation and patient withdrawal from the trial.

A 2011 systematic review and meta-analysis of 10 studies involving more than 15,000 patients with colon or rectal cancer looked at the effect of timing of adjuvant therapy after primary tumor resection.\textsuperscript{275} Results of this analysis showed that each 4-week delay in chemotherapy results 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.\textsuperscript{276} The optimal duration of adjuvant treatment in rectal cancer is still unclear.\textsuperscript{277,278} In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.\textsuperscript{279} The use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) is justified when preoperative chemoRT is administered.

Although conclusive data on the benefits of adjuvant therapy in patients with stage II/III rectal cancer are lacking, the panel recommends adjuvant treatment with FOLFOX or CAPEOX following resection when not following the TNT approach.

### NCCN Recommendations for Nonmetastatic Rectal Cancer

#### Recommendations for Patients With T1 and T2 Lesions

Node-negative T1 lesions are treated with transabdominal resection or transanal local excision, as appropriate (see REC-2, page 1141, and “Surgical Approaches,” page 1146). If pathology review after local excision reveals no high-risk features, then no additional treatment is required. If, however, pathology review after local excision reveals a poorly differentiated histology, positive margins, invasion into the sm3 level, or LVI or if the tumor is restaged to pT2, additional treatment is required (see REC-3, page 1142). The options are (1) transabdominal resection (preferred) followed by adjuvant therapy based on pathologic stage (see “Adjuvant Treatment Recommendations for cT1–2 N0 Rectal Cancer,” next section); or (2) chemoRT. For patients treated with transanal local excision and then chemoRT, options for the next phase of treatment depend on whether there is evidence of residual disease. If there is no evidence of disease, observation or chemotherapy without resection may be considered. If there is evidence of disease, transabdominal resection should be performed, with or without adjuvant chemotherapy. Results of a meta-analysis suggest that transanal local excision followed by chemoRT without a transabdominal resection may be associated with higher rates of local recurrence than transanal local excision followed by transabdominal resection.\textsuperscript{280} Careful surveillance of patients forgoing transabdominal resection in this setting is advised.

Node-negative T2 lesions are treated with transabdominal resection, because local recurrence rates of 11%–45% have been observed for T2 lesions after local excision alone.\textsuperscript{17,281,282} Following transabdominal resection of patients with clinical stage T1–2 N0 rectal cancer, patients should receive adjuvant therapy based on pathologic stage (see “Adjuvant Treatment Recommendations for cT1–2 N0 Rectal Cancer,” next section).

#### Adjuvant Treatment Recommendations for cT1–2 N0 Rectal Cancer

Patients who have a transabdominal resection for stage cT1–2 rectal cancer are given further treatment based on the pathologic stage as delineated in detail on REC-4 (page 1143). Patients with tumors staged as pT1–2, N0, M0 require no further treatment. If pathology review reveals pT3, N0, M0, chemoRT, given either before or after chemotherapy, is one option. Observation can also be considered in these patients 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 the upper rectum.\textsuperscript{283} Finally, chemotherapy with FOLFOX or CAPEOX alone is an option for margin-negative proximal tumors.

For resected patients with positive nodes and/or pT4 disease, chemotherapy and chemoRT can be given sequentially with chemotherapy followed by concurrent chemoRT or vice-versa.\textsuperscript{127,160,161} The panel recommends perioperative therapy for a total duration of up to 6 months.

#### Recommendations for Patients With T3, N any Lesions With Clear CRM by MRI or With T1–2, N1–2 Lesions

Patients with disease clinically staged as T3, N any with prediction of clear margins using MRI have the same treatment options as those with disease clinically staged as T1–2, N1–2. Prediction of CRM status by MRI was discussed previously (see “Preoperative Pelvic Imaging in Rectal Cancer,” page 1143). Two potential treatment courses are recommended for this group of patients: either TNT followed by transabdominal resection or a more traditional perioperative therapy approach, including both neoadjuvant and adjuvant therapy (see REC-5, page 1144).

Of these 2 options, the preferred approach is TNT, consisting of chemotherapy with FOLFOX or CAPEOX given either before or after chemoRT. Alternatively, short-course RT may be used in place of long-course chemoRT when following a TNT approach. If short-course RT is considered, its feasibility should be evaluated in a multidisciplinary setting with discussion of the need for downstaging and the possibility of
long-term toxicity. After neoadjuvant therapy, the tumor should be restaged before transabdominal resection. The second option for the sequence of treatment in this population is chemoRT or short-course RT followed by restaging, transabdominal resection, and then adjuvant chemotherapy.

In those patients who experience a complete clinical response to neoadjuvant therapy 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 nonoperative management should involve a careful discussion with the patient of his or her risk tolerance, and a careful surveillance schedule must be followed. The data supporting this approach are discussed in “Watch-and-Wait Nonoperative Approach for Clinical Complete Responders” (page 1156).

When a TNT approach is followed, resection should be performed unless a clear contraindication is present or a watch-and-wait nonoperative approach is being pursued. When resection is contraindicated following primary treatment, patients should be treated with a systemic regimen for advanced disease (see discussion of “Systemic Therapy for Advanced or Metastatic Disease” in the NCCN Guidelines for Colon Cancer, available at NCCN.org). FOLFIRINOX is not recommended in this setting.

**Recommendations for Patients With T3, N any Lesions With Involved or Threatened CRM by MRI, With T4, N any Lesions, With Locally Unresectable Disease, or Who Are Medically Inoperable**

For patients with higher-risk stage II or III rectal cancer, including cT3 lesions with involved or threatened CRM by MRI, cT4 lesions, and locally unresectable or medically inoperable disease, TNT is the only recommended approach (see REC-6, page 1145). This is because a pathologic complete response is less likely after an initial course of only chemoRT or short-course RT, and the full course of neoadjuvant chemoRT/short-course RT and chemotherapy is warranted before resection. In the TNT approach, 12 to 16 weeks of chemotherapy are followed by chemoRT or short-course RT, restaging, and transabdominal resection. Alternatively, a TNT approach may start with chemoRT or short-course RT, followed by 12 to 16 weeks of chemotherapy, then restaging and transabdominal resection. FOLFOX or CAPEOX are generally used for chemotherapy, although FOLFIRINOX is also an option for T4, N+ disease (see “Total Neoadjuvant Therapy Approach,” page 1149).

In those patients who experience a complete clinical response to neoadjuvant therapy 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 nonoperative management should involve a careful discussion with the patient of his/her risk tolerance and a careful surveillance schedule must be followed. The data supporting this approach are discussed in “Watch-and-Wait Nonoperative Approach for Clinical Complete Responders” (page 1156).

When resection is contraindicated following primary treatment, patients should be treated with a systemic regimen for advanced disease (see discussion of “Systemic Therapy for Advanced or Metastatic Disease” in the NCCN Guidelines for Colon Cancer, available at NCCN.org). For unresectable cancers, doses higher than 54 Gy may be required; the dose of RT to the small bowel should be limited to 50 Gy. For patients with T4 tumors or recurrent cancers or if margins are very close or positive, intraoperative RT, which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment, may be considered as an additional boost to facilitate resection.

**Summary**

The NCCN Rectal Cancer Panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology/colorectal surgery, radiation oncology, and radiology is necessary for treating patients with rectal cancer. Adequate pathologic assessment of the resected lymph nodes is important. Patients with very-early-stage tumors that are node-negative by endorectal ultrasound or endorectal or pelvic MRI and who meet carefully defined criteria can be managed with a transanal local excision. A transabdominal resection is appropriate for other rectal lesions. A TNT approach consisting of chemoRT and chemotherapy is preferred for most patients with suspected or proven T3–4 disease and/or regional node involvement.

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### Individual Disclosures for the NCCN Rectal Cancer Panel

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<th>Panel Member</th>
<th>Clinical Research Support/Data Safety Monitoring Board</th>
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<td>Nâgler Azad, MD</td>
<td>ActaGestiva Pharmaceuticals LP; GlaxoSmithKline, Incyte Corporation; Merix</td>
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<td>Al B. Benson, Jr, MD</td>
<td>Thebancor, Apogenix, Amarela BioMed, Bristol-Myers Squibb Company; Gilead, HalioGen, Janzen Oncology, Merck Sharp &amp; Dohme; Nokia, Pfizer Inc; Hospira Inc.; TEVA, Xencor</td>
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<td>Y-Jen Chen, MD, PhD</td>
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<td>Kristen E. Coinborn, MD</td>
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<td>Stacey Cohen, MD</td>
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<td>Dustin Denning, MD</td>
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<td>Ignacio Gorrini-Lagues, PhD, MD</td>
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<td>J. L. Green, MD</td>
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<td>Andrew Gut, MD</td>
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<td>J. Randolph Hecht, MD</td>
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<td>Sarah Hofs, MD</td>
<td>Galera, second trial, OREDO-2, pending activation; Varian Medical Systems, Inc.; Veeva</td>
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<td>Natalie Krizik, MD</td>
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<td>Srintha Krishnarvuthi, MD</td>
<td>AstraZeneca Pharmaceuticals Inc.; Bristol-Myers Squibb Company; Nokia, Pfizer Inc</td>
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<td>Jennifer K. Maratt, MD</td>
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<td>Jeffrey Mayehr, MD, MPH</td>
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<td>Eric D. Miller, MD, PhD</td>
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<td>Mary P. Mulady, MD</td>
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<td>Steven Nuckels, MD, MS</td>
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<td>Michael J. Overman, MD</td>
<td>3dmed; Actavis Inc.; agilens, Inc.; Gilead Sciences, Inc.; gynotrop, Janzen Pharmaceuticals Products LP, Merck &amp; Co., Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Phanes; Taiho Pharmaceutical North-America, Inc.</td>
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### Ajay A. Parikh, MD

- AbbVie Inc., Bayer HealthCare, Biotherics, Bristol-Myers Squibb Company; Celldex, Celldare, Celldar, Combinatix, Foundation Medicine, Genentech Inc., Geniparin, biotech; Guardant, Invesco, Merix, Nucara, Novartis Pharmaceuticals Corporation, Pfizer Inc.; Poxel, PMV Pharma, PureTech, Roche Laboratories Inc.; Seagen, Teklia Pharmaceuticals Co., Ltd., Value Analytics Lab

### Hitendra Patel, MD

- Epistope

### Katrina Pedersen, MD, MS

- Nordic Biosciences, Novartis Pharmaceuticals Corporation; Taiho Pharmaceuticals Co., Ltd

### Leonard Saha, MD

- Genor Biopharma

### Christopher G. Willett, MD

- None

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Katrina Pedersen, MS, MD: UpToDate*