

NCCN Guidelines® Insights

Rectal Cancer, Version 2.2015

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Rectal Cancer begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, surgical management, perioperative treatment, posttreatment surveillance, management of recurrent and metastatic disease, and survivorship. The NCCN Rectal Cancer Panel meets at least annually to review comments from reviewers within their institutions, examine relevant new data from publications and abstracts, and reevaluate and update their recommendations. These NCCN Guidelines Insights summarize major discussion points from the 2015 NCCN Rectal Cancer Panel meeting. Major discussion topics this year were perioperative therapy options and surveillance for patients with stage I through III disease. (*J Natl Compr Canc Netw* 2015;13:719–728)

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Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guidelines Panel discussion, including the literature reviewed.**

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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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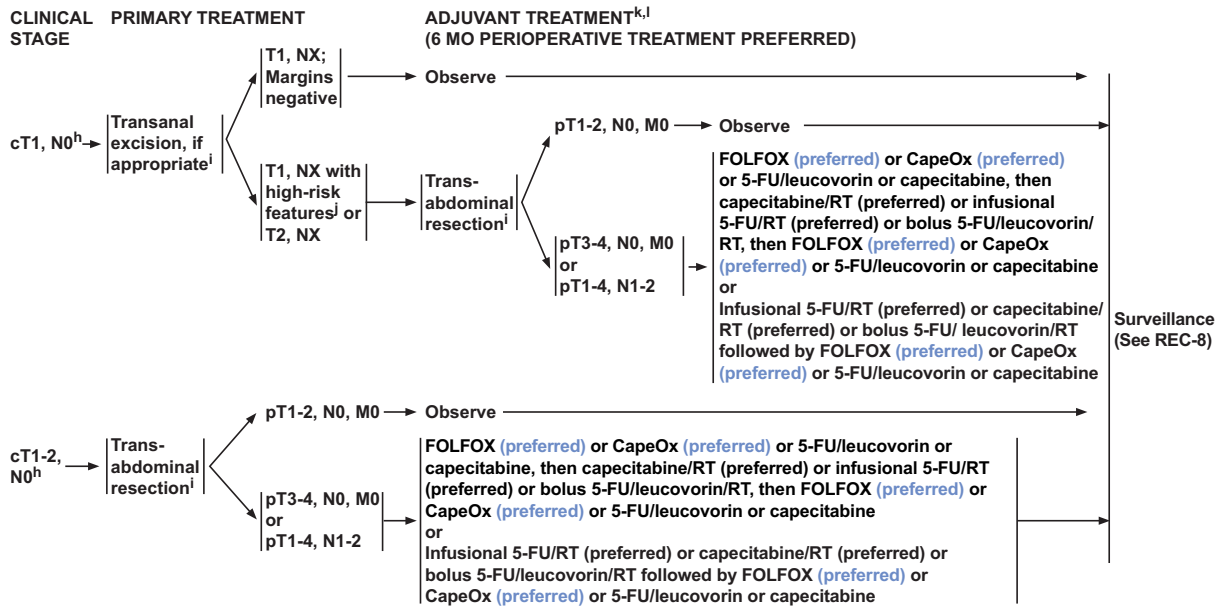
Al B. Benson III, MD, Panel Chair, has disclosed that he is a scientific advisor for Bayer HealthCare, Bristol-Myers Squibb Company, Celgene Corporation, Genentech, Inc., Genomic Health, Inc., Lilly/Imclone, Merck & Co., Inc., National Cancer Institute, Precision Therapeutics, Inc., sanofi-aventis U.S., Spectrum, and Vicus.

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^hT1-2, N0 should be based on assessment of endorectal ultrasound or MRI.
ⁱSee Principles of Surgery (REC-B).
^jHigh-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion.

^kSee Principles of Adjuvant Therapy (REC-C).
^lSee Principles of Radiation Therapy (REC-D).
 The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.

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REC-3

NCCN Categories of Evidence and Consensus

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

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

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

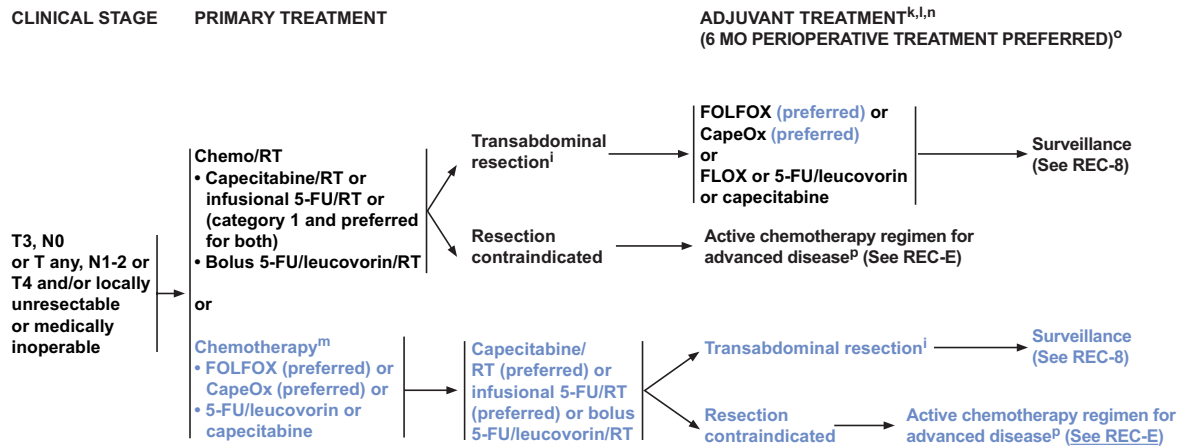
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States; in 2014, an estimated 40,000 new cases of rectal cancer occurred (23,380 cases in men; 16,620 cases in women). During the same year, it is estimated that 50,310 people died of rectal and colon cancer combined.^{1,2} Despite these statistics, the incidence per 100,000 population of CRCs decreased from 60.5 in 1976 to 46.4 in 2005.³ In fact, from 2006 to 2010, the incidence of CRC decreased at a rate of 3.3% per year in men and 3.0% in women.¹ The incidence rate for CRC reported by the Centers for Disease Control and Prevention (CDC) for 2010 is 40.4 per 100,000 persons.⁴ In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,⁵ and in 2010 was down by 46% from peak mortality rates.¹ These improvements in incidence of and mortality from CRC are thought to be a result of cancer prevention and



ⁱSee Principles of Surgery (REC-B).

^kSee Principles of Adjuvant Therapy (REC-C).

^lSee Principles of Radiation Therapy (REC-D).

^mFernandez-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.

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.

ⁿPostoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

^oTotal duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.

^pFOLFOXIRI is not recommended in this setting.

The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.

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REC-4

earlier diagnoses through screening, and of better treatment modalities. Despite the observed improvements in the overall CRC incidence rate, however, a retrospective cohort study of the SEER CRC registry found that the incidence of CRC in patients younger than 50 years has been increasing.⁶ The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients aged 20 to 34 years by 2030. The cause of this trend is currently unknown.

Treatment of Localized Rectal Cancer

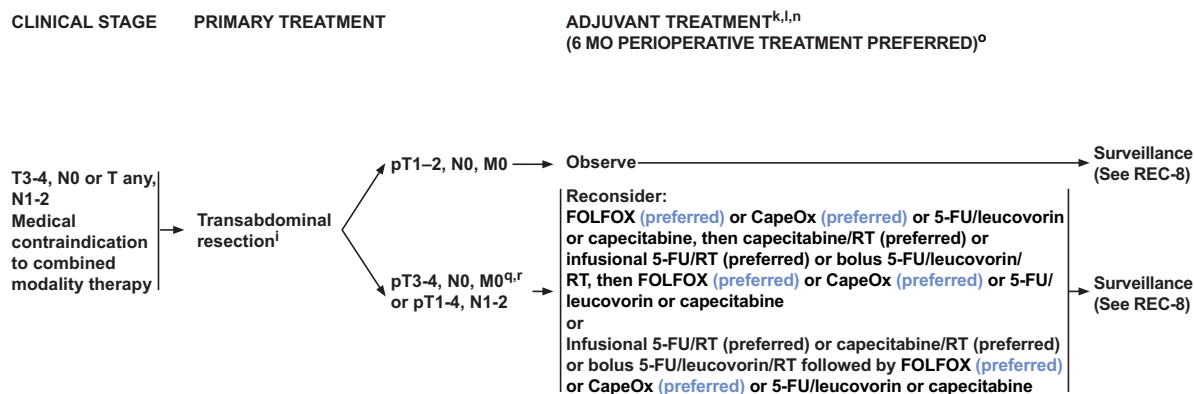
Rectal cancer is defined as a cancerous lesion located within 12 cm of the anal verge by rigid proctoscopy.⁷ The risk of pelvic recurrence is higher in patients with rectal cancer compared with those with colon cancer, and locally recurrent rectal cancer has frequently been associated with a poor prognosis.⁸⁻¹⁰ This risk is associated with the proximity of the rectum to pelvic

structures and organs, absence of a serosa surrounding the rectum, and technical difficulties associated with obtaining wide surgical margins at resection.

Because of the relatively high risk of locoregional recurrence, perioperative therapy of stage II (T3–4, node-negative disease with tumor penetration through the muscle wall) or stage III (node-positive disease without distant metastasis) rectal cancer includes locoregional treatment. In contrast, adjuvant treatment of colon cancer is more focused on preventing distant metastases, because this disease is characterized by lower rates of local recurrence. Combined-modality therapy consisting of surgery, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis (chemoradiation [chemoRT]), and chemotherapy is recommended for most patients with stage II or III rectal cancer.

The determination of an optimal treatment plan for an individual patient with locoregional rectal cancer is a complex process. Consideration must be

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ⁱSee Principles of Surgery (REC-B).

^kSee Principles of Adjuvant Therapy (REC-C).

^lSee Principles of Radiation Therapy (REC-D).

^mPostoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

^oTotal duration of perioperative chemotherapy, inclusive of chemotherapy and radiation therapy, should not exceed 6 months.

^qThe use of agents other than fluoropyrimidines (eg, oxaliplatin) are not recommended concurrently with RT.

^rFor patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy alone.

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REC-5

given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence and preserving genitourinary functions. For patients with distal rectal cancer in particular, the simultaneous achievement of the goals of cure and minimal impact on quality of life can be challenging.¹¹ Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoRT and chemotherapy with operative treatment are recommended.

Perioperative Therapy in Stage II/III Rectal Cancer

The use of perioperative treatment in patients with stage II/III rectal cancer continues to evolve. Historically, these patients received chemoRT preoperatively and chemotherapy postoperatively. This year, the panel added another possible sequence of therapy: induction chemotherapy followed by chemoRT followed by resection. In all cases, the total duration of perioperative therapy should not exceed 6 months.

Induction Chemotherapy: Several small trials have tested the utility of neoadjuvant chemotherapy preceding chemoRT and resection for stage II/III rectal cancer.¹²⁻¹⁷ In the Spanish GCR-3 phase II trial, patients were randomized to receive CapeOx either before chemoRT or after surgery.¹⁴ Similar pathologic complete response rates were seen, and induction chemotherapy seemed to be less toxic and better tolerated. Another phase II trial randomized patients to chemoRT and surgery with or without FOLFOX induction therapy; adjuvant chemotherapy was administered at the investigator's discretion.¹⁵ No differences were seen in clinical outcomes, but the group receiving induction therapy experienced higher toxicity. The single-arm phase II AVACROSS study assessed the safety and efficacy of adding bevacizumab to induction therapy with CapeOx before capecitabine/bevacizumab-chemoRT and surgery.¹⁶ The regimen was well tolerated, with a pathologic complete response rate of 36%.

SURVEILLANCE^x

- History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA^y every 3–6 mo for 2 y, then every 6 mo for a total of 5 y for T2 or greater lesions
- Chest/abdominal/pelvic CT^f annually for up to 5 y for patients at high risk for recurrence^z
- Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo
 - ▶ If advanced adenoma, repeat in 1 y
 - ▶ If no advanced adenoma,^{aa} repeat in 3 y, then every 5 y^{bb}
- Consider proctoscopy every 6 mo x 3–5 y for patient status post LAR or transanal excision
- PET-CT scan is not routinely recommended
- See Principles of Survivorship (REC-F)

Serial CEA elevation or documented recurrence

See Workup and Treatment (REC-9)

^fCT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

^xDesch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. *J Clin Oncol* 2005;23(33):8512-8519.

^yIf patient is a potential candidate for resection of isolated metastasis.

^zCT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor; poorly differentiated tumors).

^{aa}Villous polyp, polyp >1 cm, or high-grade dysplasia.

^{bb}Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2006;130(6):1865-71.

~~Patients with rectal cancer should also undergo limited endoscopic evaluation of the rectal anastomosis to identify local recurrence. Optimal timing for surveillance is not known. No specific data clearly support rigid versus flexible proctoscopy. The utility of routine endoscopic ultrasound for early surveillance is not defined.~~

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REC-8

A group at Memorial Sloan Kettering Cancer Center recently reported on their experience using initial FOLFOX followed by chemoRT and resection in patients with locally advanced rectal cancer.¹² Of the approximately 300 patients, 61 received initial FOLFOX, 4 of whom declined chemoRT after an excellent response and underwent resection. Nine patients experienced a complete clinical response to neoadjuvant therapy and did not undergo resection; 2 other patients were not resected because of persistent or metastatic disease. A total of 49 of the patients underwent resection, and all had R0 resections, with 13 (27%) experiencing a pathologic complete response and an additional 10 patients (20%) experiencing tumor response greater than 90%. The Brown University Oncology Group also recently reported their experience with a similar neoadjuvant treatment approach, with a similar pathologic complete response rate of 33%.¹⁷

During the review of the NCCN Guidelines for the 2015 update, reviewers from 2 different NCCN Member Institutions raised the question of adding this induction chemotherapy approach as an option for the treatment of patients with stage II/III rectal cancer. The panel cited various pilot data and phase II studies and noted that it is highly unlikely that a large study addressing this question will ever be conducted. The panel also noted that the chemotherapy-first approach is well tolerated and has several possible benefits, including the early prevention or eradication of micrometastases, higher rates of pathologic complete response, minimizing the time patients need an ileostomy, facilitating resection, and improving the tolerance and completion rates of chemotherapy. In particular, reports indicate that only approximately 43% to 57% of patients get all the planned chemotherapy when given postoperatively.^{14,18} In contrast, rates of completion of neo-

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adjuvant chemotherapy of 71% to 94% have been reported in this setting.^{12,14,17} Furthermore, the panel discussed the fact that current cooperative group proposals are adopting this chemotherapy-first approach as the basis for exploring new therapies by adding new initial treatments, and the fact that this approach is being used by increasingly more centers.

Therefore, the panel added this induction chemotherapy approach to the 2015 version of these NCCN Guidelines as an acceptable option, using most of the same postoperative chemotherapy options: FOLFOX (preferred), CapeOx (preferred), 5-FU/leucovorin (LV), or capecitabine (see REC-4, page 722). The exception is FLOX, which is listed as an option only in the postoperative setting. The panel noted that they do not recommend bevacizumab as induction chemotherapy and that if induction chemotherapy is given, additional adjuvant chemotherapy should not be given. The total duration of perioperative therapy, including chemotherapy and chemoRT, should not exceed 6 months.

Adjuvant Therapy: Adjuvant chemotherapy is given to patients with localized rectal cancer in several situations. Most commonly, patients with clinical stage II/III rectal cancer receive adjuvant chemotherapy if preoperative treatment was limited to chemoRT (see REC-4, page 722). In addition, patients with stage I disease, determined clinically by preoperative imaging, receive adjuvant chemotherapy if they are pathologically staged as stage II or III after transanal excision (performed only in select cases) or transabdominal resection (see REC-3, page 721). Furthermore, patients who did not receive preoperative therapy because of medical contraindication to combined modality therapy can be reconsidered for adjuvant treatment (see REC-5, page 723). In cases where chemoRT was not given preoperatively, chemoRT is included postoperatively, with chemotherapy given either before or before and after chemoRT.

During the 2015 NCCN Guidelines update, the panel discussed the choice of chemotherapy in the adjuvant setting. Previously, data in the adjuvant setting for rectal cancer were limited, and the panel made recommendations based on extrapolation from data in colon cancer (see previous footnote on REC-4, page 722).^{19,20} However, results of 2 studies in patients with rectal cancer were recently reported. The open-label phase II ADORE trial randomized 321

patients with resected rectal cancer and neoadjuvant chemoRT to adjuvant 5-FU/LV or FOLFOX.²¹ The FOLFOX arm had higher 3-year disease-free survival (DFS), at 71.6% versus 62.9% (hazard ratio [HR], 0.66; 95% CI, 0.43–0.99; $P < .05$). Similarly, 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%; $P = .03$).²²

Based on these results, the panel agreed that CapeOx and FOLFOX should be preferred over 5-FU/LV or capecitabine in the adjuvant setting. The panel thus changed their previous recommendation for chemotherapy in the stage II/III adjuvant setting (“5-FU ± leucovorin or FOLFOX or capecitabine ± oxaliplatin”) to “FOLFOX (preferred) or CapeOx (preferred) or FLOX or 5-FU/leucovorin or capecitabine” (see REC-4, page 722). In postoperative regimens that include chemoRT (ie, when no preoperative treatment was given), the panel now lists “FOLFOX (preferred) or CapeOx (preferred) or 5-FU/leucovorin or capecitabine” as chemotherapy options (see REC-3 and -5, pages 721 and 723).

Preoperative Chemotherapy With Selective Use of ChemoRT: Recently, 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, followed by resection in all patients.²³ Tumor regression was seen in 30 of 32 patients after preoperative chemotherapy, and they proceeded to resection without chemoRT. The other 2 patients experienced toxicities and did not complete the planned chemotherapy; these 2 patients received preoperative chemoRT. All 32 of the participants had R0 resections, and the 4-year DFS was 84% (95% CI, 67%–94%).

This approach could potentially spare patients the morbidities associated with radiation, but the panel does not recommend this approach at this time because of the limited data supporting it. The ongoing randomized phase II/III N1048/C81001/Z6092 PROSPECT trial by The Alliance for Clinical Trials in Oncology is comparing the approach of neoadjuvant FOLFOX with chemoRT only in patients with less than 20% tumor regression, versus a standard approach of neoadjuvant chemoRT/resection/adjuvant chemotherapy in stage II or III rectal cancer (ClinicalTrials.gov identifier: NCT01515787).

Wait-and-See 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 al²⁴ retrospectively compared the outcomes of 71 patients who were observed without surgery after complete clinical response (27% of patients) with the outcomes of 22 patients (8%) who had incomplete clinical responses but complete pathologic responses after resection. The overall survival 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 have been skeptical of the approach.²⁵

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; outcomes of these patients were compared with those of 20 patients with a complete pathologic response after resection.²⁶ Only 1 patient in the nonoperative group developed a local recurrence after a mean follow-up of 25 months; that patient underwent successful surgery. No statistical differences in long-term outcomes were seen between the groups. The cumulative probabilities for 2-year DFS and overall survival were 89% (95% CI, 43%–98%) and 100%, respectively, in the wait-and-see 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 wait-and-see group, with better bowel function scores, less incontinence, and 10 patients avoiding permanent colostomy.

Another 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 local recurrence-free survival of 69%, which was converted to 94% after resections were performed.²⁷

Despite these impressive results, the panel believes that longer follow-up, larger sample sizes, and additional careful observational studies are needed before patients with a clinical complete response are routinely managed by a wait-and-see approach.²⁸

Furthermore, recent studies have found that neither FDG-PET, MRI, or CT can accurately determine a pathologic complete response, complicating the selection of appropriate patients for a nonoperative approach.^{29–34} In addition, lymph node metastases are still seen in a subset of patients with pathologic complete response.³⁵ Overall, the panel does not support this approach in the routine management of localized rectal cancer at this time.

Surveillance After Treatment of Localized Rectal Cancer

Following curative-intent surgery, posttreatment surveillance of patients with rectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, and identify new metachronous neoplasms at a preinvasive stage. The approach to monitoring and surveillance of patients with rectal cancer is very similar to that described for colon cancer. One exception has been the recommendation that proctoscopy be considered every 6 months for 3 to 5 years after resection or excision of rectal cancer. During the 2015 update of the NCCN Guidelines, an institutional reviewer commented that proctoscopy should not be listed in the guidelines for surveillance of those who have had definitive treatment (ie, chemoRT), because isolated local recurrences are rarely found in this population. In fact, the panel noted that rates of isolated local recurrence after combined modality treatment of less than 4% have been reported.^{36,37} Furthermore, the panel noted that these recurrences are rarely curable, with a reported overall 5-year relative survival rate of 15.6%.³⁸ Therefore, proctoscopy likely benefits less than 1% of patients who received chemoRT, and the panel decided to remove the use of proctoscopy to evaluate the rectal anastomosis for local recurrence in these patients in the 2015 version of the NCCN Guidelines (see REC-8, page 724).

Summary and Conclusions

In summary, the panel discussed several pertinent issues this year, and made the following changes to the 2015 recommendations (indicated in blue in the algorithms on pages 721–724):

- The panel added the approach of neoadjuvant chemotherapy preceding chemoRT and resec-

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tion as an option for the sequence of perioperative treatment in stage II/III rectal cancer.

- The panel listed FOLFOX and CapeOx as preferred options for chemotherapy in the adjuvant setting based on new data.
- The panel removed consideration of proctoscopy from the list of recommended surveillance modalities after definitive treatment (ie, chemoRT) of localized rectal cancer.

The panel also discussed some novel approaches to the perioperative treatment of patients with localized rectal cancer. However, the panel did not add these approaches because of the limited data supporting them at this time. These novel approaches remove modalities in the treatment of selected patients, allowing them to avoid associated morbidities. In particular, the panel discussed:

- Avoiding preoperative chemoRT in patients experiencing response to neoadjuvant chemotherapy.
- Avoiding surgery (with careful observation) in patients experiencing a complete clinical response to neoadjuvant therapy.

Thus, the management of patients with nonmetastatic rectal cancer continues to evolve. Although improvement in incidence of and mortality from rectal cancer have been seen over the past decades, current 5-year relative survival rates of 88.2% for localized disease and 69.5% for regional disease leave room for additional gains.²

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Posttest Questions

1. A patient with stage II rectal cancer undergoes neoadjuvant capecitabine-based chemoRT and an R0 resection. Which of the following adjuvant therapy options are preferred according to the 2015 NCCN Guidelines for Rectal Cancer?
 - a. FOLFOX or CapeOx
 - b. 5-FU/LV or capecitabine
 - c. FOLFOX or CapeOx + bevacizumab
 - d. No adjuvant chemotherapy is required
2. True or False: The panel added proctoscopy to the list of recommended surveillance modalities in the 2015 NCCN Guidelines for Rectal Cancer.
3. Which of the following options for the perioperative treat-

ment of patients with stage II or III rectal cancer are acceptable according to the 2015 NCCN Guidelines for Rectal Cancer:

- a. ChemoRT, followed by resection, followed by adjuvant chemotherapy
- b. ChemoRT, followed by careful observation in patients with a complete clinical response
- c. Chemotherapy, followed by chemoRT, followed by resection
- d. Chemotherapy, followed by resection, omitting chemoRT in patients with a response to treatment
- e. a or c
- f. All of the above

