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Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: July 10, 2020; Expiration date: July 10, 2021

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

The NCCN staff listed below discloses no relevant financial relationships:

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Alyse Johnson-Chilla, MS, Guidelines Coordinator, NCCN, has disclosed that she has no relevant financial relationships.

Lisa A. Gurski, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

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Rectal Cancer, Version 6.2020

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Rectal Cancer provide recommendations for the diagnosis, evaluation, treatment, and follow-up of patients with rectal cancer. These NCCN Guidelines Insights summarize the panel discussion behind recent important updates to the guidelines. These updates include clarifying the definition of rectum and differentiating the rectum from the sigmoid colon; the total neoadjuvant therapy approach for localized rectal cancer; and biomarker-targeted therapy for metastatic colorectal cancer, with a focus on new treatment options for patients with *BRAF* V600E– or HER2 amplification–positive disease.

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*Provided content development and/or authorship assistance.

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

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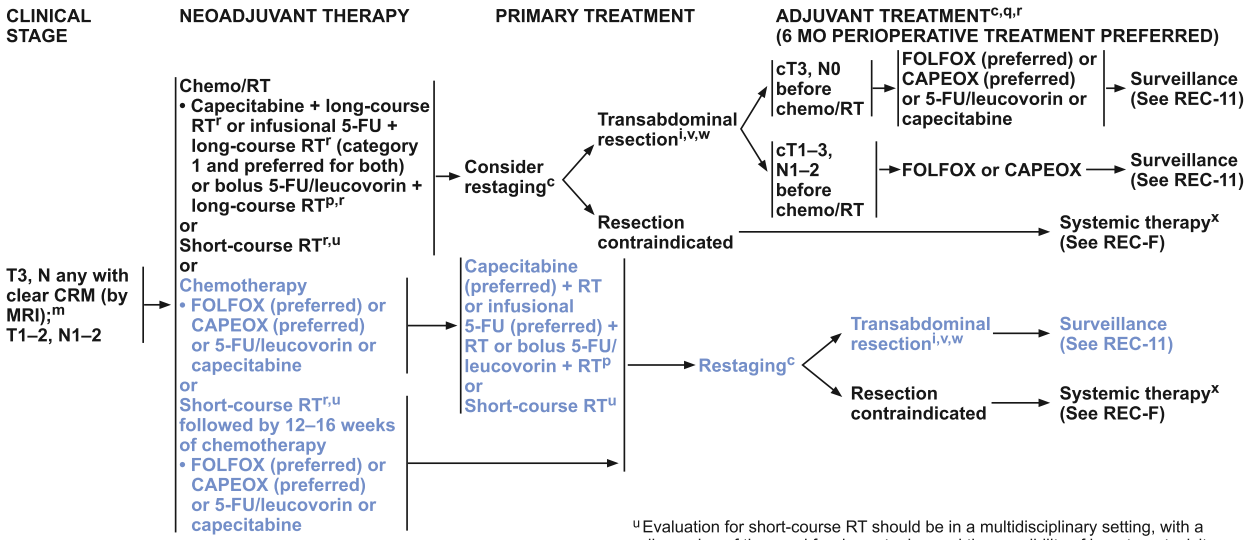


[c] See Principles of Imaging (REC-A).
[i] See Principles of Surgery (REC-C).
[m] CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.
[p] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[q] See Principles of Adjuvant Therapy (REC-D).
[r] See Principles of Radiation Therapy (REC-E).
[u] 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.
[v] If patient treated with short-course RT, surgery should be within 1 week or delayed 6–8 weeks.
[w] 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. 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.
[x] FOLFOXIRI is not recommended in this setting.

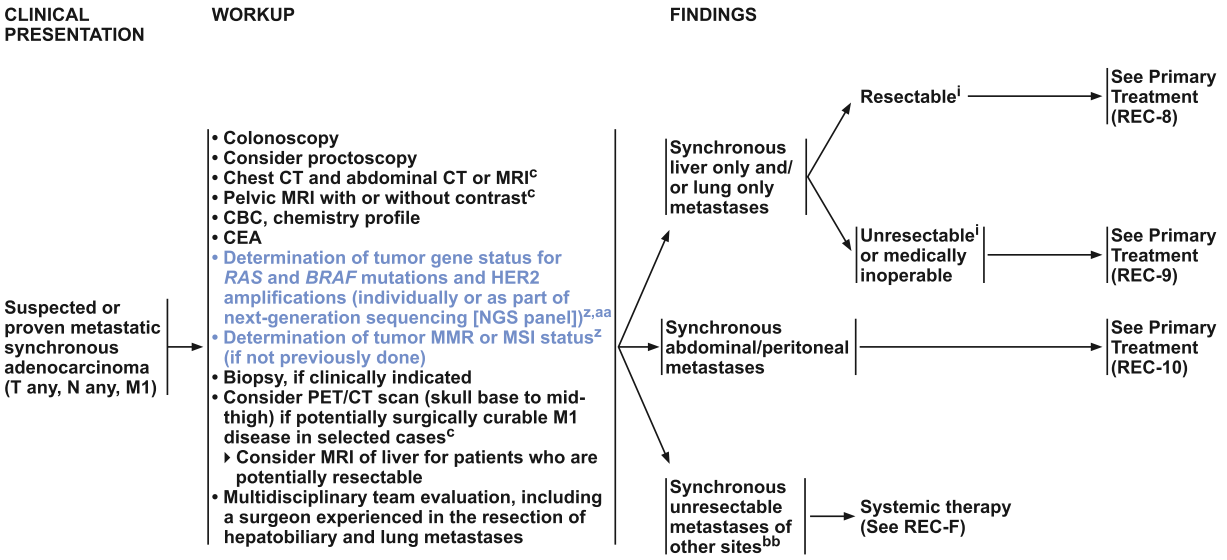
REC-5

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2020, an estimated 43,340 new cases of rectal cancer will occur in the United States (25,960 in men; 17,380 in women), and an estimated 53,200 people will die of rectal and colon cancer combined.[1] Despite these statistics, the incidence per 100,000 population of colon and rectal cancers decreased from 60.5 in 1976 to 46.4 in 2005.[2] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[3] and is currently reduced by approximately 50% from peak mortality rates.[1] These improvements in incidence of and mortality from CRC are thought to be a result of cancer prevention and earlier diagnoses due to screening and of better treatment modalities. More recent data show continued rapid declines in incidence among individuals aged ≥65 years, with a decrease of 3.3% annually from 2011 through 2016.[4] Conversely, incidence has increased among those aged <65 years, with a 1% annual increase among those aged 50 to 64 years and a 2% annual increase among 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.[4]

The determination of an optimal treatment plan for an individual patient with localized rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative vs 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.[5] 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.[6–8] For most patients with localized rectal cancer, multimodality therapy that combines chemoradiotherapy (chemoRT), chemotherapy, and surgery is recommended.[9]

For metastatic CRC (mCRC), the goal of treatment may be curative if the tumor and metastases are resectable or potentially able to be converted to resectable;



[c] See Principles of Imaging (REC-A).
[i] See Principles of Surgery (REC-C).
[z] See Principles of Pathologic Review (REC-B 5 of 9) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[aa] If known RAS/RAF mutation, HER2 testing is not indicated. NGS panels have the ability to pick up rare and actionable mutations and fusions.
[bb] Consider resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

REC-7

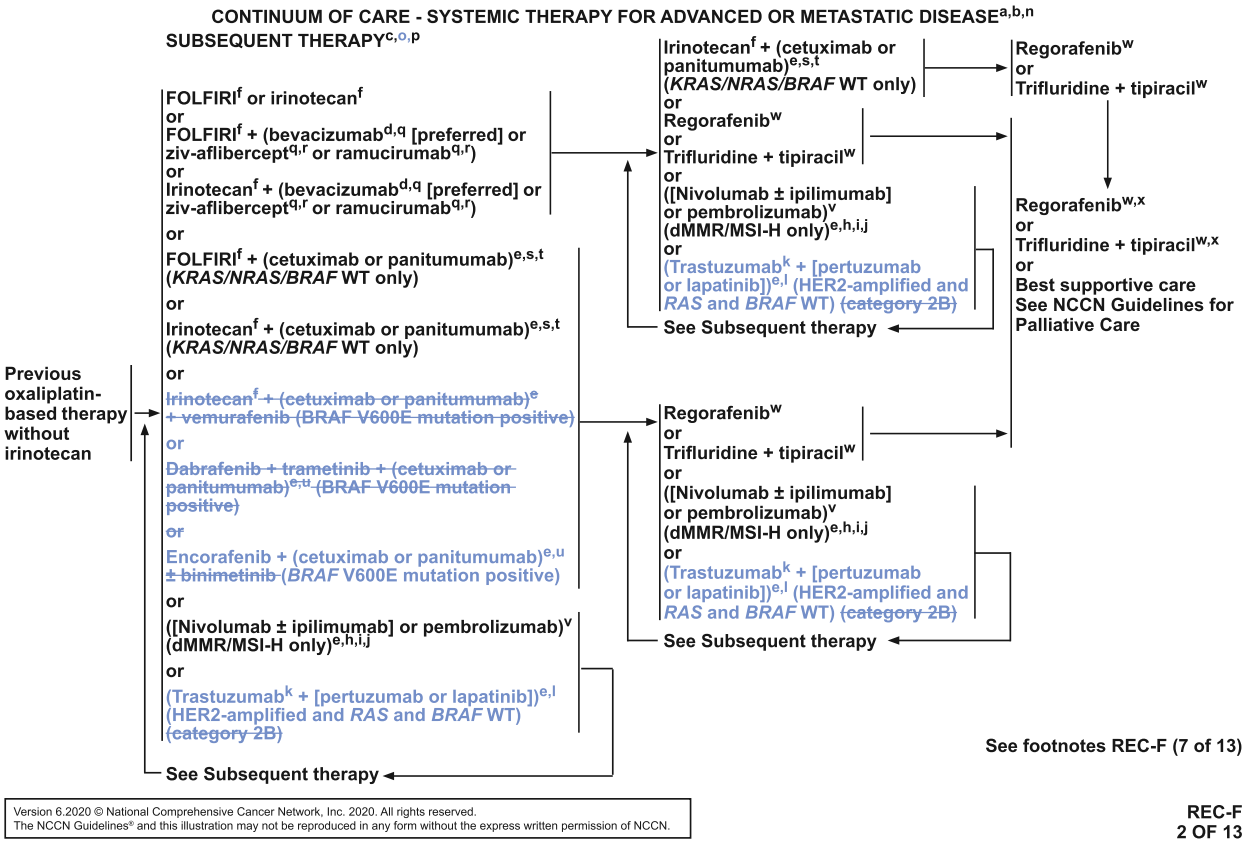
however, most patients with mCRC have unresectable disease.[10] For patients with unresectable metastatic disease, treatment most commonly consists of systemic therapy, with the goal of prolonging quantity and maintaining quality of life. Systemic therapy for mCRC involves various active drugs, either in combination or as single agents. Choice of therapy is based on consideration of the goals of therapy, type and timing of prior therapy, mutational profile of the tumor, and differing efficacy and toxicity profiles of the constituent drugs.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Rectal Cancer provide recommendations for the diagnosis, evaluation, treatment, and follow-up of patients with rectal cancer. These NCCN Guidelines Insights summarize the panel discussion behind recent important updates to the guidelines. These updates include clarifying the definition of rectum and differentiating the rectum from the sigmoid colon; the total neoadjuvant therapy (TNT) approach for localized rectal cancer; and biomarker-targeted therapy for mCRC, with a focus on new treatment options for patients with *BRAF* V600E– or HER2 amplification–positive disease.

Definition of the Rectum

There are a number of different anatomic definitions available in the literature that can be used to differentiate the colon from the rectum and the rectum from the anus. Accuracy of this definition is important, because the recommended treatment modalities for localized colon, rectal, and anal cancer differ significantly. Specifically, accurate differentiation between upper rectal and sigmoid colon tumors can be particularly difficult. Because radiotherapy (RT) is rarely recommended for localized colon tumors but is an integral part of the treatment of many rectal cancers, proper identification of a tumor as originating from the colon or rectum can substantially impact treatment decisions.

An NCI guideline published in 2000 defined the rectum as ≤12 cm from the anal verge as determined by rigid proctoscopy.[11] This definition was based on a study showing differences in local recurrence rates for lesions located >12 cm from the anal verge (9.6%) compared with those located in the mid- or low-rectum (30.1% and 30.7%, respectively).[12] Although this definition has been commonly used in the medical community, this definition is fundamentally imprecise in that it fails to account for differences in body habitus (ie, a measured distance



of 12 cm from the anal verge would yield very different anatomic features in a patient who is 4 feet tall compared with one who is 7 feet tall). Furthermore, the panel considers MRI to be a superior tool compared with rigid proctoscopy for determining the anatomic landmarks that truly distinguish the colon from the rectum.

Based on these discussions, the NCCN Guidelines have defined the rectum as lying 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 rectum can be further divided into the upper-, mid, and lower-rectum based on the location of the anterior peritoneal reflection as determined by MRI or CT.[13,14] The upper-rectum occurs above the anterior peritoneal reflection, the midrectum at the anterior peritoneal reflection, and the lower-rectum below. Because the anterior and posterior aspects of the peritoneal reflection often are not at the same level, this definition of the rectum clarifies its relation to the peritoneal cavity.

Panel members have also remarked that the 2019 publication of an international, expert-based Delphi Consensus provides an alternative, accurate definition of the rectum. This publication defines the rectum as the point of sigmoid take-off where the mesocolon elongates as the ventral and horizontal course of the sigmoid on axial and sagittal views, respectively, on cross-sectional imaging.[15] Although this definition is not currently incorporated into the NCCN Guidelines for Rectal Cancer, it may be considered by the panel in the future.

TNT for Localized Rectal Cancer

Several small trials have tested the utility of a course of chemotherapy preceding chemoRT and resection without the expectation of using chemotherapy postoperatively.[16–21] This approach is referred to as a TNT approach. In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CAPEOX either before chemoRT or after surgery.[18,22] Similar pathologic complete response (CR) rates were seen, and induction chemotherapy appeared to be less toxic and better tolerated. Another phase II trial randomized patients to chemoRT and surgery with or without FOLFOX induction therapy.[20] There were no differences between the clinical outcomes, but the group receiving induction therapy experienced higher toxicity. The phase II AVACROSS study

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE
FOOTNOTES

[a] For chemotherapy references, see Chemotherapy Regimens and References (REF-F [8 of 13]).
[b] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[c] Chest/abdominal/pelvic CT with contrast or chest CT and abdominal/pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used. See Principles of Imaging (REC-A).
[d] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[e] See Principles of Pathologic Review (REC-B 5 of 9).
[f] Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. Guidelines for use in clinical practice have not been established.
[g] FOLFOXIRI should be strongly considered for patients with excellent performance status.
[h] These therapies are FDA approved for colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. However, a number of patients in the clinical trials had not received all three prior systemic therapies. Thirty-seven percent of patients received nivolumab monotherapy and 24% received ipilimumab/nivolumab combination therapy in first- or second-line, and 28% and 31% of patients had not received all three indicated prior therapies before treatment with nivolumab or ipilimumab/nivolumab, respectively.
[i] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[j] If disease response, consider discontinuing checkpoint inhibitor after 2 years of treatment.
[k] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[l] If no previous HER2 inhibitor.
[m] The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.
[n] Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases. See Principles of Surgery (REC-C).
[o] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.
[p] If patients had therapy stopped for reasons other than progression (eg, cumulative toxicity, elective treatment break, patient preference), rechallenge is an option at time of progression.
[q] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[r] There are no data to suggest activity of FOLFIRI-ziv-aflibercept or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.
[s] If neither previously given.
[t] Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
[u] In the second-line setting for *BRAF* V600E mutation positive tumors, there is phase 3 evidence for better efficacy with targeted therapies over FOLFIRI.
[v] If no previous treatment with a checkpoint inhibitor.
[w] Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.
[x] If not previously given.

assessed the safety and efficacy of adding bevacizumab to induction therapy with CAPEOX prior to capecitabine/bevacizumab-chemoRT and surgery.[21] The regimen was well tolerated with a pathologic CR rate of 36%. 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.[23] Of the 269 patients who were included, 91.1% completed chemotherapy, 88.1% completed chemoRT, and 89.2% underwent curative surgery. Rates of 5-year progression-free survival (PFS) and overall survival (OS) were 66.4% and 73.3%, respectively.

A single-institution retrospective cohort analysis of patients with T3/4 or node-positive rectal cancer compared the outcomes after either a traditional approach of neoadjuvant chemoRT then resection with planned adjuvant chemotherapy (n=320), or a TNT approach of induction chemotherapy then chemoRT before resection (n=308).[24] Patients in the TNT group received a greater percentage of the planned chemotherapy dose than those in the adjuvant chemotherapy group. CR rates were 36% and 21% in the TNT and adjuvant chemotherapy groups, respectively.

The NCCN panel discussed possible benefits of using chemotherapy first, including the early prevention or eradication of micrometastases, higher rates of pathologic CR, minimizing the length of time patients need an ileostomy, facilitating resection, and avoiding the need to compromise chemotherapy delivery because of bone marrow suppression or postsurgical complications. One potential downside to this approach is the possibility of overtreating low-risk stage II rectal cancer. The panel continues to monitor the literature supporting a TNT approach to the treatment of rectal cancer, and this approach is currently reflected within the guideline recommendations (see REC-5, page 808).

Biomarker-Targeted Therapy for mCRC

As the role of targeted therapy for treatment of advanced or mCRC has become increasingly prominent, the NCCN Guidelines for Rectal Cancer have expanded its recommendations regarding biomarker testing. Currently, determination of tumor gene status for *KRAS*/*NRAS* and *BRAF* V600E mutations, as well as HER2 amplifications, is recommended for patients with mCRC. HER2 testing is not indicated in cases in which the tumor has a known *RAS* or *RAF* mutation. Determination of mismatch repair (MMR) or microsatellite instability (MSI) status is also recommended in all patients with newly diagnosed colon

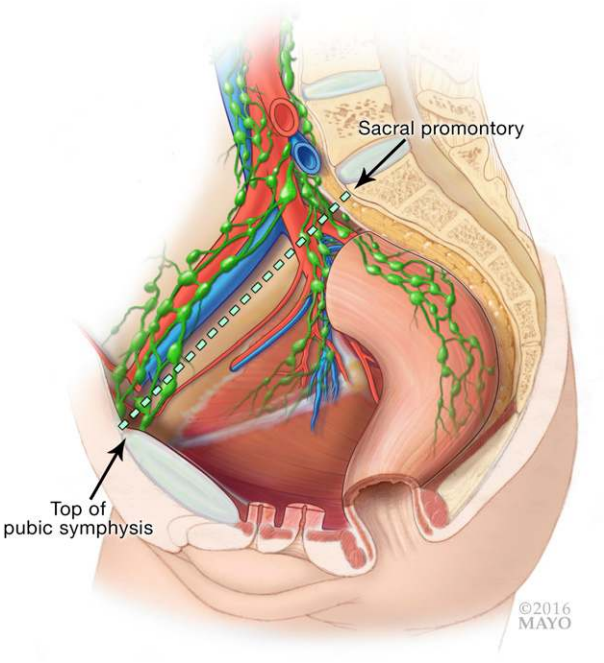


Figure 1. Definition of rectum, used with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

or rectal cancer (see REC-7, page 809). The "Principles of Pathologic Review" section (REC-B in the complete version of these guidelines, available at NCCN.org) has been updated to provide additional information on biomarker testing recommendations. Biomarker testing may be performed for individual genes or as part of a next-generation sequencing (NGS) panel, although the NCCN panel does not recommend any specific testing methodology over the other. However, NGS panels do have the advantage of being able to detect rare and actionable genetic alterations, such as *NTRK* fusions.

Although EGFR-targeted monoclonal antibodies (cetuximab or panitumumab) have been included in the guidelines for *RAS* wild-type mCRC for more than a decade, the number of biomarker-targeted therapies recommended for mCRC has substantially expanded in recent versions, now including checkpoint inhibitors (pembrolizumab, nivolumab ± ipilimumab) for dMMR/MSI-high disease, as well as BRAF-, HER2-, and TRK-targeted therapy options. BRAF- and HER2-targeted therapies are discussed in more detail in following sections.

NTRK gene fusions are relatively rare in CRC, with recent studies estimating that approximately 0.2% to 1.0% of CRCs carry these fusions.[25,26] *NTRK* fusions are most likely to be found in cancers that are *KRAS*, *NRAS*, and *BRAF* wild-type but MMR-deficient.[27] Two targeted therapies, larotrectinib and entrectinib, have been FDA-approved for the treatment of patients with metastatic, unresectable solid tumors that have an *NTRK* gene fusion and no satisfactory alternative treatment options, regardless of the location of the primary tumor.[28,29] These therapies were studied using pooled analyses of phase I and II trials, which included small numbers of patients with *NTRK* gene fusion–positive CRC (4 patients for larotrectinib, 4 for entrectinib).[30,31] Based on these data, but taking into account the rarity of *NTRK* gene fusions in mCRC as well as concerns from some panel members regarding the CRC-specific efficacy outcomes, the panel decided to include the recommendation for larotrectinib or entrectinib in patients with *NTRK* gene fusion–positive disease as a footnote for subsequent therapy options throughout the systemic therapy pages of the guidelines (see REC-F 2 of 13 and REC-F 7 of 13, pages 810 and 811).

BRAF *V600E–Targeted Therapies*

Approximately 5% to 9% of CRCs are characterized by a specific mutation in the *BRAF* gene (V600E).[32,33] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[32–34] The NCCN panel currently recommends encorafenib with either cetuximab or panitumumab for patients with mCRC that harbors the *BRAF* V600E mutation.

The first *BRAF* V600E–targeted therapy regimen that was recommended in the NCCN Guidelines for Rectal Cancer was a combination of irinotecan, vemurafenib, and cetuximab or panitumumab. This combination was tested in the phase II SWOG S1406 trial of patients with *BRAF* V600E–mutated mCRC.[35] Ninety-nine patients with *BRAF*-mutant, *RAS* wild-type tumors who received 1 or 2 prior regimens were randomized to irinotecan and cetuximab with or without vemurafenib. An abstract presenting results of this trial at the 2017 ASCO Annual Meeting reported that the primary endpoint of median PFS was improved in the vemurafenib arm (4.4 vs 2.0 months; hazard ratio [HR], 0.42; 95% CI, 0.26–0.66; $P<.001$).[35] However, the NCCN panel voted to remove the recommendation for the vemurafenib combination from the guidelines in the version 1.2020 update based on the availability of new BRAF V600E–targeted regimens with more mature data and/or lower toxicity.

Another previously recommended regimen for *BRAF* V600E–mutated mCRC is a combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib and either cetuximab or panitumumab. A phase I study investigated the combination of dabrafenib + panitumumab, trametinib + panitumumab, or a combination of all 3 therapies in 142 patients with *BRAF* V600E mutation–positive mCRC.[36] Response rates were 10%, 21%, and 0% for dabrafenib + panitumumab, dabrafenib + trametinib + panitumumab, and trametinib + panitumumab, respectively. The most common grade

3 or 4 adverse events noted for the dabrafenib, trametinib, and panitumumab combination were diarrhea (7%), nausea (2%), and dermatitis acneform (10%). Seventy percent of patients treated with the triplet therapy had a grade 3 or 4 adverse event.[36] The NCCN panel voted to remove this regimen from the guidelines during the version 2.2020 update, again based on the availability of a BRAF V600E–targeted option with more mature data and/or lower toxicity.

A combination of the BRAF inhibitor encorafenib and the MEK inhibitor binimetinib with cetuximab has been investigated in the randomized, phase III BEACON trial for metastatic, *BRAF* V600E mutation–positive CRC.[37,38] The safety lead-in of the BEACON trial showed promising efficacy results, with an overall response rate (ORR) of 48% (95% CI, 29.4%–67.5%) among the 29 patients included in the efficacy analysis. Among the 30 treated patients in the safety lead-in, the most common grade 3 or 4 adverse events were fatigue (13%), anemia (10%), increased creatine phosphokinase levels (10%), increased aspartate aminotransferase levels (10%), and urinary tract infections (10%).[38] Subsequently, the randomized portion of the BEACON trial reported similarly encouraging results, including a positive OS result.[39] Within this portion of the study, 665 patients were randomized to receive either the triplet combination, an encorafenib and cetuximab doublet, or a control regimen of cetuximab plus either irinotecan or FOLFIRI. Confirmed ORR was 26% (95% CI, 18%–35%) for the triplet compared with 2% (95% CI, 0%–7%) for control ($P<.0001$). After a median follow-up of 7.8 months, median OS was 9 months for the triplet regimen compared with 5.4 months for control (HR, 0.52; 95% CI, 0.39–0.70; $P<.0001$). Median OS for the doublet regimen was 8.4 months. Adverse events were as expected based on previous studies. Grade ≥3 adverse events occurred in 58% of patients on the triplet regimen, 50% on the doublet, and 61% on the control arm.[39] Based on these results, the NCCN panel added both the doublet and triplet regimens as options for patients with *BRAF* V600E mutation–positive CRC in the version 1.2020 update of the guidelines.

Updated results of BEACON were then presented at ASCO's 2020 Gastrointestinal Cancers Symposium.[40] After a median follow-up of 12.8 months, median OS was 5.9 months, 9.3 months, and 9.3 months for the control, doublet, and triplet arms, respectively. ORRs were 2%, 20%, and 27%, respectively, and grade ≥3 adverse event rates continued to be higher in the triplet arm than in the doublet arm. The triplet including binimetinib did not lead to additional improvements in OS or ORR over the doublet, but had higher rates of grade ≥3 adverse events. Results of quality of life (QoL) assessments were also reported in this presentation. They showed that the doublet and triplet regimens led to a similarly longer maintenance of QoL compared with control. Based on this report, the panel removed the triplet option in the version 2.2020 update of the guidelines. Thus, the panel concluded that only the doublet regimen of encorafenib with either cetuximab or panitumumab should be recommended for patients with *BRAF* V600E–mutated mCRC at that time.

Results are awaited of this combination targeted therapy in the first-line setting for patients with *BRAF* V600E–mutated mCRC, and therefore the panel does not currently recommend this as initial treatment. However, because these cancers may progress rapidly beyond the first line, this therapy must be considered early in the clinical course of these patients. The panel expressed no preference between cetuximab or panitumumab for use with encorafenib, although some panel members mentioned that they might preferentially use one agent over the other based on institutional practice, differences in the dosing schedule, and/or the possibility of infusion site reactions.

HER2-Targeted Therapies

HER2 is a member of the same family of signaling kinase receptors as EGFR and has been successfully targeted in breast cancer in both the advanced and adjuvant settings. HER2 is rarely amplified/overexpressed in CRC (~3% overall), but the prevalence is higher in *RAS/BRAF* wild-type tumors (reported at 5%–14%).[41–43] Two regimens are recommended by the panel as options for subsequent treatment of mCRC with HER2 amplifications: trastuzumab plus either pertuzumab or lapatinib (see REC-F 2 of 13, page 810). Several biosimilars are now available in the US market, including 5 biosimilars for trastuzumab. Trastuzumab-anns, -dkst, -qyyp, -dttb, and -pkrb are not FDA-approved for CRC, but have been approved for other cancer types (breast and gastric).[44–48] The panel added a note that FDA-approved biosimilars may be substituted for trastuzumab wherever the therapy is recommended within these guidelines (see REC-F 7 of 13, page 811). Results of clinical trials supporting each of these regimens are detailed below.

A combination regimen of the HER2 inhibitors trastuzumab and pertuzumab was studied in a subset analysis of MyPathway, a phase IIa multiple basket study.[49] This subset included 57 patients with previously treated, HER2-amplified mCRC who were treated with the combination of pertuzumab and trastuzumab. ORR was 32% (95% CI, 20%–45%), with 1 CR and 17 partial responses; 37% of patients treated with trastuzumab + pertuzumab had grade 3 or 4 adverse events, with hypokalemia and abdominal pain the most common.[49]

The combination of trastuzumab plus the dual HER2/EGFR inhibitor lapatinib was studied in the

multicenter phase II HERACLES trial.[41] This trial included 27 patients with previously treated, HER2-positive tumors that were treated with trastuzumab and lapatinib. ORR was 30% (95% CI, 14%–50%), with 1 patient experiencing CR, 7 experiencing partial responses, and 12 with stable disease; 22% of patients treated with trastuzumab + lapatinib had grade 3 adverse events, including fatigue (n=4), skin rash (n=1), and increased bilirubin (n=1).[41]

HER2-targeted therapies were first included as a category 2B recommendation in the NCCN Guidelines for Rectal Cancer in the version 2.2019 update of the guidelines; however, this was recently updated to a category 2A recommendation as the data matured and panel consensus on the utility of these regimens strengthened.

Conclusions

Recent medical advances have improved treatment of patients with rectal cancer through an improved ability to distinguish rectal cancer from colon or anal cancers, new treatment approaches for localized rectal cancer, and targeted therapy options for mCRC. An updated definition of the rectum, using improved imaging techniques, allows physicians to more accurately distinguish rectal cancer from colon or anal, yielding more appropriate treatment. Likewise, the TNT approach for treating localized rectal cancer allows higher CR rates, minimizes the length of time patients need an ileostomy, facilitates resection, and improves the completion rates of chemotherapy. For mCRC, new biomarker testing recommendations can inform the use of targeted therapies for HER2 amplifications and *BRAF* V600E mutations, among other genetic alterations.

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