Rectal Cancer

Clinical Practice Guidelines in Oncology

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Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2012, an estimated 40,290 new cases of rectal cancer will occur in the United States (23,500 cases in men; 16,790 cases in women) and 51,690 people will die of rectal and colon cancer combined. 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. In addition, mortality from colorectal cancer decreased by almost 35% from 1990 to 2007, possibly because of ear-

Abstract

These NCCN Clinical Practice Guidelines in Oncology provide recommendations for the management of rectal cancer, beginning with the clinical presentation of the patient to the primary care physician or gastroenterologist through diagnosis, pathologic staging, neoadjuvant treatment, surgical management, adjuvant treatment, surveillance, management of recurrent and metastatic disease, and survivorship. This discussion focuses on localized disease. The NCCN Rectal Cancer Panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology, is necessary for treating patients with rectal cancer. (JNCCN 2012;10:1528–1564)

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.

Please Note

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This discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing rectal cancer. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist, and go on to address diagnosis, pathologic staging, neoadjuvant treatment, surgical management, adjuvant treatment, management of recurrent and metastatic disease, patient surveillance, and survivorship. These guidelines overlap considerably with the NCCN Guidelines for Colon Cancer, especially in the treatment of metastatic disease (to view the most recent version of these guidelines, visit NCCN.org). The recommendations in these guidelines are classified as category 2A except where noted. The panel unanimously endorses patient participation in a clinical trial over standard or accepted therapy, especially for cases of advanced disease and for patients with locally aggressive colorectal cancer who are undergoing combined modality treatment.

**Risk Assessment**

Approximately 20% of cases of colorectal cancer are associated with familial clustering, and first-degree relatives of patients with newly diagnosed colorectal adenomas or invasive colorectal cancer are at increased risk for colorectal cancer. Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as HNPCC).
### CLINICAL PRESENTATION

- Pedunculated polyp or sessile polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer

### WORKUP

- **Pedunculated polyp or sessile polyp (adenoma [tubular, tubulovillous, or villous]) with invasive cancer**
  - Pathology review
  - Colonoscopy
  - Marking of cancerous polyp site (at time of colonoscopy or within 2 weeks)
- **Rectal cancer appropriate for resection**
  - Biopsy
  - Pathology review
  - Colonoscopy
  - Rigid proctoscopy
  - Chest/abdominal/pelvic CT
  - CEA
  - Endorectal ultrasound or pelvic MRI
  - Enterostomal therapist as indicated for preoperative marking of site, teaching
  - PET-CT scan is not routinely indicated

### FINDINGS/CLINICAL STAGE

- **Pedunculated polyp with invasive cancer**
  - Single specimen, completely removed with favorable histologic features and clear margins (T1 only)
  - Pedunculated polyp with invasive cancer
    - Pedunculated polyp with invasive cancer
      - Observe
  - Sessile polyp with invasive cancer
    - Sessile polyp with invasive cancer
      - Observe or See Primary Treatment (facing page)
- **Fragmented specimen or margin cannot be assessed or unfavorable histologic features**
  - Fragmented specimen or margin cannot be assessed or unfavorable histologic features
    - Fragmented specimen or margin cannot be assessed or unfavorable histologic features
      - See Primary and Adjuvant Treatment (facing page)
- **T1-2,N0**
  - T1-2,N0
    - See Primary Treatment (facing page)
- **T3,N0 or T4,N1-2**
  - T3,N0 or T4,N1-2
    - See Primary Treatment (page 1532)
- **T4 and/or locally unresectable**
  - T4 and/or locally unresectable
    - See Primary Treatment (page 1532)

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9. All patients with rectal cancer should be counseled for family history. Patients with suspected hereditary nonpolyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP should see the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colorectal Cancer Screening. To view the most recent version of these guidelines, visit NCCN.org.

10. Confirm the presence of invasive cancer (pT1). pTis has no biologic potential to metastasize.

11. It has not been established whether molecular markers are useful in treatment determination (predictive markers) and prognosis. (College of American Pathologists Consensus Statement 1999. Prognostic factors in colorectal cancer. Arch Pathol Lab Med 2000;124:979-994.)


13. Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, or hematogenous metastasis, but not lymph node metastasis) than with polypoid malignant polyps. See Principles of Pathologic Review: Endoscopically Removed Malignant Polyps (pages 1534–1536).

14. CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a noncontrast chest CT if either CT of abdomen/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.
Rectal Cancer, Version 2.2013

### Clinical Stage

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>Primary Treatment</th>
<th>Adjuvant Treatment¹ (6 MO Perioperative Treatment Preferred)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>cT1,N0</strong></td>
<td>Transanal excision, if appropriate ³</td>
<td>T1,NX; margins negative</td>
</tr>
<tr>
<td><strong>T1-T2,NX with high risk features ³ or T2,NX</strong></td>
<td>Transabdominal resection ³</td>
<td>pT1-2, N0,M0</td>
</tr>
<tr>
<td><strong>pT1-2, N0,M0</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>cT1-2,N0¹</strong></td>
<td>Transabdominal resection ³</td>
<td>pT3,N0, M0 or pT1-3, N1-2</td>
</tr>
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<td><strong>pT3,N0, M0 or pT1-3, N1-2</strong></td>
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</tbody>
</table>

¹T1-2,N0 should be based on assessment of endorectal ultrasound or MRI.
³See Principles of Surgery (page 1537).
³High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion.
³See Principles of Adjuvant Therapy (page 1538).
³See Principles of Radiation Therapy (page 1539).
³The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data on colon cancer.
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SURVEILLANCE

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y.
- CEA 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 annually for up to 5 y for patients at high risk for recurrence.
- Colonoscopy in 1 y except if no preoperative colonoscopy because of obstructing lesion, colonoscopy in 3-6 mo:
  - If advanced adenoma, repeat in 1 y.
  - If no advanced adenoma, repeat in 3 y, then every 5 y.
- Consider proctoscopy every 6 mo x 5 y for patient status post LAR.
- PET-CT scan is not routinely recommended.
- See Principles of Survivorship (page 1540).

WORKUP

- Physical exam
- Colonoscopy
- Chest/abdominal/pelvic CT
- Consider PET-CT scan
- CEA elevation
- Recurrence
- Isolated pelvic/anastomotic recurrence

TREATMENT

- Consider PET-CT scan
- Reevaluate chest/abdominal/pelvic CT in 3 mo
- Potentially resectable
- Unresectable
- Chemotherapy + RT
- Resection or Preoperative 5-FU + RT
- See treatment below

For documented metachronous metastases, see REC-8 in the full version of these guidelines, available online at NCCN.org.

**Note:**

- CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a noncontrast chest CT if either CT of abdomen/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.
- See Principles of Radiation Therapy (page 1539).
- Determination of tumor KRAS (if KRAS nonmutated, consider BRAF testing). See Principles of Pathologic Review: KRAS and BRAF Mutation Testing (available online, in these guidelines, at NCCN.org [REC-A, 5 of 8]).
- If patient is a potential candidate for resection of isolated metastasis.
- 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.
- Patients should be evaluated by a multidisciplinary team, including surgical consultation for potentially resectable patients.

REC-7, -8
PRINCIPLES OF PATHOLOGIC REVIEW

Endoscopically Removed Malignant Polyps
- A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered to be a “malignant polyp.”
- Favorable histologic features grade 1 or 2, no angiolympathic invasion, and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as: 1) tumor <1 mm from the transected margin, 2) tumor >2 mm from the transected margin, and 3) tumor cells present within the diathermy of the transected margin.1-4
- Unfavorable histologic features grade 3 or 4, angiolympathic invasion, or a “positive margin.” See above for definition of a positive margin.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcome (residual disease, recurrent disease, mortality, or hematogenous metastasis, but not lymph node metastasis) than do polyoid malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable for adverse outcome, and endoscopically removed malignant sessile polyps with grade I or II histology, negative margin, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.3-7

Transanal Excision
- Favorable histopathologic features: <3 cm size, T1, grade I or II, no lymphatic or venous invasion, or negative margins,8,9
- Unfavorable histopathologic features: >3 cm in size, T1, with grade III, or lymphovascular invasion, positive margin, or sm3 depth of tumor invasion,8,10

Rectal Cancer Appropriate for Resection
- Histologic confirmation of primary malignant rectal neoplasm

Pathologic Stage
- The following parameters should be reported:
  • Grade of the cancer
  • Depth of penetration (T), the T stage, is based on viable tumor. Acellular mucin pools are not considered to be residual tumor in those cases treated with neoadjuvant therapy.
  • Number of lymph nodes evaluated and number positive (N). Acellular mucin pools are not considered to be residual tumor in those cases treated with neoadjuvant therapy.
  • Status of proximal, distal, and circumferential (radial) margins.11-12
  • A positive circumferential resection margin (CRM) has been defined as ≤1 mm13-14 See Staging (available online, in these guidelines, at NCCN.org [ST-I])
  • CRM15,16,18,19
  • Lymphovascular invasion15,16,20
  • Perineural invasion21-23
  • Extramural tumor deposits24-25
  • CRM: A positive CRM is defined as tumor ≤1 mm from the margin. This assessment includes both tumor within a lymph node and direct tumor extension. However, if CRM positivity is based solely on intranodal tumor, it should be stated in the pathology report. A positive CRM is a more powerful predictor of local recurrence in patients treated with neoadjuvant therapy. A positive CRM secondary to lymph node metastasis in some studies has been associated with lower recurrence rates than by direct extension.13-17
  • Neoadjuvant treatment effect: the most recent College of American Pathologists Guidelines on examination specimens of the rectum and the AJCC Cancer Staging Manual, 7th Edition require commenting on treatment effect after neoadjuvant therapy. The minimum requirement is:
    • Treatment effect present.
    • No definitive response identified.

The system used to grade tumor response as modified from Ryan R, Gibbons D, Hyland JM, et al. Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Histopathology 2005;47:141-146:
  • 0 (complete response) - no viable cancer cells.
  • 1 (moderate response) - single cells or small groups of cancer cells.
  • 2 (minimal response) - residual cancer outgrown by fibrosis.
  • 3 (poor response) - minimal or no tumor kill; extensive residual cancer.

According to the College of American Pathologists, it is optional to grade the tumor response to treatment. However, the NCCN Rectal Cancer Panel recommends grading tumor response.15,16,18,19

See references on page 1536.
Pathologic Stage (continued)

- Perineural invasion (PNI): the presence of PNI is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer-specific and overall disease-free survival. For stage II rectal cancer, those with PNI have a significantly worse 5-year disease-free survival compared to those without PNI (29% vs. 82%; P=0.005). In stage III rectal cancer, those with PNI have a significantly worse prognosis.21-23
- Extramedullary tumor deposits: irregular discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered to be extramedullary tumor deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular invasion or, more rarely, PNI. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report.

Lymph Node Evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately identify early-stage colorectal cancers.11,12,24 The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, >30,26-34 Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and >10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.30,33 The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade, and tumor site.27 For stage II (pN0) colon cancer, if fewer than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs. 19, P<0.05; 7 vs. 10, P<0.001).35,36 If 12 lymph nodes is considered the number needed to accurately stage stage II tumors, then only 20% of cases treated with neoadjuvant therapy had adequate lymph node sampling.36 To date, the number of lymph nodes needed to accurately stage neoadjuvant-treated cases is unknown. However, it is not known what is the clinical significance of this in the neoadjuvant setting, because postoperative therapy is indicated in all patients who receive preoperative therapy regardless of the surgical pathology results.

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry

- Examination of the sentinel lymph node allows an intense histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple H&E sections and/or immunohistochemistry (IHC) to detect cytokeratin-positive cells.37-39 The AJCC Cancer Staging Manual, 7th Edition16 considers "tumor clusters" <0.2 mm to be isolated tumor cells (pN0) and not metastatic carcinoma. However, some investigators believe that size should not affect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.40,41
- Some studies have shown that the detection of IHC cytokeratin-positive cells in stage II (N0) colon cancer (defined by H&E) has a worse prognosis, whereas others have failed to show this survival difference. In these studies, isolated tumor cells were considered to be micrometastases.42-46
- Currently, the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.37-39,42-46

KRAS and BRAF Mutation Testing

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

Evaluation of Mesorectum (TME)

- The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal two-thirds).47-49

See references on page 1536.
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Rectal Cancer, Version 2.2013

PRINCIPLES OF PATHOLOGIC REVIEW

References
Rectal Cancer, Version 2.2013

PRINCIPLES OF SURGERY

Transanal Excision: 1

• Criteria
  ➤ <30% circumference of bowel
  ➤ <3 cm in size
  ➤ Margin clear (>3 mm)
  ➤ Mobile, nonfixed
  ➤ Within 8 cm of anal verge
  ➤ T1 only
  ➤ Endoscopically removed polyp with cancer or indeterminate pathology
  ➤ No lymphovascular invasion or PNI
  ➤ Well to moderately differentiated
  ➤ No evidence of lymphadenopathy on pretreatment imaging
• When the lesion can be adequately identified in the rectum, transanal endoscopic microsurgery (TEM) may be used. TEM for more proximal lesions may be technically feasible.

Transabdominal Resection: abdominoperineal resection or low anterior resection or colonic anastomosis using total mesorectal excision

• Management principles
  ➤ The treating surgeon should perform a rigid proctoscopy before initiating treatment.
  ➤ Remove primary tumor with adequate margins.
  ➤ Laparoscopic surgery is preferred in the setting of a clinical trial. 2
  ➤ Treat draining lymphatics by total mesorectal excision.
  ➤ Restore organ integrity, if possible.
  ➤ Surgery should be 5-10 weeks following full-dose 5.5-week neoadjuvant chemoradiation.
• Total mesorectal excision
  ➤ Reduces positive radial margin rate.
  ➤ Extend 4-5 cm below distal edge of tumors for an adequate mesorectal excision. In distal rectal cancers (ie, <5 cm from anal verge), negative distal bowel wall margin of 1-2 cm may be acceptable; this must be confirmed to be tumor-free by frozen section.
  ➤ Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.
• Lymph node dissection 3, 4
  ➤ Biopsy or remove clinically suspicious nodes beyond the field of resection if possible.
  ➤ Extended resection is not indicated in the absence of clinically suspected nodes.

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2 Long-term outcomes from laparoscopic surgery have not been reported. Current clinical trials are exploring open versus laparoscopic approach.
PRINCIPLES OF ADJUVANT THERAPY

Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy. A total of approximately 6 months of perioperative treatment is preferred.

Postoperative Adjuvant Chemotherapy:

- **mFOLFOX 6**
  - Oxaliplatin, 85 mg/m² IV over 2 h, day 1, leucovorin*, 400 mg/m² IV over 2 h, day 1, 5-FU, 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46-48 h)† continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.
  - Simplified biweekly infusional 5-FU/leucovorin (SLVSFU2)‡
  - Leucovorin, 400 mg/m² IV over 2 h on day 1, followed by 5-FU, bolus 400 mg/m² and then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46-48 h)† continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.
  - Capecevitabine
  - Capecevitabine, 1250 mg/m² twice daily 1-14 every 3 weeks to a total of 6 mo perioperative therapy.
  - CapeOx§
  - Oxaliplatin, 130 mg/m² over 2 h, day 1. Capecevitabine, 1000 mg/m² twice daily days 1-14 every 3 weeks. Repeat every 3 weeks to a total of 6 mo perioperative therapy.
  - 5-FU, 500 mg/m² IV bolus weekly x 6 + leucovorin, 500 mg/m² IV weekly x 6, each 8-week cycle. Repeat every 8 weeks to a total of 6 mo perioperative therapy.

Dosing Schedules for Concurrent Chemotherapy/RT:

- XRT + continuous infusion 5-FU¶
  - 5-FU, 225 mg/m² over 24 h 5 or 7 days/week during XRT

- XRT + 5-FU/leucovorin
  - 5-FU, 400 mg/m² IV bolus + leucovorin, 20 mg/m² IV bolus for 4 days during week 1 and 5 of XRT

- XRT + capecitabine
  - Capecevitabine, 825 mg/m² twice daily 5 or 7 days/week + XRT x 5 weeks

*Leucovorin, 400 mg/m² is the equivalent of levo-leucovorin 200 mg/m².
†NCCN recommends limiting chemotherapy orders to 24-h units (ie, 1200 mg/m²/d NOT 2400 mg/m² over 48 h) to minimize medication errors.

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PRINCIPLES OF RADIATION THERAPY

- Radiation therapy fields should include the tumor or tumor bed, with a 2- to 5-cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
- Multiple radiation therapy fields should be used (generally a 3- or 4-field technique). Positioning and other techniques to minimize the volume of small bowel in the fields should be encouraged.
- For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields. IMRT should only be used in the setting of a clinical trial or in unique clinical situations, including reirradiation of recurrent disease after previous radiotherapy.
- Radiation doses:
  - 45-50 Gy in 25-28 fractions to the pelvis.
  - For resectable cancers, after 45 Gy a tumor bed boost with a 2-cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
  - Small bowel dose should be limited to 45 Gy.
- Intraoperative radiation therapy (IORT), if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. If IORT is not available, 10-20 Gy external beam radiation and/or brachytherapy to a limited volume could be considered soon after surgery, before adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
- 5-FU-based chemotherapy should be delivered concurrently with radiation therapy.
- In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3D conformal radiotherapy, IMRT, or stereotactic body radiation therapy (SBRT; category 3)
- Side effect management:
  - Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.
  - Male patients should be counseled on infertility risks and given information regarding sperm banking.
  - Female patients should be counseled on infertility risks and given information regarding oocyte, egg, or ovarian tissue banking before treatment.

REC-D
PRINCIPLES OF SURVIVORSHIP
Colorectal Long-term Follow-up Care

Colorectal Cancer Surveillance:

- See page 1533
- Long-term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years.

Management of Late Sequelae of Disease or Treatment:

- Chronic diarrhea or incontinence
  - Consider antidiarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.
  - Screen for sexual dysfunction, erectile dysfunction, dyspareunia, and vaginal dryness
  - Screen for urinary incontinence, frequency, and urgency
  - Consider referral to urologist or gynecologist for persistent symptoms.

Prescription for Survivorship and Transfer of Care to Primary Care Physician:

- Include overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received.
- Describe possible clinical course, including expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.
- Include survivorship recommendations.
- Delineate appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist.

Cancer Screening Recommendations:

These recommendations are for average-risk patients. Recommendations for high-risk individuals should be made on an individual basis.

- Breast cancer: See the NCCN Guidelines for Breast Cancer Screening*
- Cervical cancer: See the NCCN Guidelines for Cervical Cancer Screening*
- Prostate cancer: See the NCCN Guidelines for Prostate Early Detection*

Counseling Regarding Healthy Lifestyle and Wellness:

- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (at least 30 minutes of moderate-intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy).
- Consume a healthy diet with an emphasis on plant sources.
- Limit alcohol consumption.
- Seek smoking cessation counseling as appropriate.

Additional health monitoring and immunizations should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.

*To view the most recent version of these guidelines, visit NCCN.org.

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known as hereditary nonpolyposis colorectal cancer)\(^9\,\text{and familial adenomatous polyposis}.\(^{10}\) Therefore, it is recommended that all patients with colorectal cancer be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening (to view the most recent version of these guidelines, visit NCCN.org).

Lynch syndrome is the most common form of genetically determined colorectal cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases.\(^{8,9,11,12}\) This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2). Although identifying a germline mutation in an MMR gene through sequencing is definitive for Lynch syndrome, patients usually undergo 2 rounds of selection before sequencing: the first based on family history and the second based on initial tests on tumor tissue. Two initial tests are performed on colorectal cancer specimens to identify individuals who might have Lynch syndrome: immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation, and analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as an altered amount of short repeated DNA sequences in tumor tissue caused by the insertion or deletion of repeated units.\(^{13}\) Testing the \textit{BRAF} gene for mutation is indicated when immunohistochemical analysis shows that \textit{MLH1} expression is absent in the tumor. The presence of a \textit{BRAF} mutation indicates that \textit{MLH1} expression is downregulated through somatic methylation of the promoter region of the gene and not through a germline mutation.\(^{13}\)

The panel recommends that MMR protein testing be performed for all patients younger than 50 years with colon cancer, based on an increased likelihood of Lynch syndrome in this population.\(^\text{14}\) Some centers, however, now perform immunohistochemistry (and sometimes MSI) testing on all colorectal tumors to determine which patients should have genetic testing for Lynch syndrome. The cost-effectiveness of this so-called reflex testing approach has been confirmed for colorectal cancer, and this approach was endorsed by the Evaluation of Genomic Applications in Prevention and Practice working group at the Centers for Disease Control and Prevention.\(^\text{15}\) A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening (available at NCCN.org).

**TNM Staging**

The NCCN Guidelines for Rectal Cancer adhere to the current TNM staging system of the 7th edition of the AJCC Cancer Staging Manual (Table 1, available online at NCCN.org [ST-1]).\(^\text{16}\) Several changes to the staging of colorectal cancer were made in this edition.\(^\text{17}\) For instance, based on new data showing differential prognosis,\(^{16}\) T4 lesions have now been subdivided into T4a (tumor penetrates to the surface of the visceral peritoneum) and T4b (tumor directly invades or is adherent to other organs or structures). Another notable change is the subdivision of N1 into N1a (metastasis in 1 node), N1b (metastasis in 2–3 nodes), and N1c (without regional nodal metastases, but with tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues); and of N2 into N2a (metastasis in 4–6 nodes) and N2b (metastasis in ≥7 nodes). These subsets reflect new data showing that the number of involved nodes influences prognosis,\(^{19}\) and new data on the prognostic value of tumor deposits within the lymph drainage area of the primary tumor.\(^{20-24}\)

Stage I rectal cancer is defined as T1–T2,N0,M0. Stage II disease is subdivided into IIA (if the primary tumor is T3,N0,M0), IIB (for T4a,N0,M0 lesions), and IIC (for T4b,N0,M0). Stage III disease is subdivided into IIIA (T1–2,N1/N1c,M0 or T1,N2a,M0), IIIB (T3–4a,N1/N1c,M0 or T2–T3,N2a,M0 or T1–T2,N2b,M0), and IIIC (T4a,N2a,M0 or T3–4a,N2b,M0 or T4b,N1–2,M0). Stage IVA disease is defined as any T, any N, and the presence of distant metastasis confined to 1 organ or site (M1a). Stage IVB disease is defined as any T, any N, with metastases in more than 1 organ or site or in the peritoneum (M1b).\(^\text{16}\) The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging after neoadjuvant therapy, respectively.\(^\text{16}\)

**Pathology**

Pathologic staging information is provided through examination of the surgical specimen. Some of the information that should be detailed in the report of the pathologic evaluation of rectal cancer\(^\text{25}\) includes 1) gross description of the tumor and specimen; 2)
grade of the cancer; 3) depth of penetration and extension to adjacent structures (T); 4) number of regional lymph nodes evaluated; 5) number of positive regional lymph nodes (N); 6) presence of distant metastases to other organs or sites, including nonregional lymph nodes (M); 7) status of proximal, distal, and circumferential (radial) margins; 8) neoadjuvant treatment effect; 9) lymphovascular invasion; 10) perineural invasion; and 11) number of tumor deposits.

The 7th edition of the AJCC Cancer Staging Manual includes the suggestion that the surgeon mark the area of the specimen with the deepest tumor penetration so that the pathologist can directly evaluate the status of the resection margins. The completeness of the resection is scored as R0 for complete tumor resection with all margins negative; R1 for incomplete tumor resection with microscopic involvement of a margin; and R2 for incomplete tumor resection with gross residual tumor that was not resected.

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer. Although the radial margin for resected segments of the colon that are completely encased by a peritonealized (serosal) surface is also referred to as the peritoneal margin, the CRM is very important in segments of the colon or rectum that are either not encased or only partially encased in peritoneum. The CRM is the closest radial margin between the deepest penetration of the tumor and the edge of resected soft tissue around the rectum (ie, the retroperitoneal or subperitoneal aspect of the tumor) or from the edge of a lymph node and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen, which often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen. The panel defines a positive CRM as tumor within 1 mm from the transected margin.

Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important, because the CRM has been shown to be a strong predictor of both local recurrence and overall survival, including in patients undergoing neoadjuvant therapy, and is an important consideration when postoperative treatment decisions are made. Furthermore, in a retrospective study of more than 17,000 patients with rectal cancer, CRM was found to be a better predictor of local recurrence for patients undergoing surgery as initial therapy than for those who had received preoperative therapy. CRM positivity based solely on intranodal tumor should be noted as such; some studies have shown that positive intranodal CRM is associated with lower recurrence rates than a positive CRM by direct tumor extension. Additional components of the pathologic evaluation of the surgical specimen after a total mesorectal excision (TME) are described in “Surgical Approaches,” page 1545.

The AJCC and the College of American Pathologists (CAP) recommend evaluation of 10 to 14 and 12 to 18 lymph nodes, respectively, to accurately identify early-stage colorectal cancers. The number of lymph nodes that can be retrieved varies with age and gender of the patient and based on tumor grade or site. The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify early-stage rectal cancer. Most of these studies have combined rectal and colon cancers and reflect cases for which surgery was the initial treatment. Two studies confined only to rectal cancer have reported 14 and greater than 10 lymph nodes as the minimal number to accurately identify stage II rectal cancer. Furthermore, the mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy was significantly less than the number from those treated with surgery alone (13 vs. 19; P < .05 and 7 vs. 10; P ≤ .0001, respectively).

Results have been reported from studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells, and the identification of particular tumor antigens through immunohistochemical analysis. Although some of these results seem promising, no uniformity exists in the definition of “true” clinically relevant metastatic carcinoma. Some studies have considered detection of single cells through immunohistochemistry or H&E, so-called isolated tumor cells, to be micrometastasis. In addition, results of one study showed that, after neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%. Furthermore, in a recent study involving 156 patients with colon cancer and 44 patients with rectal cancer, this “ultra-staging” of lymph nodes only changed the staging for 1% of
patients.\textsuperscript{52} Others have noted that micrometastasis found in node-negative patients did not predict outcome.\textsuperscript{53} Currently, the use of sentinel lymph nodes and detection of cancer cells through immunohistochemistry should be considered investigational, and the results should be used with caution in clinical management decisions.

Assessing regional lymph nodes for isolated tumor cells also has potential benefit. One study of 312 consecutive patients with pN0 disease found that positive cytokeratin staining was associated with a higher risk of recurrence.\textsuperscript{54} Relapse occurred in 14\% of patients with positive nodes compared with 4.7\% of those with negative nodes (hazard ratio [HR], 3.00; 95\% CI, 1.23–7.32; \( P = .013 \)). A recent systematic review and meta-analysis had a similar conclusion, finding decreased survival in patients with pN0 disease who had evidence of tumor cells in regional nodes on immunohistochemistry or reverse transcriptase polymerase chain reaction.\textsuperscript{55} As with sentinel nodes, the molecular detection of cancer cells in regional nodes should be also considered investigational, and the results should be used with caution in clinical management decisions.

The 7th edition of the AJCC Cancer Staging Manual and the most recent CAP guidelines require that the pathology report comment on treatment effects of neoadjuvant therapy.\textsuperscript{16,25} The minimum requirement is a yes/no whether a definitive treatment effect is identified. However, it is the opinion of the panel, and of the CAP, that the tumor response should be graded on a scale of 0 (complete response: no viable cancer cells observed) to 3 (poor response: minimal or no tumor kill; extensive residual cancer).\textsuperscript{16,25,31,32}

Several studies have shown that the presence of perineural invasion (PNI) is associated with a significantly worse prognosis.\textsuperscript{34–36} For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at 1 institution found a 4-fold greater 5-year survival in patients without PNI versus patient whose tumors invaded nearby neural structures.\textsuperscript{35} Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year disease-free survival compared with those without PNI (29\% vs. 82\%; \( P = .0005 \)).\textsuperscript{16} Similar results were seen for patients with stage III disease.\textsuperscript{14}

Extranodal tumor deposits, or satellite nodules, are irregular discrete tumor deposits in the perirectal fat that are away from the leading edge of the tumor and show no evidence of residual lymph node tissue, but that are within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to be from lymphovascular invasion or occasionally PNI. The number of extranodal tumor deposits should be recorded in the pathology report, because they have been shown to be associated with reductions in disease-free and overall survival.\textsuperscript{20–24} Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5\% 5-year survival rate compared with 37.0\% for patients with pN0 tumors and the presence of satellite nodules (\( P = .0001 \)).\textsuperscript{24} Extranodal tumor deposits are classified as pN1c.\textsuperscript{16}

The Role of Vitamin D in Colorectal Cancer

Prospective studies have suggested that vitamin D deficiency may contribute to colorectal cancer incidence and that vitamin D supplementation may decrease colorectal cancer risk.\textsuperscript{36–39} Furthermore, 3 prospective studies showed that low vitamin D levels were associated with increased mortality of patients with colorectal cancer, especially in those with stage III and IV disease.\textsuperscript{60,61} Moreover, in a study of 515 patients with stage IV colorectal cancer, 82\% were found to be vitamin D–insufficient (levels <30 ng/mL) and 50\% found to be vitamin D–deficient (<20 ng/mL).\textsuperscript{62} Nonetheless, no study has yet examined whether vitamin D supplementation improves patient outcomes. In a recent report, the Institute of Medicine concluded that data supporting a role for vitamin D were only conclusive in bone health, not in cancer and other diseases.\textsuperscript{63} Citing this report and the lack of level 1 evidence, the panel does not currently recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with colorectal cancer.

Clinical Presentation and Treatment of Nonmetastatic Disease

Management of Polyloid Cancer

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp...
Rectal Cancer

or villous adenoma, physicians should review pathology and consult with the patient. A malignant rectal polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis. The panel recommends marking the cancerous polyp site at the time of colonoscopy or within 2 weeks.

In patients with pedunculated polyps with invasive cancer (tubular, tubulovillous, or villous adenoma), no additional surgery is required if the polyp has been completely resected with favorable histologic features. Favorable histologic features include lesions of grade 1 or 2 without angiolymphatic invasion and with a negative resection margin. For patients with a completely removed, single-specimen, sessile polyp (pT1) with favorable histologic features and clear margins, observation may be considered, with the understanding that this is associated with a significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than polyploid malignant polyps. Also see “Principles of Pathologic Review: Endoscopically Removed Malignant Polyps” (page 1534). Rectal surgery is also an option for these patients.

Rectal surgery is also recommended for patients with polyps with unfavorable histologic features or when the specimen is fragmented or margins cannot be assessed. Unfavorable histologic features for adenomas are grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. In these cases, the risk of nodal involvement is higher. Currently no consensus exists as to the definition of what constitutes a positive margin of resection. A positive margin for an endoscopically removed polyp has been defined as the presence of tumor within 1 to 2 mm from the transected margin or by the presence of tumor cells within the diathermy of the transected margin.

For a polyp with fragmented specimen or margins that cannot be assessed, either a transanal excision or a transabdominal resection is recommended. In patients with unfavorable pathologic features, transabdominal resection should be considered to include lymphadenectomy. Results from a preoperative endoscopic ultrasound evaluation may provide additional information to guide choice of surgical approach, although the accuracy of this method in detecting residual cancer is limited (see “Clinical Evaluation/Staging,” this page). All patients who have resected polyps should undergo surveillance as described in the guidelines.

Management of Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge on rigid proctoscopy. Some support for this definition comes from the study by Kapiteijn et al, which included a subgroup analysis of the risk of recurrence of rectal cancer based on tumor location. Univariate analyses indicated that local recurrence rates were low for patients who had tumors with an inferior margin of 10.1 cm or more from the anal verge, and that no significant differences between patients in this group receiving radiotherapy (RT) and surgery were observed compared with those undergoing surgery alone. A recent retrospective review of patients with rectal or rectosigmoid cancer showed that treatment options were impacted by whether the location of the rectal lesion was characterized by rigid proctoscopy or colonoscopy.

Determining an optimal treatment plan for an individual patient with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative or palliative), consideration must also be given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence and preserving genitourinary functions. For patients with distal rectal cancer, in particular, the simultaneous achievement of the goals of cure and 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 has frequently been associated with a poor prognosis. Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoradiation (chemoRT) with operative treatment for selected patients are recommended.

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

Patients who present with rectal cancer appropriate for resection require a complete staging evaluation, including total colonoscopy to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum, and rigid proctoscopy to provide a determination of the location of the cancer (ie, the distance of the tumor from the anal verge should be measured by the responsible surgeon using rigid proctoscopy). These patients also require a complete physical examination, including carcinoembryonic antigen (CEA) determination and assessment of performance status to determine operative risk. In addition, the accessibility of rectal cancer to evaluation by certain imaging modalities, such as endorectal ultrasound and MRI, enables preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases. The consensus of the panel is that a PET scan is not routinely indicated. Additional information regarding the extent of disease and the occurrence of distant metastases can be determined preoperatively through CT scans. Thus, endorectal ultrasound or pelvic MRI, and CT scans of the chest, abdomen, and pelvis are recommended for the preoperative staging of rectal cancer. CT should be performed with intravenous contrast plus a noncontrast chest CT should be measured by the responsible surgeon using rigid proctoscopy. These patients also require a complete physical examination, including carcinoembryonic antigen (CEA) determination and assessment of performance status to determine operative risk. In addition, the accessibility of rectal cancer to evaluation by certain imaging modalities, such as endorectal ultrasound and MRI, enables preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.

The consensus of the panel is that a PET scan is not routinely indicated. Additional information regarding the extent of disease and the occurrence of distant metastases can be determined preoperatively through CT scans. Thus, endorectal ultrasound or pelvic MRI, and CT scans of the chest, abdomen, and pelvis are recommended for the preoperative staging of rectal cancer. CT should be performed with intravenous contrast plus a noncontrast chest CT should be considered.

Results from a meta-analysis of 90 studies involving the accuracy of endoscopic ultrasound, MRI, and CT in preoperatively staging rectal cancer showed that endoscopic ultrasound and MRI have similarly high sensitivities for evaluating the depth of tumor penetration into the muscularis propria (94%), although endoscopic ultrasound was found to be more specific than MRI in the evaluation of local tumor invasion (86% vs. 69%). Only a limited number of studies have been performed using CT for the purpose of T staging, and it is not currently considered an optimal method for staging the extent of tumor penetration. Accurate assessment of nodal status is one of the greatest challenges in the preoperative staging of rectal cancer. In the meta-analysis of Bi et al, the sensitivities and specificities of the 3 imaging modalities for accurately evaluating lymph node involvement were comparable: CT (55% and 74%, respectively); endoscopic ultrasound (67% and 78%, respectively); and MRI (66% and 76%, respectively). However, only CT and MRI can evaluate iliac and mesenteric or retroperitoneal nodes. Results from another recent meta-analysis of 84 articles indicated that none of the 3 imaging modalities were significantly superior to another method with respect to an accurate determination of tumor N stage. A disadvantage of endoscopic ultrasound is a high degree of operator dependence. An advantage of MRI is its ability to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia. Hence, MRI evaluation of patients with more advanced rectal cancer has the potential to provide information useful in predicting the CRM before radical surgery.

Clinical staging is also based on histopathologic examination of the specimen obtained via biopsy or local excision (eg, excised polyps). Endoscopic biopsy specimens of the lesion should undergo careful pathology review for evidence of invasion into the muscularis mucosa. If removal of the rectum is contemplated, early consultation with an enterostomal therapist is recommended for preoperative marking of the site and patient teaching purposes. Surgical Approaches: A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions. These methods include local procedures, such as polypectomy, transanal excision, and transanal endoscopic microsurgery (TEM), and more invasive procedures involving a transabdominal resection (eg, low anterior resection [LAR], proctectomy with TEM and coloanal anastomosis, abdominoperineal resection [APR]). Transanal excision may be appropriate for selected T1,N0 early-stage cancers. Small (≤3 cm), well to moderately differentiated tumors that are within 8 cm of the anal verge and limited to less than 30% of the rectal circumference and for which no evidence is seen of nodal involvement can be approached with transanal excision with negative margins. TEM can facilitate excision of small tumors through the anus when lesions can be adequately identified in the rectum. TEM may be technically feasible for more
proximal lesions. Both transanal excision and TEM involve a full-thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (>3 mm) deep and mucosal margins are required, and tumor fragmentation should be avoided. The excised specimen should be oriented and pinned before fixation and brought to the pathologist by the surgeon to facilitate an oriented histopathologic evaluation of the specimen. Advantages of a local procedure include minimal morbidity (eg, a sphincter-sparing procedure) and mortality and rapid postoperative recovery.\textsuperscript{74,85} If pathologic examination reveals adverse features, such as positive margins, lymphovascular invasion, poor differentiation, or invasion into the lower third of the submucosa (sm3 level),\textsuperscript{86,87} a more radical resection is recommended. Data are limited on long-term patient outcomes, including risk of local recurrence, for patients undergoing local excision for T2 tumors.\textsuperscript{85}

Limitations of a transanal excision include the absence of pathologic staging of nodal involvement. Furthermore, evidence indicates that lymph node micrometastases are common in early rectal lesions and unlikely to be identified by endorectal ultrasound.\textsuperscript{88} These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.\textsuperscript{85,89} A recent retrospective study of 282 patients undergoing either transanal excision or radical resection for T1 rectal cancer from 1985 to 2004 showed respective local recurrence rates of 13.2% and 2.7% for these 2 groups, respectively (P = .001).\textsuperscript{89} A similar retrospective study of 2124 patients showed local recurrence rates of 12.5% and 6.9% for patients undergoing local excision versus standard resection, respectively (P = .003).\textsuperscript{85}

Patients with rectal cancer who do not meet requirements for local surgery should be treated with a transabdominal resection. Organ-preserving procedures that maintain sphincter function are preferable, but not possible in all cases. Preoperative chemoradiotherapy may result in tumor downsizing and a decrease in tumor bulk (see “Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease,” page 1547); sphincter preservation may become possible in patients in whom initial tumor bulk prevented consideration of this surgery and exposure to the tumor is improved by chemoradiotherapy.

In transabdominal resections, TME is recommended. A TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a “tumor package” through sharp dissection and is designed to spare the autonomic nerves.\textsuperscript{74,84,90} The lymphatic drainage regions of rectal tumors are influenced by their position in the rectum. Tumors located more distally are more likely to be characterized by both upward and lateral lymphatic drainage, whereas the likelihood of only upward mesorectal drainage is much higher for more proximal tumors.\textsuperscript{91} The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.\textsuperscript{92} The panel does not recommend extension of nodal dissection beyond the field of resection (eg, into the distribution of iliac lymph nodes) unless these nodes are clinically suspicious. When anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis.

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

An APR should be performed when the tumor directly involves the anal sphincter or the levator muscles. An APR is also necessary when a margin-negative resection of the tumor would result in loss of anal sphincter function and incontinence. An APR involves en bloc resection of the rectosigmoid, rectum, and anus, and the surrounding mesentery, mesorectum (TME), and perianal soft tissue, and necessitates creation of a colostomy.\textsuperscript{93}

Pathologists play a key role in evaluating the surgical specimen after TME, which includes a macroscopic assessment of both its external appearance/completeness and the CRM.\textsuperscript{94,95} Detailed descriptions of how the quality of the mesorectal specimens should be scored were provided in the Dutch Rectal Cancer Trial, and these guidelines are endorsed by the NCCN panel.\textsuperscript{28}

Recent retrospective comparisons of the outcomes of patients undergoing an APR versus a LAR in the treatment of rectal cancer have shown that those treated with an APR have worse local control and overall survival.\textsuperscript{96,97} Whether these differences
can be attributed to the surgical procedure alone, to patient- and tumor-related characteristics, or some combination of these factors is currently unclear. However, results from a recent retrospective study of 3633 patients with T3–4 rectal cancer tumors included in 5 large European trials suggest an association between the APR procedure itself and the increased risks of recurrence and death.96

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer are limited.98,99 One large prospective multicentre study, which included 4405 patients with rectal cancer but was not randomized, found no differences in recurrence or survival, although complications and other measures of quality indicated a benefit to the laparoscopic approach.100 The COREAN trial randomized patients with stage II or III low- to mid-rectal cancer to an open or laparoscopic resection.101 The primary end point, 3-year disease-free survival, has not yet been reported, but short-term benefits were seen with the laparoscopic approach.

To date, the highest level of evidence for the benefits of the laparoscopic approach comes from the CLASICC trial. In the CLASICC trial comparing laparoscopically assisted and open resection, nearly half of the 794 patients were diagnosed with rectal cancer.98 No significant differences in local recurrence, disease-free survival, or overall survival were observed between the groups of patients with colon or rectal cancer based on surgical approach. A 5-year follow-up of the CLASICC trial showed that this lack of difference in local recurrence, disease-free survival, or overall survival was maintained for patients with rectal cancer, despite a trend toward better 5-year overall survival after laparoscopic surgery (52.9% and 60.3% for open and laparoscopic surgery, respectively; \( P = .132 \)).102 Factors that may confound conclusions drawn from randomized studies comparing open and laparoscopically assisted surgery for colorectal cancer have been described,103 and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Reviews and meta-analyses including these and additional small trials have also been published.104–107 They found the laparoscopic approach to be safe and feasible. Laparoscopic resection seems to have long-term outcomes similar to or better than those of open resection, but additional high-level evidence is required. Additional clinical trials exploring open versus laparoscopic surgery for rectal cancer are ongoing (including ClinicalTrials.gov identifiers NCT00297791 [COLOR II], NCT00470951 [CTS-179], NCT00726622 [ACOSOG-Z6051], and NCT00147134 [JCOG0404]). Currently, laparoscopic surgery for rectal cancer is preferred in the setting of a clinical trial.

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

Although 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.38,106 It has been suggested that some patients with disease at lower risk of local recurrence (eg, proximal rectal cancer staged as T3,N0,M0, characterized by clear margins and favorable prognostic features) may be adequately treated with surgery and adjuvant chemotherapy.38,109,110 However, according to results of a recent retrospective multicenter study, 22% of 188 patients clinically staged with T3,N0 rectal cancer by either endoscopic ultrasound or MRI who subsequently received preoperative chemoRT had positive lymph nodes after pathologic review of the surgical specimens,111 suggesting that many patients are understaged and would benefit from chemoRT. Therefore, the guidelines recommend preoperative chemoRT for patients with T3,N0 disease.

Combined modality therapy consisting of surgery, RT, and chemotherapy is recommended for most patients with stage II or III rectal cancer. Use of perioperative pelvic RT in the treatment of patients with stage II/III rectal cancer continues to evolve. In these patients, the current guidelines recommend
Rectal Cancer

concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis preoperatively and chemotherapy postoperatively. A total of 6 months of perioperative chemotherapy with or without RT is preferred.

Preoperative Versus Postoperative Radiation: Several studies have compared the administration of radiation preoperatively versus postoperatively. A large prospective, randomized trial from the German Rectal Cancer Study Group (the CAO/ARO/AIO-94 trial) compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer. Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs. 13%; \(P=.006\)) and treatment-associated toxicity (27% vs. 40%; \(P=.001\)), although overall survival was similar in the groups. Long-term follow-up of this trial was recently published. The improvement in local control persisted, with the 10-year cumulative incidence of local recurrence at 7.1% and 10.1% in the preoperative and postoperative treatment arms, respectively (\(P=.048\)). Overall survival at 10 years was again similar between the groups (59.6% and 59.9%, respectively; \(P=.85\)), as was disease-free survival and the occurrence of distant metastases.

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue. First of all, reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Although some studies have indicated that preoperative radiation or chemoRT is associated with increased rates of sphincter preservation in patients with rectal cancer, this conclusion is not supported by 2 meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer. Second, irradiating tissue that is surgery-naive and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by postsurgical adhesions. Finally, preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected). One disadvantage of using preoperative RT is the possibility of overtreating early-stage tumors that do not require adjuvant radiation. Improvements in preoperative staging techniques, such as MRI or CT scans, have allowed for more accurate staging, but the risk of overstaging disease has not been eliminated. Weighing these advantages and disadvantages, the panel recommends preoperative chemoRT for patients with stage II/III rectal cancer.

Postoperative chemoRT is recommended when stage I rectal cancer is upstaged to stage II or III after pathologic review of the surgical specimen. Postoperative chemoRT regimens commonly use a "sandwich" approach, whereby chemotherapy (typically 5-FU-based) is administered before and after the chemoRT regimen. The use of FOLFOX or capecitabine chemotherapy before and after postoperative chemo RT is an extrapolation of the available data in colon cancer.

Concurrent Chemotherapy With Radiation: Several randomized trials have evaluated the effectiveness of adding chemotherapy to radiation administered either preoperatively after clinical evaluation/staging (eg, T3–4 by endoscopic ultrasound) or postoperatively after pathologic staging of rectal cancer as pT3 and/or N1–2. Putative benefits of the addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (ie, eradication of micrometastases). Preoperative chemoRT also has the potential to increase rates of pathologic complete response and sphincter preservation.

In a study of patients with T3–4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative RT alone or preoperative concurrent chemoRT with 5-FU/leucovorin, no difference in overall survival or sphincter preservation was observed between the groups, although patients receiving chemoRT were significantly more likely to exhibit a pathologic complete response (11.4% vs. 3.6%; \(P<.05\)) and grade 3/4 toxicity (14.6% vs. 2.7%; \(P<.05\)) and less likely to exhibit local recurrence of disease (8.1% vs. 16.5%; \(P<.05\)). These conclusions were supported in a 2009 systematic review that included 4 randomized controlled trials.

Preliminary results of a phase III trial that included an evaluation of the addition of chemotherapy to preoperative RT in patients with T3–4 resectable rectal cancer showed that use of 5-FU/
leucovorin chemotherapy enhanced the tumoricidal effect of RT when the 2 approaches were used concurrently.\textsuperscript{125} Significant reductions in tumor size, pTN stage, and lymphatic, vascular, and PNI rates were observed with use of combined modality therapy compared with use of RT and surgery without chemotherapy.\textsuperscript{125} More mature results from this trial, however, which included 4 treatment groups (preoperative RT; preoperative chemoRT; preoperative RT plus postoperative chemotherapy; and preoperative chemoRT plus postoperative chemotherapy), indicated that no significant differences in overall survival were associated with adding 5-FU–based chemotherapy pre- or postoperatively.\textsuperscript{126} Although local recurrence rates were significantly higher in the group receiving preoperative RT alone, the addition of chemotherapy after concurrent chemoRT did not significantly impact local recurrence rates. In subsequent exploratory analyses of data from the group of patients in this trial who underwent complete tumor resection without evidence of distant disease before or at surgery, those patients with disease characterized as ypT0–2 showed significant benefit from adjuvant chemotherapy with respect to disease-free and overall survivals.\textsuperscript{127} These findings may indicate that patients are more likely to benefit from adjuvant therapy if their disease can be downstaged by chemoRT. Notably, patients with stage II/III rectal cancer enrolled in this trial were found to be 2.6 times more likely to develop distant metastases than local recurrence after a median follow-up of more than 5 years.\textsuperscript{126}

With respect to the type of chemotherapy administered concurrently with RT,\textsuperscript{110} the equivalence of bolus 5-FU/leucovorin and infusional 5-FU in concurrent chemoRT for rectal cancer is supported by the results of a phase III trial (median follow-up of 5.7 years) in which similar outcomes with respect to overall and relapse-free survivals were observed when an infusion of 5-FU or bolus 5-FU plus leucovorin was administered concurrently with postoperative RT, although hematologic toxicity was greater in the group of patients receiving bolus 5-FU.\textsuperscript{120} On the other hand, results from an earlier trial from the North Central Cancer Treatment Group (NCCTG) showed that postoperative administration of infusional 5-FU during pelvic irradiation was associated with longer overall survival when compared with bolus 5-FU.\textsuperscript{119} Most of the patients in this study had node-positive disease.

Recent studies have shown that capecitabine is equivalent to 5-FU in perioperative chemoRT.\textsuperscript{128,129} The randomized NSABP R-04 trial compared the preoperative use of infusional 5-FU with or without oxaliplatin versus capecitabine with or without oxaliplatin in 1608 patients with stage II or III rectal cancer.\textsuperscript{129} No differences in complete pathologic response, sphincter-saving surgery, or surgical downstaging were seen among the regimens, whereas toxicity was increased with the inclusion of oxaliplatin. Similarly, a phase III randomized trial in which 401 patients with stage II or III rectal cancer received capecitabine- or 5-FU–based chemoRT either pre- or postoperatively showed that capecitabine was noninferior to 5-FU with regard to 5-year overall survival (capecitabine 75.7\% vs. 5-FU 66.6\%; \(P=.0004\)), with capecitabine showing showed borderline significance for superiority (\(P=.053\)).\textsuperscript{129} Furthermore, in this trial capecitabine showed a significant improvement in 3-year disease-free survival (75.2\% vs. 66.6\%; \(P=.034\)).\textsuperscript{128} Because of these studies, capecitabine given concurrently with RT is now listed in the guidelines as a category 2A recommendation. The panel believes that capecitabine is an acceptable alternative to infusional 5-FU in patients who are able to manage the responsibilities inherent in self-administered oral chemotherapy.

In attempt to improve on the outcomes achieved with neoadjuvant 5-FU/RT or capecitabine/RT, several large randomized phase III trials (ACCORD 12, STAR-01, R-04, and CAO/ARO/AIO-04) added oxaliplatin to the regimens. In a planned interim report of primary tumor response in the STAR-01 trial, grade 3 and 4 adverse events occurred more frequently in patients receiving infusional 5-FU/oxaliplatin/RT than in those receiving infusional 5-FU/RT (24\% vs. 8\%; \(P<.001\)), whereas no difference was seen in pathologic response between the arms (16\% pathologic complete response in both arms).\textsuperscript{130} Recently reported results of the NSABP R-04 trial also showed that the addition of oxaliplatin did not improve clinical outcomes, including the end points of ypCR, sphincter-saving surgery, and surgical downstaging, whereas it increased toxicity.\textsuperscript{129} Further follow-up of these trials is necessary to see if a difference in local recurrence rates and progression-free survival is seen over time. The primary end points of overall survival for the STAR-01 trial and local tumor control for the R-04 trial will be reported in the future.
Rectal Cancer

Similar results were seen in the ACCORD 12/0405-Prodige 2 trial, in which capecitabine/RT (45 Gy) was compared with capecitabine/oxaliplatin (CapeOx)/RT (50 Gy) and the primary end point was pathologic complete response (ypCR). Here, the grade 3 and 4 toxicity rates were 25% and 11% (P<.001) and the ypCR rates were 19.2% and 13.9% (P=.09) for the oxaliplatin-containing arm and the control arm, respectively. Although patients treated with oxaliplatin and the higher radiation dose in the ACCORD 12 trial had an increased rate of minimal residual disease at the time of surgery (39.4% vs. 28.9%; P=.008), this did not translate to improved local recurrence rates, disease-free survival, or overall survival at 3 years. The addition of oxaliplatin to neoadjuvant chemoRT is thus not recommended at this time.

Initial results of the German CAO/ARO/AIO-04 trial were recently published. This trial also assessed the addition of oxaliplatin to a fluorouracil RT regimen. In contrast to STAR-01, R-04, and ACCORD 12, higher rates of pathologic complete response were seen in the oxaliplatin arm (17% vs. 13%; P=.038), but this result could be because of differences in the fluorouracil schedule between the arms. The primary end point of this trial, disease-free survival, will be reported in the future. Importantly, oxaliplatin was also added to the adjuvant therapy in the AIO-04 trial but not in the other trials, and therefore cross-trial comparisons will be limited.

The randomized phase II EXPERT-C trial assessed complete response rate with the addition of cetuximab to the radiation treatment in 165 patients. Patients in the control arm received CapeOx followed by capecitabine/RT, then surgery followed by CapeOx. Patients randomized to the cetuximab arm received the same therapy with weekly cetuximab throughout all phases. A significant improvement in overall survival was seen in patients with KRAS wild-type tumors treated with cetuximab (HR, 0.27; 95% CI, 0.07–0.99; P=.034). However, the primary end point in complete response rate was not met, and further evaluation of this regimen is warranted. Additional phase II trials assessing the effects of adding irinotecan or bevacizumab to neoadjuvant or adjuvant regimens have begun. However, the panel currently does not endorse the use of irinotecan, bevacizumab, cetuximab, panitumumab, or oxaliplatin with concurrent RT for rectal cancer.

Induction Chemotherapy: Several small trials have tested the utility of a course of neoadjuvant chemotherapy preceding chemoRT and resection. In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CapeOx either before chemoRT or after surgery. Similar pathologic complete response 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. No differences were seen between the clinical outcomes, but the group receiving induction therapy experienced higher toxicity. The phase II AVACROSS study assessed the safety and efficacy of adding bevacizumab to induction therapy with CapeOx before capecitabine/bevacizumab chemoRT and surgery. The regimen was well tolerated, with a pathologic complete response rate of 36%. This approach currently remains investigational and is not endorsed by the panel for routine care.

Preoperative Chemotherapy Without ChemoRT: The ongoing N1048/C81001/Z6092 trial by The Alliance for Clinical Trials in Oncology is asking whether chemotherapy alone is effective in treating stage II or III high rectal cancer in patients with at least 20% tumor regression after neoadjuvant treatment (ClinicalTrials.gov identifier: NCT01515787). This approach would spare patients the morbidities associated with radiation.

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

Coordination of preoperative therapy, surgery, and adjuvant chemotherapy is important. For pa-
tients treated with preoperative chemoRT, the panel recommends an interval of 5 to 10 weeks after completion of full-dose 5.5-week chemoRT before surgical resection to allow patient recuperation from chemoRT-associated toxicities. Although longer intervals from completion of chemoRT to surgery have been shown to be associated with an increase in pathologic complete response rates, whether these longer intervals are associated with clinical benefit is unclear. Nevertheless, when longer intervals are clinically necessary, they do not seem to increase the blood loss, time associated with surgery, or positive margin rate. \(^{147}\)

**Short-Course Radiation:** Several European studies have examined the efficacy of a shorter course of preoperative radiation (25 Gy over 5 days), not combined with chemotherapy, for the treatment of rectal cancer. The results of the Swedish Rectal Cancer Trial evaluating the use of short-course RT administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence with this approach compared with surgery alone. \(^{148}\) However, a follow-up study published in 2005 showed that the patients with short-course preoperative RT had an increased relative risk for postoperative hospitalization because of bowel obstructions and other gastrointestinal complications. \(^{149}\) Several other studies also investigating the effectiveness of preoperative short-course RT in patients with rectal cancer staged as T1–3 have shown that overall survival was not significantly affected despite improvements in local control of disease. \(^{72,150,151}\)

A recent multicenter, randomized study of 1350 patients with rectal cancer compared short-course preoperative RT and no postoperative treatment versus no preoperative RT and a postoperative approach that included chemoRT in selected patients (ie, those with a positive CRM after resection) and no RT in patients without evidence of residual disease after surgery. \(^{152}\) Results indicated that patients in the former preoperative RT arm had significantly lower local recurrence rates and a 6% absolute improvement in 3-year disease-free survival \((P=0.03)\), although no difference in overall survival was observed between the arms. \(^{152,153}\)

Long-term (12-year) follow-up of one of the short-course radiation trials (the Dutch TME trial) was recently reported. \(^{154}\) The analysis showed that 10-year survival was significantly improved in patients with stage III rectal cancer with a negative circumferential margin in the RT plus surgery group compared with the group that received surgery alone \((50\% \text{ vs. } 40\%; \ P=.032)\). \(^{154}\) However, this long follow-up showed that secondary malignancies and other non–rectal cancer causes of death were more frequent in the RT group than in the control group \((14\% \text{ vs. } 9\% \text{ for secondary malignancies})\), negating any survival advantage in the node-negative subpopulation.

Few studies have directly compared preoperative short-course radiation and more conventional preoperative long-course chemoRT. One randomized study of 312 patients in Poland showed no differences in local recurrence or survival. \(^{155}\) Similarly, a Australian/New Zealand trial that randomized 326 patients to short-course radiation or long-course chemoRT found no differences in local recurrence and overall survival rates. \(^{156}\)

Overall, it seems that short-course RT provides effective local control and the same overall survival as more conventional RT schedules, and therefore may be an appropriate choice in some situations.

**Response to Neoadjuvant Treatment:** After neoadjuvant therapy, 50% to 60% of patients are downstaged, with approximately 20% showing a pathologic complete response. \(^{127,157–162}\) Recent studies have suggested that the response to neoadjuvant treatment correlates with long-term outcomes in patients with rectal cancer. In the MERCURY prospective cohort trial, 111 patients were assessed with MRI and pathologic staging. \(^{163}\) On multivariate analysis, MRI-assessed tumor regression grade was significantly associated with overall and disease-free survivals. Patients with poor tumor regression grade had 5-year survival rates of 27% versus 72% for patients with good tumor regression grade \((P=.001)\), and disease-free survival rates were 31% versus 64%, respectively \((P=.007)\). A recent retrospective review of 725 patients with rectal cancer found similar results. \(^{160}\) In this study, pathologically determined response to neoadjuvant treatment correlated with long-term outcomes. Five-year recurrence-free survival rates were 90.5%, 78.7%, and 58.5% for patients with complete, intermediate, and poor responses, respectively \((P<.001)\). Distant metastases and local recurrences also correlated with the level of response.

In addition to its prognostic value, some initial evidence shows predictive value associated with neo-
Rectal Cancer

adjuvant treatment response. Subgroup analysis of the EORTC 22921 trial showed that patients downstaged to ypT0–2 were more likely to benefit from adjuvant chemotherapy than patients with ypT3–4 staging. Similar results were seen from another retrospective review. Although no prospective data exist to predict the benefit of adjuvant therapy in patients with tumor downstaging or a pathologic complete response, the panel believes that these patients should be strongly considered for adjuvant chemotherapy.

Wait-and-See Nonoperative Approach for Patients With a Clinical Complete Response: As preoperative treatment and imaging modalities have improved, some have suggested that patients with a complete clinical response to chemoRT may be able to be spared the morbidities of surgery. In 2004, Habr-Gama et al retrospectively compared the outcomes of 71 patients who were observed without surgery after complete clinical response (27%) with the outcomes of 22 patients who had incomplete clinical responses but complete pathologic responses post-TME (8%). The overall and disease-free survival rates at 5 years were 100% and 92%, respectively, in the nonoperative group compared with 88% and 83%, respectively, in the resected group. However, other studies did not achieve as impressive results, and many clinicians were skeptical of the approach.

A more recent prospective study included a more thorough assessment of treatment response and used very strict criteria to select 21 of 192 patients (11%) with clinical complete responses who were then observed with careful follow-up and compared with 20 patients with a complete pathologic response after resection. Only 1 patient in the nonoperative group developed a local recurrence after a mean follow-up of 25 months, and that patient underwent successful salvage surgery. No statistical differences in long-term outcomes were seen between the groups. The cumulative probabilities for 2-year disease-free and overall survivals 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.

Despite these impressive results, many still believe that longer follow-up, larger sample sizes, and additional careful observational studies are needed before patients with a clinical complete response can be routinely managed with a wait-and-see approach.

Adjuvant Chemotherapy: Adjuvant chemotherapy is recommended for all patients with stage II/III rectal cancer after neoadjuvant chemoRT/surgery regardless of the surgical pathology results, although few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well defined. The addition of 5-FU–based adjuvant chemotherapy to preoperative chemoRT provided no benefit to the rate of local recurrence in the EORTC Radiotherapy Group Trial 22921. However, this study did show an improvement in disease-free survival (HR, 0.87; 95% CI, 0.72–1.04; P=.13) for patients receiving adjuvant chemotherapy (+/− RT) after preoperative RT (+/− 5-FU–based chemotherapy). A recent systematic review and meta-analysis of 9785 patients with nonmetastatic rectal cancer from 21 randomized controlled trials from 1975 until March 2011 concluded that overall and disease-free survivals are improved with the addition of postoperative 5-FU–based therapy.

Most support for the use of FOLFOX or capecitabine as adjuvant chemotherapy in rectal cancer is an extrapolation from the data available for colon cancer. The phase III ECOG E3201 trial was designed to investigate the effect of adding either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) to 5-FU/leucovorin–based adjuvant chemotherapy administered to patients with stage II/III rectal cancer after either preoperative or postoperative chemoRT. This study was replaced with an alternative trial with bevacizumab, but results from an initial 165 patients indicate that adjuvant FOLFOX can be safely used in this patient population. Nevertheless, the optimal duration of treatment with adjuvant FOLFOX in rectal cancer is still unclear. In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX. The use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) is justified when preoperative chemoRT is administered.

A recent systematic review and meta-analysis of 10 studies involving more than 15,000 patients with colorectal cancer examined the effect of timing of adjuvant therapy after resection. Results of this analysis showed that each 4-week delay in chemo-
therapy results in a 14% decrease in overall survival, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses.\textsuperscript{176} Leucovorin Shortage: A shortage of leucovorin currently exists in the United States. No specific data are available to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m\textsuperscript{2} of levo-leucovorin is equivalent to 400 mg/m\textsuperscript{2} of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, because the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg of leucovorin gave similar survival and 3-year recurrence rates as 25 mg of leucovorin when given with bolus 5-FU to patients as adjuvant therapy after R0 resections for colorectal cancer.\textsuperscript{177} Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m\textsuperscript{2}) or low-dose (20 mg/m\textsuperscript{2}) leucovorin.\textsuperscript{178} Additionally, the Mayo Clinic and NCCTG determined that there was no therapeutic difference between the use of high-dose (200 mg/m\textsuperscript{2}) or low-dose (20 mg/m\textsuperscript{2}) leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.\textsuperscript{179} Finally, if none of these options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without experiencing grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

\textbf{Recommendations for Patients With T1 and T2 Lesions:} Node-negative T1 lesions are treated with transabdominal resection or transanal excision, as appropriate (see “Surgical Approaches,” page 1545). If pathology review after local excision reveals a poorly differentiated histology, positive margins, invasion into the lower third of the submucosa (sm3 level), or lymphovascular invasion, or if the tumor is restaged to T2, then a transabdominal re-resection should be performed.\textsuperscript{86,87} For these high-risk patients who cannot undergo additional surgery, systemic chemotherapy with chemoRT (a “sandwich regimen,” as described later) should be considered as an adjuvant treatment to avoid the risk of undertreatment, considering that the lymph node status is unknown.

Node-negative T2 lesions are treated with transabdominal resection, because local recurrence rates of 11% to 45% have been observed for T2 lesions after local excision alone.\textsuperscript{74,180,181} In selected lesions that are staged with endoscopic ultrasound or MRI as T1–2,N0 and without adverse pathologic features (eg, negative margins, no lymphovascular invasion, well to moderately differentiated, and no sm3 invasion), local excision with negative margins may provide comparable results to transabdominal resection.\textsuperscript{182}

After transabdominal resection, patients with tumors staged as pT1–2,N0,M0 require no further treatment. If pathology review reveals pT3,N0,M0 or node-positive disease, a “sandwich regimen” is recommended consisting of 1) an optional first round of adjuvant chemotherapy with 5-FU with or without leucovorin or FOLFOX or capecitabine with or without oxaliplatin,\textsuperscript{183} followed by 2) concurrent 5-FU/RT (infusional [preferred] or bolus infusion along with leucovorin) or capecitabine/RT (preferred), followed by 3) 5-FU with or without leucovorin or FOLFOX or capecitabine with or without oxaliplatin.

The panel recommends perioperative therapy for approximately 6 months. For patients with pathologic evidence of proximal T3,N0,M0 disease with clear margins and favorable prognostic features after an upfront resection, the incremental benefit of RT is likely to be small and chemotherapy alone can be considered, although most patients are not likely to be part of this subset.

\textbf{Recommendations for Patients With T3 Lesions and Lesions With Nodal Involvement:} Patients clinically staged as having resectable T3,N0 or Tany,N1–2 lesions should initially be treated with preoperative combined modality therapy unless medically contraindicated. Preoperative infusional 5-FU/RT or capecitabine/RT are the preferred treatment options (category 1 for both). An alternative regimen is bolus 5-FU/leucovorin/RT. Patients who receive preoperative RT should undergo transabdominal resection 5 to 10 weeks after completion of neoadjuvant therapy. The panel recommends postoperative adjuvant therapy for a duration, giving approximately 6 months total of pre- and postopera-
Rectal Cancer

Posttreatment Surveillance

After curative-intent surgery, posttreatment surveillance of patients with colorectal 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 similar to that described for colon cancer, with the addition of proctoscopy to evaluate the rectal anastomosis for local recurrence for patients who have undergone an LAR. The optimal timing for surveillance of the rectal anastomosis is not known. Furthermore, no specific data clearly support the use of rigid versus flexible proctoscopy, and the utility of endoscopic ultrasound for early surveillance is not defined.

The advantages of more intensive follow-up of patients with stage II and/or III rectal cancer have been shown prospectively in several studies and in 3 meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance. Other study results impacting on the issue of posttreatment surveillance of colorectal cancer include those from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials. This meta-analysis showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor. However, in the final analysis of Intergroup trial 0114 comparing bolus 5-FU with bolus 5-FU/leucovorin in patients with surgically resectable rectal cancer, local recurrence rates continued to increase after 5 years. Furthermore, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year relative survival rate of 15.6%), thereby providing support for more intensive posttreatment follow-up in these patients. Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.

The following panel recommendations for posttreatment surveillance pertain to patients with stage I–III disease who have undergone successful treatment (ie, no known residual disease): history and physical examination every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years; and a CEA test at baseline and every 3 to 6 months for 2 years, then every 6 months for a total of 5 years if the patient is a potential candidate for resection of isolated metastases. Colonoscopy is recommended at approximately 1 year after resection for unresectable cancers, doses higher than 54 Gy may be required; the dose of radiation to the small bowel should be limited to 45 Gy.

Recommendations for Patients With T4 Lesions and/or Locally Unresectable Disease: Patients with T4 and/or locally unresectable disease are treated with preoperative infusional 5-FU/RT or bolus 5-FU with leucovorin/RT or capecitabine/RT. If possible, resection should be considered after preoperative chemoRT. For patients with T4 tumors or recurrent cancers or if margins are very close or positive, intraoperative RT, which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment, should be considered as an additional boost to facilitate resection. If intraoperative RT is not available, 10 to 20 Gy and/or brachytherapy to a limited volume can be considered soon after surgery, before adjuvant chemotherapy. Adjuvant therapy to complete 6 months with either 5-FU with or without leucovorin; or FOLFOX; or capecitabine with or without oxaliplatin is recommended regardless of the surgical pathology results.

For unresectable cancers, doses higher than 54 Gy may be required; the dose of radiation to the small bowel should be limited to 45 Gy.
(or at approximately 3 to 6 months postresection if not performed preoperatively because of an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia), in which case colonoscopy should be repeated in 1 year.\textsuperscript{199} More frequent colonoscopies may be indicated in patients who present with colorectal cancer before 50 years of age.\textsuperscript{199} Proctoscopy should be considered every 6 months for 5 years to evaluate for local recurrence at the rectal anastomosis for patients who have undergone an LAR, as discussed earlier. Chest, abdominal, and pelvic CT scans are recommended annually for up to 5 years in patients with stage II and III disease (ie, patients considered at high risk of recurrence, such as those with lymphatic or venous invasion by the tumor or with poorly differentiated tumors).\textsuperscript{190,196} Routine CEA monitoring and CT scanning are not recommended beyond 5 years. Routine use of PET/CT to monitor for disease recurrence is not recommended. The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore not of ideal quality for routine surveillance.

Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps because data show that patients with a history of colorectal cancer have an increased risk of developing second cancers,\textsuperscript{200} particularly in the first 2 years after resection; the use of posttreatment surveillance colonoscopy has not been shown to improve survival through early detection of recurrence of the original colorectal cancer.\textsuperscript{199} CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and liver. Hence, CT scan is not routinely recommended in patients who are not candidates for potentially curative resection of liver or lung metastases.

**Managing An Increasing CEA Level**

Managing patients with an elevated CEA level after resection should include colonoscopy; chest, abdominal, and pelvic CT scans; physical examination; and consideration of a PET/CT scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans are recommended every 3 months until either disease is identified or CEA level stabilizes or declines. Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (ie, some panel members favored use of PET/CT in this scenario whereas others noted that the likelihood of PET/CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). Use of PET/CT scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called blind or CEA-directed laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,\textsuperscript{201} nor do they recommend use of radiolabeled anti-CEA scintigraphy.

**Treatment of Locally Recurrent Disease**

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease. In a single-center study, Yu et al\textsuperscript{202} reported low rates of 5-year local recurrence (ie, 5-year locoregional control rate of 91%) for patients with rectal cancer treated with surgery and either RT or chemoRT, and 49% of recurrences occurred in the low pelvic and presacral regions, with an additional 14% occurring in the mid and high pelvis. Patients with disease recurrence at the anastomotic site are more likely than those with an isolated pelvic recurrence to be cured after re-resection.\textsuperscript{203,204}

Potentially resectable isolated pelvic/anastomotic recurrence is optimally managed with resection followed by adjuvant chemoRT or with preoperative RT and concurrent infusional 5-FU. Intraoperative radiotherapy (IORT) or brachytherapy should be considered with resection if it can be safely delivered.\textsuperscript{205–207} In a study of 43 consecutive patients with advanced pelvic recurrence of colorectal cancer who had not undergone prior RT, treatment with 5 weeks of 5-FU through infusion concurrent with RT enabled most patients (77%) to undergo re-resection with curative intent.\textsuperscript{204} Studies of patients who previously received pelvic RT show that reirradiation can be effective, with acceptable rates of toxicity.\textsuperscript{208,209} In one such study of 48 patients with recurrent rectal cancer and a history of pelvic radiation, the 3-year rate of grade 3 to 4 late toxicity was 35%, and 36% of treated patients were able to undergo surgery after radiation.\textsuperscript{208} Intensity-modulated radiotherapy can be used in this setting of reirradiation.

Patients with unresectable lesions are treated with chemotherapy with or without radiation according to their ability to tolerate therapy. Debulking that results in gross residual cancer is not recommended.
Survivorship

Posttreatment surveillance for all patients also includes a survivorship care plan involving disease-preventive measures, such as immunizations; early disease detection through periodic screening for second primary cancers (eg, breast, cervical, prostate cancers); and routine good medical care and monitoring. Additional health monitoring should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.

Other recommendations include monitoring for late sequelae of rectal cancer or associated with the treatment of rectal cancer, such as chronic diarrhea or incontinence (eg, patients with stomas). Urogenital dysfunction after resection and/or pelvic irradiation is common. Patients should be screened for sexual dysfunction, erectile dysfunction, dyspareunia, vaginal dryness, and urinary incontinence, frequency, and urgency. Referral to a gynecologist or urologist can be considered for persistent symptoms. Specific management interventions to address side effects of colorectal cancer are described in a recent review, and a survivorship care plan for patients with colorectal cancer was recently published.

Evidence indicates that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy body mass index (BMI), engaging in regular exercise, and making certain dietary choices, are associated with improved outcomes after treatment for colon cancer. For example, a retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI of 35 kg/m² or greater had an increased risk of disease recurrence and death. In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, disease-free survival was found to be directly correlated with how much exercise these patients received. Furthermore, a diet consisting of more fruits, vegetables, poultry, and fish and less red meat, and higher in whole grains and lower in refined grains and concentrated sweets, was found to be associated with an improved outcome in terms of cancer recurrence or death. In addition, a recent study of a large cohort of men treated for stage I–III colorectal cancer showed an association between increased physical activity and lower rates of colorectal cancer-specific mortality and overall mortality. A discussion of lifestyle characteristics that may be associated with a decreased risk of colorectal cancer recurrence, such as those recommended by the American Cancer Society, also provides “a teachable moment” for the promotion of overall health and an opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle.

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written if the primary physician will be assuming cancer surveillance responsibilities. The prescription should include an overall summary of treatments received, including surgeries, radiation treatments, and chemotherapy. The possible clinical course should be described, including the expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment. Surveillance recommendations should be included, as should a delineation of the appropriate timing of transfer of care, with specific responsibilities identified for the primary care physician and oncologist.

Summary

The panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology, is necessary for treating patients with rectal cancer. Adequate pathologic assessment of the resected lymph nodes is important, with a goal of evaluating at least 12 nodes when possible. Patients with very-early-stage tumors that are node-negative on endorectal ultrasound or endorectal or pelvic MRI and who meet carefully defined criteria can be managed with a transanal excision. A transabdominal resection is appropriate for all other rectal lesions. Preoperative chemoRT is preferred for most patients with suspected or proven T3–4 disease and/or regional node involvement, and adjuvant chemotherapy is recommended. Patients with recurrent localized disease should be considered for resection with or without RT.

Patients with metastatic disease in the liver or lung should be considered for surgical resection if they are candidates for surgery and if complete resection (R0) can be achieved. Preoperative che-
Rectal Cancer

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Rectal Cancer

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Rectal Cancer


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### Individual Disclosures for the NCCN Rectal Cancer Panel Members

<table>
<thead>
<tr>
<th>Panel Member</th>
<th>Clinical Research Support</th>
<th>Advisory Boards, Speakers Bureau, Expert Witness, or Consultant</th>
<th>Patent, Equity, or Royalty</th>
<th>Other</th>
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<td>Amgen Inc.; and Bayer HealthCare</td>
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The NCCN guidelines staff have no conflicts to disclose.