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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Rectal Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Rectal Cancer

Disclosure of Relevant Financial Relationships

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Rectal Cancer, Version 3.2024
Featured Updates to the NCCN Guidelines

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Abstract

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. Particularly for patients with distal rectal cancer, finding a balance between curative-intent therapy while having minimal impact on quality of life can be challenging. 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. Careful patient selection and the use of sequenced multimodality therapy following a multidisciplinary approach is recommended. These NCCN Guidelines Insights detail recent updates to the NCCN Guidelines for Rectal Cancer, including the addition of endoscopic submucosal dissection as an option for early-stage rectal cancer, updates to the total neoadjuvant therapy approach based on the results of recent clinical trials, and the addition of a "watch-and-wait" nonoperative management approach for clinical complete responders to neoadjuvant therapy.

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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. The majority of the large bowel is referred to as the colon, while the most distal portion of approximately 15 cm (6 inches) is called the rectum. Approximately a third of CRCs occur in the rectum. In 2024, an estimated 46,220 new cases of rectal cancer will occur in the United States (27,330 cases in males; 18,890 cases in females). During the same year, it is estimated that 53,010 people will die of rectal and colon cancer combined.[1] Despite these high numbers, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005 and, more recently, 38.7 in 2016.[2,3] In addition, mortality from CRC has been decreasing for decades (since 1947 in females and since 1980 in males) and is currently down by >50% from peak mortality rates.[1,3] These improvements in incidence of 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 individuals aged ≥65 years, with a decrease of 3.3% annually between 2011 and 2016.[3] 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.[3] 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 health care and other social determinants of health, comorbidities, and tumor characteristics.

Conversely, incidence has increased among individuals aged <65 years, with a 1% annual increase in those aged 50 to 64 years and 2% annual increase in those aged <50 years. CRC death rates also showed age-dependent trends, declining by 3% annually for those aged ≥65 years, compared with a 0.6% annual decline for individuals aged 50 to 64 years and a 1.3% annual increase for individuals aged <50 years.[3] A retrospective cohort study of the

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The full and most current version of these NCCN Guidelines is available at NCCN.org.

SEER CRC registry demonstrated the rising incidence of CRC in patients aged <50 years.[4] The authors estimated that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for individuals aged 20 to 34 years by 2030. The cause of this trend is currently unknown. One review suggests that CRC that occurs in patients aged <45 years may be clinicopathologically and genetically different from CRC in adults aged ≥45 years, 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.[5] In a cohort study of 1,959 patients with metastatic CRC (mCRC), patients who developed mCRC at a younger age (<50 years) showed worse survival outcomes and unique adverse event (AE) profiles, which the authors partially attribute to distinct genetic profiles.[6] On the other hand, other studies show no difference between early and late onset CRC, so more research is needed.[7,8]

Endoscopic Submucosal Dissection for T1, N0 Rectal Cancer

Endoscopic submucosal dissection (ESD) is a technique that was first described in Japan as an alternative to endoscopic mucosal resection (EMR) of early gastric cancers.[9,10] ESD has been performed worldwide for more than 20 years and in the United States for more than a decade.[9] As advances in hands-on educational opportunities have increased in the United States, ESD is now a procedure offered at many US medical centers.[11]

ESD is a minimally invasive, organ-preserving procedure that can provide curative resection for early rectal cancers through the removal of large complex polyps in an en-bloc manner.[10] ESD involves using a submucosal injection to lift the polyp, followed by a circumferential incision of the mucosa using an endoscopic knife, and submucosal dissection underneath the lesion, above the muscularis propria, to fully resect the lesion en-bloc.[10,12] The benefit of ESD compared with EMR is that ESD can offer higher rates of curative resection and the intact specimen produced by ESD allows for more accurate pathologic and oncologic assessment.[9,10] Curative resection is often achieved after R0 resection in conjunction with other favorable criteria, including well to moderately differentiated histology, <1,000 μm invasion into the submucosa, and lack of lymphovascular invasion.[9,10] Furthermore, when ESD is noncurative, the pathology findings can help drive appropriate subsequent therapy. Last, en-bloc resection with ESD is safe and effective for lesions in the rectum because part of the rectum is below the peritoneal reflection, making ESD in the rectum relatively less technically challenging and safer than in other regions of the colon.[10] Furthermore, ESD can reach lesions in the proximal rectum that may be challenging to reach surgically because of their location.[13,14] A recently published large prospective study in North America found that among 188 rectal lesions removed, 88.8% were removed en bloc, 85.6% achieved R0 resection, and 79.8% were deemed curative.[13] The AE rate for rectal lesions in this study was 5.9% and included delayed bleeding and perforation; however, none of the patients required surgery for an AE after rectal ESD. Also, 70% of these patients were discharged on the same day, and among those admitted, the average length of stay was 1.13 days.

Transanal local excision using advanced techniques, such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS), are also well-established surgical procedures for the resection of early rectal cancers. Compared with radical resection, these approaches help to preserve function and reduce the morbidity associated with radical resection approaches.[15] Although there are no published prospective studies comparing ESD to TEM/TAMIS, there is an ongoing randomized controlled trial in the Netherlands comparing TAMIS to ESD[16] and several retrospective studies comparing TAMIS to ESD.[17–19] A systematic review and meta-analysis of these studies found that ESD and surgical techniques do not differ in terms of outcomes, including local recurrence, en bloc/R0 resection rate, and AEs.[20]

Local excision of rectal cancer has also been associated with an increased risk of local recurrence, with some studies showing rates of 1.1% to 6.3%, which are higher than observed with early colon cancers (0%–1.9%).[21–23] Intraluminal recurrence after en bloc, R0 ESD of rectal neoplasia, is rare, with rates ≤2.5%.[24–27] However, if rectal cancer does recur, it can be distant and appear after 3 to 5 years. For these reasons, after curative resection of a T1 rectal adenocarcinoma with favorable prognostic factors, a flexible sigmoidoscopy is recommended at 3 to 6 months post ESD

and every 6 months after for a total of 5 years from ESD.[9] Endoscopic ultrasound or pelvic MRI with contrast is recommended every 3 to 6 months for 2 years, then every 6 months for a total of 5 years.

With the increasing availability of ESD in North America, and the evidence supporting its use, the NCCN panel voted to add ESD as a treatment option for both surgical and nonsurgical candidates with T1, N0 rectal cancer (see Figure 1). It was noted that not all institutions have the expertise needed to perform this technique. The panel discussed whether it would be appropriate to add ESD as an option within the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer, because some institutions do use the technique for early-stage colon cancers. The panel decided against this because it was noted that the data are stronger for rectal cancer and the technique may be safer when performed in the rectum, as opposed to the colon. A section was written for the "Principles of Surgery" detailing therapeutic principles of ESD, pre-ESD endoscopic evaluation, criteria for resection with ESD, guidelines for when resection can be considered curative, surveillance after ESD, and decision-making between surgery and ESD (see REC-C 3 of 5 in the full version of the guidelines, available online at NCCN.org). Several panel members stressed that understaging of rectal cancers is common and, therefore, thorough staging should be performed prior to considering ESD as a treatment option. Furthermore, if unfavorable tumor characteristics were discovered following ESD (eg, lymphovascular invasion), the patient should consult with a multidisciplinary team including an endoscopist, surgeon, and pathologist in a shared decision-making process to decide whether to proceed with surgery.

Updates to the Total Neoadjuvant Therapy Approach

A treatment approach for clinical stage II or III rectal cancer, including both chemoradiotherapy (chemoRT) and chemotherapy given before transabdominal resection, has been gaining prominence. This approach, called total neoadjuvant therapy (TNT), was first tested in several small, phase II trials,[28–36] but its acceptance has more recently been supported by phase III trial data. The apparent benefits of the TNT approach include higher rates of pathologic complete response (pCR) and longer disease-free survival (DFS),[36–41] minimizing the length of time patients need an ileostomy,[37] facilitating resection, and improving the tolerance and completion rates of chemotherapy.[30,36,40,41] For some patients, surgery may be avoided if a clinical complete response (cCR) is achieved as a result of neoadjuvant therapy, as discussed later. Hence, the NCCN panel recommends TNT as the preferred approach for stage II–III rectal cancer (see Figure 2).

Use of Preoperative Short-Course Radiotherapy in TNT

Several trials have compared preoperative short-course radiotherapy (RT) to long-course chemoRT.[42–46] One such trial was STELLAR, a randomized, phase III trial that compared short-course RT followed by CAPEOX to capecitabine-based long-course chemoRT as neoadjuvant therapy in 599 patients with stage II–III rectal cancer.[47] Both groups received total mesorectal excision (TME) 6 to 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 chemoRT. There was also no significant difference in

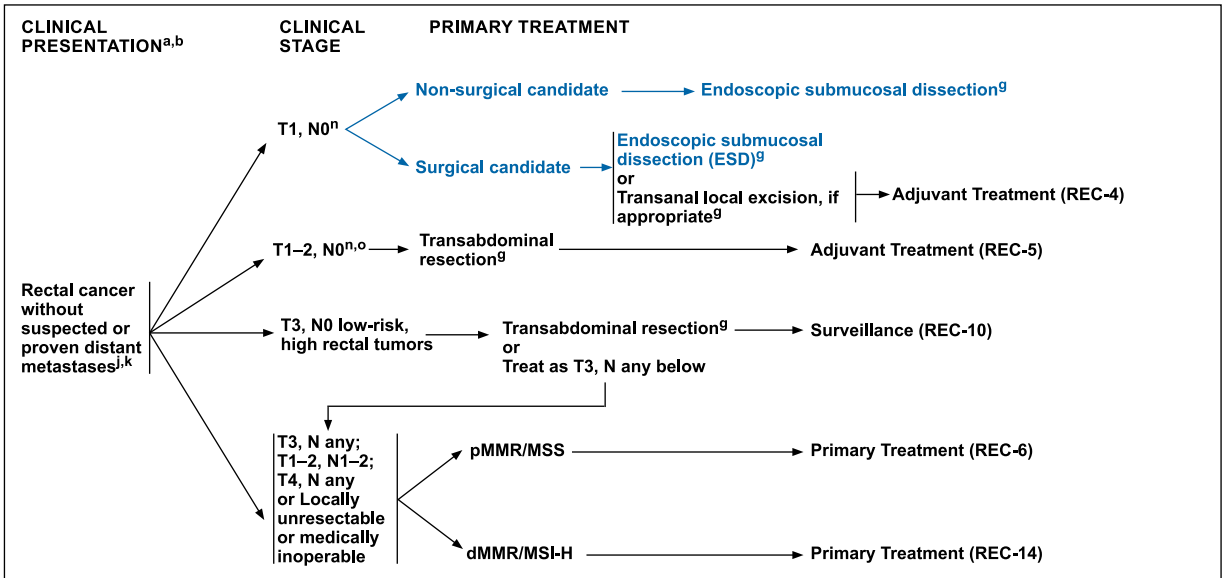
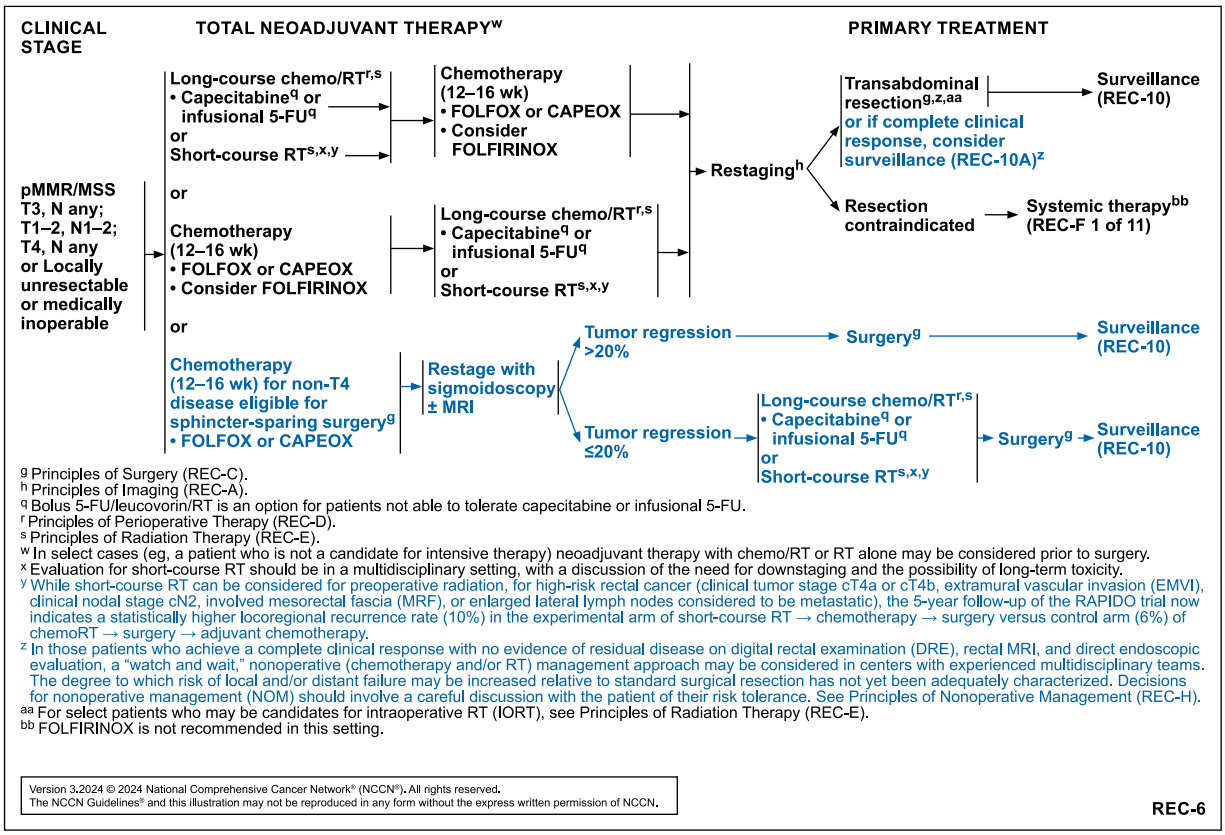


Figure 1. REC-3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer, Version 3.2024.



[g] Principles of Surgery (REC-C).
[h] Principles of Imaging (REC-A).
[q] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[r] Principles of Perioperative Therapy (REC-D).
[s] Principles of Radiation Therapy (REC-E).
[w] In select cases (eg, a patient who is not a candidate for intensive therapy) neoadjuvant therapy with chemo/RT or RT alone may be considered prior to surgery.
[x] 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.
[y] While short-course RT can be considered for preoperative radiation, for high-risk rectal cancer (clinical tumor stage cT4a or cT4b, extramural vascular invasion (EMVI), clinical nodal stage cN2, involved mesorectal fascia (MRF), or enlarged lateral lymph nodes considered to be metastatic), the 5-year follow-up of the RAPIDO trial now indicates a statistically higher locoregional recurrence rate (10%) in the experimental arm of short-course RT → chemotherapy → surgery versus control arm (6%) of chemoRT → surgery → adjuvant chemotherapy.
[z] In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination (DRE), 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. 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 (NOM) should involve a careful discussion with the patient of their risk tolerance. See Principles of Nonoperative Management (REC-H).
[aa] For select patients who may be candidates for intraoperative RT (IORT), see Principles of Radiation Therapy (REC-E).
[bb] FOLFIRINOX is not recommended in this setting.

REC-6

Figure 2. REC-6. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer, Version 3.2024.

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 ≥3 toxicities during preoperative treatment was higher with short-course RT (26.5% vs 12.6%; P<.001).

RAPIDO was another randomized phase III trial that compared standard treatment (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.[40] At 3 years after randomization, the rate of disease-related treatment failure was 23.7% with TNT compared with 30.4% with standard treatment (hazard ratio [HR], 0.75; 95% CI, 0.60–0.95; P=.019). No differences were found in the secondary endpoint of overall survival (OS). Serious AEs occurred in 38% of the TNT group and 34% in the standard treatment group. Although locoregional recurrence rates were similar between the study arms at 3 years, a 5-year follow-up of the RAPIDO trial reported an increased risk of locoregional recurrence in the experimental arm.[48] The experimental arm, consisting of treatment with short-course RT, chemotherapy, followed by surgery, had a locoregional recurrence rate of 10%, whereas the control arm, consisting of treatment with chemoRT, surgery, followed by optional adjuvant chemotherapy, had a locoregional recurrence rate of 6% (P=.027). OS after locoregional failure was comparable. Based on these updated results from RAPIDO, the NCCN panel decided to add a footnote to the TNT recommendations cautioning that preoperative short-course RT may be associated with a higher risk of local recurrence (see footnote "y" in Figure 2).

Sequencing of Therapy for TNT

It is not established whether it is better to start with chemotherapy, followed by chemoRT, or vice versa when following a TNT approach. Results from the phase II Organ Preservation in Rectal Adenocarcinoma (OPRA) trial suggest that initiating treatment with chemoRT may improve TME-free survival, though was not powered to directly compare the 2 TNT strategies.[49,50] The randomized phase II CAO/ARO/AIO-12 study also considered this question, comparing TNT approaches using either induction chemotherapy with FOLFOX followed by 5-FU/oxaliplatin chemoRT or chemoRT followed by consolidation chemotherapy.[51] This trial reported that up-front chemoRT led to higher completion rates for chemoRT, but lower completion rates for chemotherapy compared with up-front chemotherapy. pCR was observed in 17% of those who received up-front chemotherapy and 25% of those who received up-front chemoRT. In both OPRA and CAO/ARO/AIO-12 the time between radiation and assessment for complete response was substantially shorter in the arms that gave systemic chemotherapy first, and this may confound interpretation of the differences. 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%).[52] Chronic toxicity of grade ≥3 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 pCR while showing

no significant differences in DFS, locoregional recurrence, distant metastases, or toxicities. Similar to other studies, pCR is not a validated surrogate endpoint for survival outcomes. Although the NCCN panel continues to monitor the data for consideration in future updates, the induction and consolidation chemotherapy approaches are currently considered equivalent options for TNT in the guidelines.

Selective Omission of RT in TNT

Although 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.[53–55] The phase III FOWARC trial 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 pCR than regimens that included radiation (6.6% vs 14.0% for 5-FU-RT and 27.5% for FOLFOX-RT).[56] 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/RT.[57] 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/RT, FOLFOX-RT, and FOLFOX without RT, respectively.

PROSPECT was another phase III randomized study comparing neoadjuvant chemoRT to neoadjuvant chemotherapy (FOLFOX) with selective use of chemoRT based on response in patients who were candidates for sphincter-sparing surgery, and had either T2,N1–2 or T3,N0–2 rectal cancer (≤4 nodes, up to 1 cm).[58] In this trial, 1,128 patients started treatment: 585 in the FOLFOX group and 543 in the chemoRT group. After a median follow-up of 58 months, DFS was similar between the 2 groups (HR, 0.92; 95% CI, 0.74–1.14; P=.005 for noninferiority). Five-year DFS was 80.8% in the FOLFOX group compared with 78.6% in the chemoRT group. OS and local recurrence rates were also similar. Notably, 98% of patients on this trial were free of local recurrence at 5 years, a rate that the authors attributed to careful selection of patients without high-risk features in the trial protocol. In the FOLFOX group, only 9.1% of patients went on to receive preoperative chemoRT and 1.4% received postoperative chemoRT. Patient-reported outcomes on the PROSPECT trial noted worse short-term AEs of anxiety, appetite, constipation, depression, dysphagia, dyspnea, edema, fatigue, mucositis, nausea, neuropathy, and vomiting during neoadjuvant treatment with FOLFOX compared with chemoRT, whereas 12-month long term outcomes were better with FOLFOX than chemoRT in regard to fatigue, neuropathy, and sexual function.[59] Finally, initial results from the ongoing phase III CONVERT trial, comparing neoadjuvant chemotherapy with CAPEOX to neoadjuvant chemoRT, are also looking promising for this strategy.[60]

Based on these results, selective omission of chemoRT following favorable response to neoadjuvant chemotherapy may be considered an option for patients who meet the inclusion criteria of the PROSPECT trial and wish to avoid the long-term effects of RT. The NCCN Guidelines recommend restaging with sigmoidoscopy, with or without MRI, following 12 to 16 weeks of chemotherapy. If tumor regression is >20%, the treatment plan may omit chemoRT and proceed directly to surgery, whereas short-course RT or chemoRT is recommended prior to surgery if tumor regression is ≤20% (see Figure 2). Per the NCCN panel, the adjuvant chemotherapy that was given on some of these trials is not necessary and would not be recommended because TNT is now the preferred approach.

Watch-and-Wait Nonoperative Approach for Clinical Complete Responders

As preoperative treatment and imaging modalities have improved, it has become apparent that patients with a cCR to neoadjuvant therapy may be spared the morbidities of surgery, an approach called *nonoperative management* (NOM). A small prospective study included a more thorough assessment of treatment response and used very strict criteria to select 21 of 192 (11%) patients with cCR who were then observed with careful follow-up and compared with 20 patients with a complete pathologic response after resection.[61] Only one patient in the NOM 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. Short-term functional outcomes, however, were better in the NOM group, with better bowel function scores, less incontinence, and 10 patients avoiding permanent colostomy. Other nonrandomized prospective studies, case series, and systematic reviews added to the growing evidence that the NOM approach warranted further investigation.[62–68]

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 following neoadjuvant therapy and were managed by watch-and-wait.[69] 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.[70] This analysis included 793 patients with cCR 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 were 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 within the first 2 to 3 years following CR, and a more intense surveillance schedule is recommended during this time period.[69,70]

The OPRA trial was a randomized, phase II trial of the NOM approach.[50] 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. Following neoadjuvant treatment, patients received either TME or observation (NOM) based on tumor response. Organ preservation was achievable in approximately 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 relapse-free survival, distant metastasis–free survival, or OS. After a median follow-up of 5.1 years, the OPRA trial continued to show long-term organ preservation in half of the patients treated with TNT on the trial.[71] Five-year DFS was 71% in the induction chemotherapy group and 69% in the consolidation chemotherapy group. TME-free survival was 39% for induction chemotherapy and 54% for consolidation chemotherapy. Of the 81 patients with tumor regrowth, 94% occurred in the first 2 years and 99% within 3 years, highlighting the importance of close surveillance in the first 2 years. A secondary analysis of the OPRA trial suggested a 3-tier grading schema (cCR, near-CR, and incomplete response), which could be used to estimate recurrence and survival outcomes and maximize eligibility for NOM in patients who receive TNT for locally advanced rectal cancer.[72]

NOM is also being investigated as an option for patients with deficient mismatch repair (dMMR) or microsatellite instability–high (MSI-H) locally advanced rectal cancers that are treated with immune checkpoint inhibitors. Multiple retrospective series suggest a high, though not 100%, cCR rate after immunotherapy for locally advanced colon or rectal cancer.[73,74] A small prospective phase II trial studied the effects of dostarlimab, an anti–PD-1 monoclonal antibody, on 12 patients with dMMR, stage II or III rectal adenocarcinoma.[75] All 12 patients showed a cCR, with no evidence of tumor on MRI, PET/CT, endoscopic evaluation, digital rectal examination, or biopsy. At the time of study publication, with a follow-up range of 6 to 25 months, no patients had received chemoRT or surgery and no cases of progression or recurrence had been reported. An abstract presented at the 2024 ASCO Annual Meeting presented a follow-up on this trial, which, at the time, had enrolled 48 patients, reporting that all patients who had completed treatment (42 at the time of presentation) continued to show a cCR, with no patients receiving additional therapy and no cases of progression or recurrence.[76]

Because of concerns regarding the need for rigorous surveillance, the NCCN panel had held off on including the NOM approach in the guideline for several years. When NOM was included in the guidelines, it was first mentioned within a footnote, but more recently added as an option within the main flow of the algorithm, for both pMMR/MSS and dMMR/MSI-H disease (see Figures 2 and 3). Keeping these caveats in mind, the panel believes that a NOM approach may be considered in centers with experienced multidisciplinary teams after a careful discussion with the patient about their risk tolerance and the necessary surveillance schedule. A new principles section was also added to the NCCN Guidelines to better define the criteria for a complete clinical response, timing of assessment for cCR, definition of near-CR, and indications for when surgery should be performed (see "Principles of Nonoperative Management" in the full version of the guidelines, available at NCCN.org).

The NCCN panel stresses the critical importance of careful surveillance for those considering a NOM approach to detect and treat tumor regrowth in a timely manner. The OPRA 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 to 5; MRI every 6 months for the first 2 years, then every 12 months for

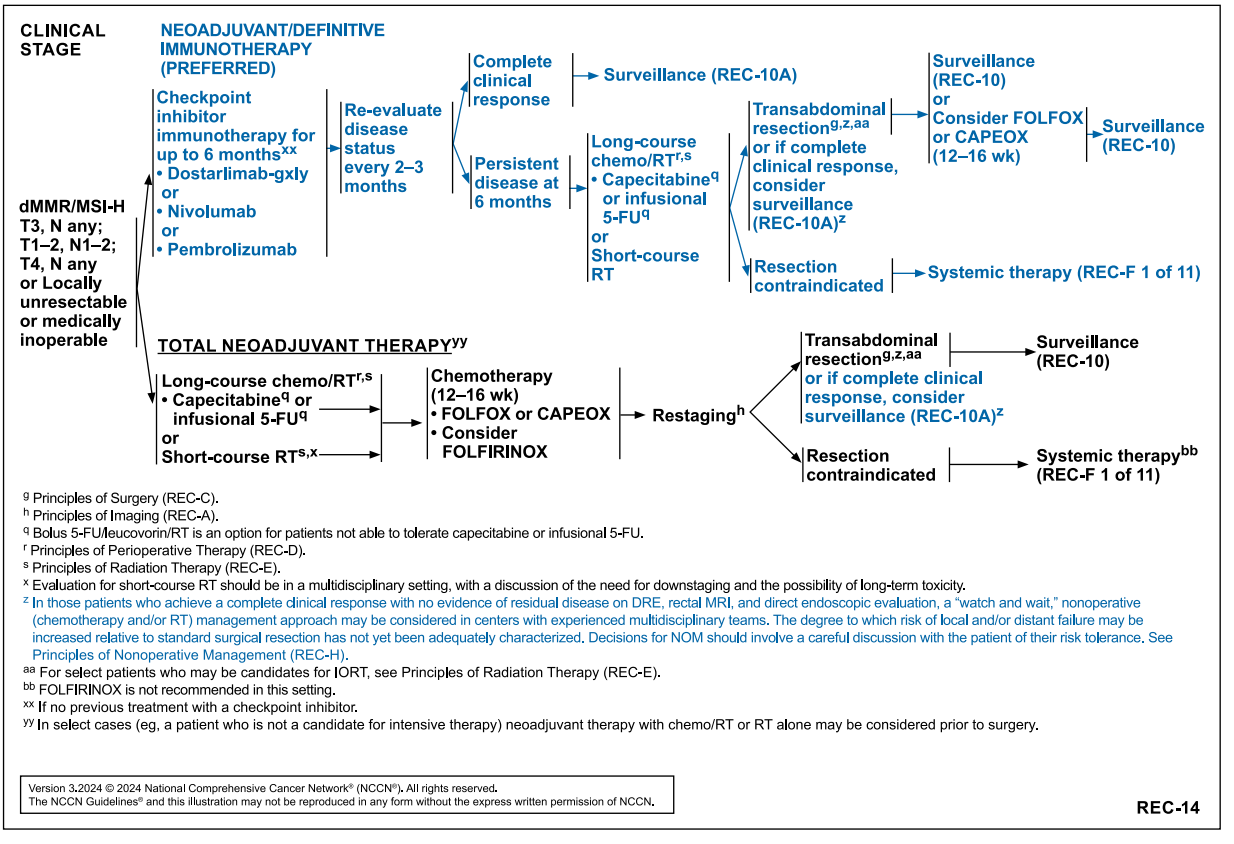


Figure 3. REC-14. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer, Version 3.2024.

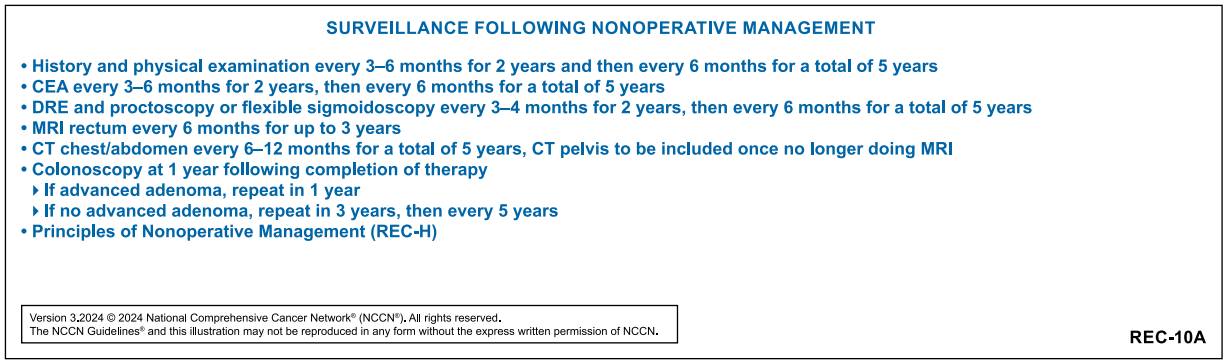


Figure 4. REC-10A. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer, Version 3.2024.

years 3 to 5; annual CT chest/abdomen/pelvis for 5 years; and colonoscopy once at year 1 and again at year 5.[50] Watch-and-wait surveillance protocols are an area of active investigation, and other protocols have been suggested.[69,70,77] The NOM surveillance schedule recommended by the NCCN panel is based on clinical and institutional experiences and is similar to the OPRA protocol. See Figure 4 for NCCN Guidelines recommendations for surveillance following nonoperative management.

Summary

The NCCN Rectal Cancer Panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology/colorectal surgery, radiation oncology, pathology, and radiology, is necessary for treating patients with rectal cancer. Patients with very-early-stage tumors that are T1, N0 and who meet carefully defined criteria can be managed with ESD or transanal local excision. A transabdominal resection is appropriate for other rectal lesions. A TNT approach, traditionally consisting of chemoRT/short-course RT and chemotherapy, is preferred when RT is being given. However, ongoing clinical trials for rectal cancer are particularly focused on treatment approaches that omit surgery or RT, with the goal of improving outcomes for eligible patients. Careful surveillance is necessary to detect and manage recurrences in a prompt and effective manner.

References

1. Siegel RL, Giaquinto AN, Jemal A. Cancer statistics, 2024. CA Cancer J Clin 2024;74:12–49.
2. Cheng L, Eng C, Nieman LZ, et al. Trends in colorectal cancer incidence by anatomic site and disease stage in the United States from 1976 to 2005. Am J Clin Oncol 2011;34:573–580.
3. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020;70:145–164.
4. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg 2014;150:17–22.
5. Weinberg BA, Marshall JL, Salem ME. The growing challenge of young adults with colorectal cancer. Oncology (Williston Park) 2017;31:381–389.
6. Meng L, Thapa R, Delgado MG, et al. Association of age with treatment-related adverse events and survival in patients with metastatic colorectal cancer. JAMA Netw Open 2023;6:e2320035.
7. Cercek A, Chatila WK, Yaeger R, et al. A comprehensive comparison of early-onset and average-onset colorectal cancers. J Natl Cancer Inst 2021;113:1683–1692.
8. Yin J, Salem ME, Dixon JG, et al. Reevaluating disease-free survival as an endpoint vs overall survival in stage III adjuvant colon cancer trials. J Natl Cancer Inst 2022;114:60–67.
9. Wang AY, Hwang JH, Bhatt A, Draganov PV. AGA clinical practice update on surveillance after pathologically curative endoscopic submucosal dissection of early gastrointestinal neoplasia in the United States: commentary. Gastroenterology 2021;161:2030–2040.e1.
10. Draganov PV, Wang AY, Othman MO, Fukami N. AGA Institute clinical practice update: endoscopic submucosal dissection in the United States. Clin Gastroenterol Hepatol 2019;17:16–25.e1.
11. Draganov PV, Coman RM, Gotoda T. Training for complex endoscopic procedures: how to incorporate endoscopic submucosal dissection skills in the West? Expert Rev Gastroenterol Hepatol 2014;8:119–121.
12. Mann R, Gajendran M, Umapathy C, et al. Endoscopic management of complex colorectal polyps: current insights and future trends. Front Med (Lausanne) 2021;8:728704.
13. Draganov PV, Aihara H, Karasik MS, et al. Endoscopic submucosal dissection in North America: a large prospective multicenter study. Gastroenterology 2021;160:2317–2327.e2.
14. Yang D, Draganov PV. Endoscopic submucosal dissection in 2018: a minimally invasive curative approach for select rectal cancers. Am J Gastroenterol 2019;114:687.
15. Atallah C, Taylor JP, Lo BD, et al. Local excision for T1 rectal tumours: are we getting better? Colorectal Dis 2020;22:2038–2048.
16. Dekkers N, Boonstra JJ, Moons LMG, et al. Transanal minimally invasive surgery (TAMIS) versus endoscopic submucosal dissection (ESD) for resection of non-pedunculated rectal lesions (TRIASSIC study): study protocol of a European multicenter randomised controlled trial. BMC Gastroenterol 2020;20:225.
17. Kim M, Bareket R, Eleftheriadis NP, et al. Endoscopic submucosal dissection (ESD) offers a safer and more cost-effective alternative to transanal endoscopic microsurgery (TEM): an international collaborative study. J Clin Gastroenterol 2023;57:486–489.
18. Kiriyama S, Saito Y, Matsuda T, et al. Comparing endoscopic submucosal dissection with transanal resection for non-invasive rectal tumor: a retrospective study. J Gastroenterol Hepatol 2011;26:1028–1033.
19. Park SU, Min YW, Shin JU, et al. Endoscopic submucosal dissection or transanal endoscopic microsurgery for nonpolypoid rectal high grade dysplasia and submucosa-invading rectal cancer. Endoscopy 2012;44:1031–1036.
20. Sagae VMT, Ribeiro IB, de Moura DTH, et al. Endoscopic submucosal dissection versus transanal endoscopic surgery for the treatment of early rectal tumor: a systematic review and meta-analysis. Surg Endosc 2020;34:1025–1034.
21. Tanaka S, Kashida H, Saito Y, et al. Japan Gastroenterological Endoscopy Society guidelines for colorectal endoscopic submucosal dissection/endoscopic mucosal resection. Dig Endosc 2020;32:219–239.
22. Kobayashi H, Mochizuki H, Morita T, et al. Characteristics of recurrence after curative resection for T1 colorectal cancer: Japanese multicenter study. J Gastroenterol 2011;46:203–211.

23. Ikematsu H, Yoda Y, Matsuda T, et al. Long-term outcomes after resection for submucosal invasive colorectal cancers. Gastroenterology 2013; 144:551–559.
24. Yang D, Aihara H, Perbtani YB, et al. Safety and efficacy of endoscopic submucosal dissection for rectal neoplasia: a multicenter North American experience. Endosc Int Open 2019;7:e1714–1722.
25. Repici A, Hassan C, Pagano N, et al. High efficacy of endoscopic submucosal dissection for rectal laterally spreading tumors larger than 3 cm. Gastrointest Endosc 2013;77:96–101.
26. Probst A, Ebigbo A, Markl B, et al. Endoscopic submucosal dissection for rectal neoplasia extending to the dentate line: European experience. Endosc Int Open 2018;6:e1355–1362.
27. Oka S, Tanaka S, Saito Y, et al. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. Am J Gastroenterol 2015;110:697–707.
28. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513–519.
29. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. J Clin Oncol 2006;24:668–674.
30. Fernandez-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo Cancer de Recto 3 study. J Clin Oncol 2010;28:859–865.
31. Perez K, Safran H, Sikov W, et al. Complete neoadjuvant treatment for rectal cancer: the Brown University Oncology Group CONTRE study. Am J Clin Oncol 2014;40:283–287.
32. Marechal R, Vos B, Polus M, et al. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. Ann Oncol 2012;23: 1525–1530.
33. Nogue M, Salud A, Vicente P, et al. Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging-defined poor-prognosis locally advanced rectal cancer: the AVACROSS study. Oncologist 2011;16: 614–620.
34. Fernandez-Martos C, Garcia-Albeniz X, Pericay C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial. Ann Oncol 2015;26:1722–1728.
35. Sclafani F, Brown G, Cunningham D, et al. PAN-EX: a pooled analysis of two trials of neoadjuvant chemotherapy followed by chemoradiotherapy in MRI-defined, locally advanced rectal cancer. Ann Oncol 2016;27:1557–1565.
36. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. Lancet Oncol 2015;16:957–966.
37. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. JAMA Oncol 2018;4: e180071.
38. Kasi A, Abbasi S, Handa S, et al. Total neoadjuvant therapy vs standard therapy in locally advanced rectal cancer: a systematic review and meta-analysis. JAMA Netw Open 2020;3:e2030097.
39. Petrelli F, Trevisan F, Cabiddu M, et al. Total neoadjuvant therapy in rectal cancer: a systematic review and meta-analysis of treatment outcomes. Ann Surg 2020;271:440–448.
40. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:29–42.
41. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:702–715.
42. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215–1223.
43. Latkauskas T, Pauzas H, Kairevice L, et al. Preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer: results of a randomized controlled trial. BMC Cancer 2016;16:927.
44. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827–3833.
45. Ciseł B, Pietrzak L, Michalski W, et al. Long-course preoperative chemoradiation vs. 5 x 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. Ann Oncol 2019;30:1298–1303.
46. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017;18:336–346.
47. Jin J, Tang Y, Hu C, et al. Multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR). J Clin Oncol 2022;40: 1681–1692.
48. Dijkstra EA, Nilsson PJ, Hospers GAP, et al. Locoregional failure during and after short-course radiotherapy followed by chemotherapy and surgery compared with long-course chemoradiotherapy and surgery: a 5-year follow-up of the RAPIDO trial. Ann Surg 2023;278:e766–772.
49. Smith JJ, Chow OS, Gollub MJ, et al. Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer 2015;15:767.
50. Garcia-Aguilar J, Patil S, Gollub MJ, et al. Organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy. J Clin Oncol 2022;40:2546–2556.
51. Fokas E, Allgauer M, Polat B, et al. Randomized phase II trial of chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for locally advanced rectal cancer: CAO/ARO/AIO-12. J Clin Oncol 2019;37:3212–3222.
52. Fokas E, Schlenska-Lange A, Polat B, et al. Chemoradiotherapy plus induction or consolidation chemotherapy as total neoadjuvant therapy for patients with locally advanced rectal cancer: long-term results of the CAO/ARO/AIO-12 randomized clinical trial. JAMA Oncol 2022;8: e215445.
53. Lai LL, Fuller CD, Kachnic LA, Thomas CR Jr. Can pelvic radiotherapy be omitted in select patients with rectal cancer? Semin Oncol 2006;33: S70–74.
54. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients—a Dutch Colorectal Cancer Group study. J Clin Oncol 2005;23: 6199–6206.
55. Rahbari NN, Elbers H, Askoxylakis V, et al. Neoadjuvant radiotherapy for rectal cancer: meta-analysis of randomized controlled trials. Ann Surg Oncol 2013;20:4169–4182.
56. Deng Y, Chi P, Lan P, et al. Modified FOLFOX6 with or without radiation versus fluorouracil and leucovorin with radiation in neoadjuvant treatment of locally advanced rectal cancer: initial results of the Chinese FOWARC multicenter, open-label, randomized three-arm phase III trial. J Clin Oncol 2016;34:3300–3307.
57. Deng Y, Chi P, Lan P, et al. Neoadjuvant modified FOLFOX6 with or without radiation versus fluorouracil plus radiation for locally advanced rectal cancer: final results of the Chinese FOWARC trial. J Clin Oncol 2019;37:3223–3233.
58. Schrag D, Shi Q, Weiser MR, et al. Preoperative treatment of locally advanced rectal cancer. N Engl J Med 2023;389:322–334.
59. Basch E, Dueck AC, Mitchell SA, et al. Patient-reported outcomes during and after treatment for locally advanced rectal cancer in the PROSPECT trial (Alliance N1048). J Clin Oncol 2023;41:3724–3734.
60. Mei WJ, Wang XZ, Li YF, et al. Neoadjuvant chemotherapy with CAPOX versus chemoradiation for locally advanced rectal cancer with uninvolved mesorectal fascia (CONVERT): initial results of a phase III trial. Ann Surg 2023;277:557–564.
61. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011;29:4633–4640.
62. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 2015;16:919–927.
63. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys 2014;88:822–828.

64. Li J, Liu H, Yin J, et al. Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: a cohort study. Oncotarget 2015;6:42354–42361.
65. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol 2019;5:e185896.
66. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2017;2:501–513.
67. Sammour T, Price BA, Krause KJ, Chang GJ. Nonoperative management or 'watch and wait' for rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy: a critical appraisal. Ann Surg Oncol 2017;24:1904–1915.
68. Kong JC, Guerra GR, Warrier SK, et al. Outcome and salvage surgery following "watch and wait" for rectal cancer after neoadjuvant therapy: a systematic review. Dis Colon Rectum 2017;60:335–345.
69. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet 2018;391:2537–2545.
70. Fernandez LM, Sao Juliao GP, Figueiredo NL, et al. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. Lancet Oncol 2021;22:43–50.
71. Verheij FS, Omer DM, Williams H, et al. Long-term results of organ preservation in patients with rectal adenocarcinoma treated with total neoadjuvant therapy: the randomized phase II OPRA trial. J Clin Oncol 2024;42:500–506.
72. Thompson HM, Omer DM, Lin S, et al. Organ preservation and survival by clinical response grade in patients with rectal cancer treated with total neoadjuvant therapy: a secondary analysis of the OPRA randomized clinical trial. JAMA Netw Open 2024;7:e2350903.
73. Loria A, Ammann AM, Olowokure OO, et al. Systematic review of neoadjuvant immunotherapy for mismatch repair deficient locally advanced colon cancer: an emerging strategy. Dis Colon Rectum 2024;67:762–771.
74. Wang QX, Xiao BY, Cheng Y, et al. Anti-PD-1-based immunotherapy as curative-intent treatment in dMMR/MSI-H rectal cancer: a multicentre cohort study. Eur J Cancer 2022;174:176–184.
75. Cercek A, Lumish M, Sinopoli J, et al. PD-1 blockade in mismatch repair-deficient, locally advanced rectal cancer. N Engl J Med 2022;386:2363–2376.
76. Cercek A, Sinopoli JC, Shia J, et al. Durable complete responses to PD-1 blockade alone in mismatch repair deficient locally advanced rectal cancer. J Clin Oncol 2024;42:Abstract LBA3512.
77. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol 2016;17:174–183.