NCCN National Comprehensive Cancer Network®

The NCCN

Rectal Cancer

Clinical Practice Guidelines in Oncology™

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Overview

In 2009 an estimated 40,870 new cases of rectal cancer will occur in the United States (23,580 cases in men; 17,290 cases in women). During the same year, an estimated 49,920 people will die from rectal and colon cancers.[1] Although colorectal cancer is ranked as the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States, mortality from colorectal cancer has decreased during the past 30 years. This decrease may be due to earlier diagnosis through screening and better treatment modalities.

The recommendations in these clinical practice guidelines are classified as category 2A except where noted, meaning that there is uniform NCCN consensus, based on lower-level evidence (including

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Key Words

NCCN Clinical Practice Guidelines, rectal neoplasms, colorectal surgery, adjuvant chemotherapy, adjuvant radiotherapy, fluorouracil, neoplasm staging, neoplasm recurrence, irinotecan, oxaliplatin (*JNCCN* 2009;7:838-881)

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

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

Please Note

These guidelines are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Rectal Cancer Guidelines Panel

At the beginning of each NCCN guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and on-line. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Rectal Cancer Guidelines Panel members can be found on page 881. (To view the most recent version of these guidelines and accompanying disclosures, visit the NCCN Web site at www.nccn.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.nccn.org.

clinical experience), that the recommendation is appropriate. The panel unanimously endorses patient participation in clinical trials over standard or accepted therapy. This is especially true for cases of advanced disease and for patients with locally aggressive colorectal cancer who are receiving combined modality treatment. These guidelines overlap considerably with the NCCN Clinical Practice Guidelines in Oncology: Colon Cancer (in this issue; to view the most recent version, visit the NCCN Web site at www.nccn.org). First-degree relatives of patients with newly diagnosed adenomas[2] or invasive carcinoma[3] are at increased risk for colorectal cancer. Therefore, all rectal cancer patients should be counseled regarding their family history as outlined in the NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).

TNM Staging

The NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer adhere to the current TNM staging system included in the 6th edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual (available online, in these guidelines, at www.nccn.org [ST-1]).[4,5] 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) and IIB (T4, N0, M0). Stage III disease is subdivided into IIIA (T1-2, N1, M0), IIIB (T3-4,

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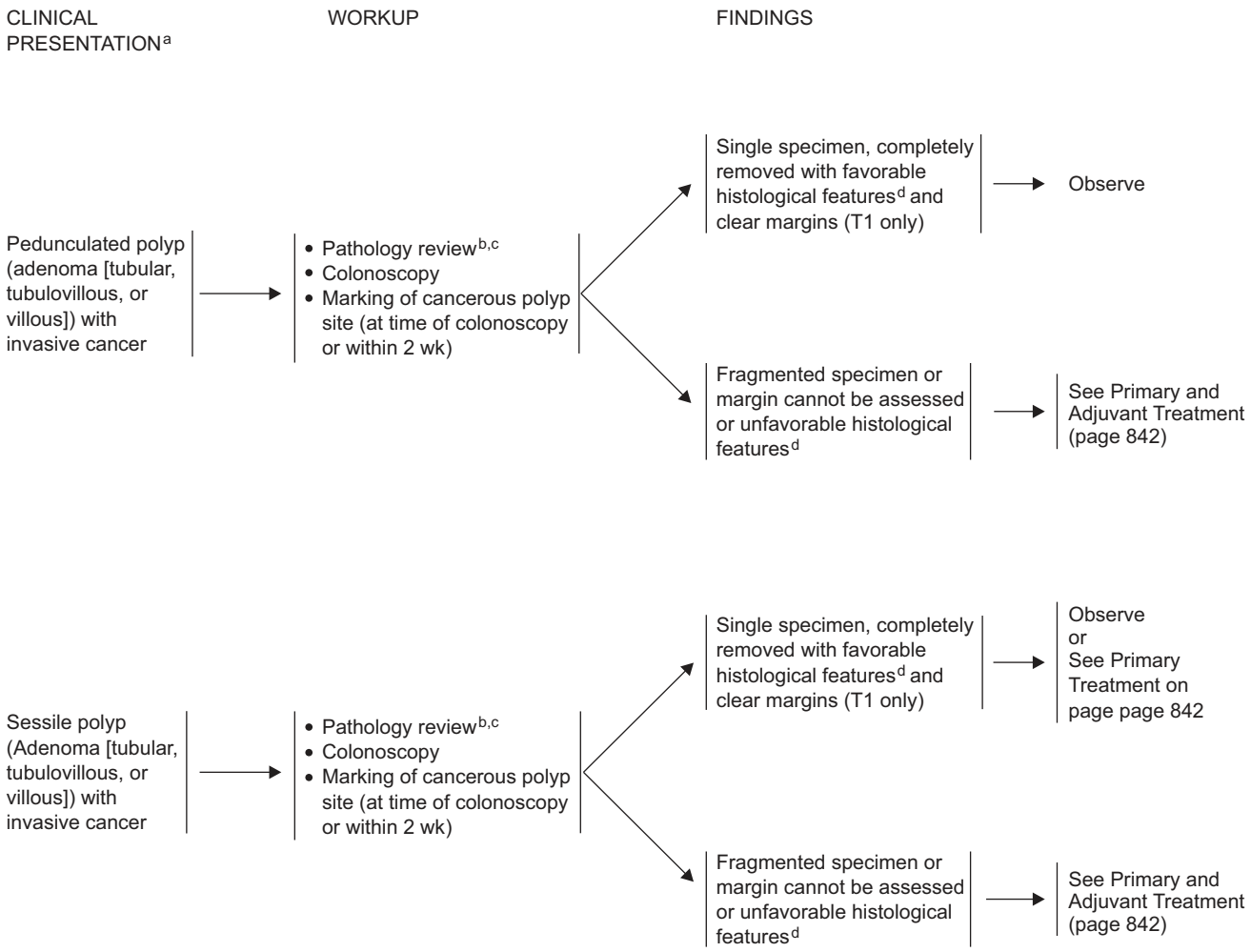

[a] All patients with colon cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP), and attenuated FAP should see the NCCN Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).
[b] Confirm the presence of invasive cancer (pT1). pTis has no biological potential to metastasize.
[c] It has not been established if 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.
[d] See Principles of Pathologic Review (page 848): Endoscopically Removed Malignant Polyp.

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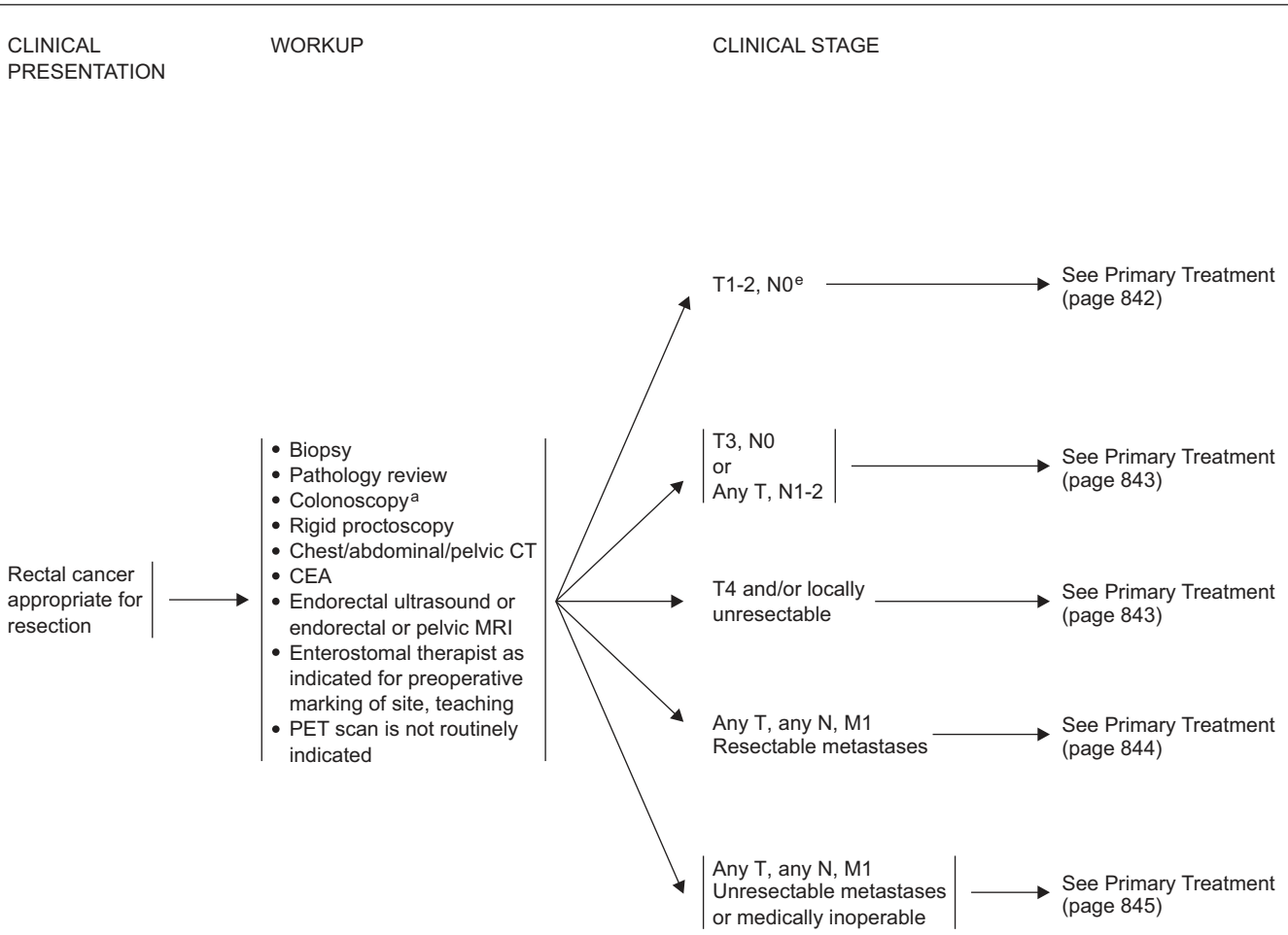
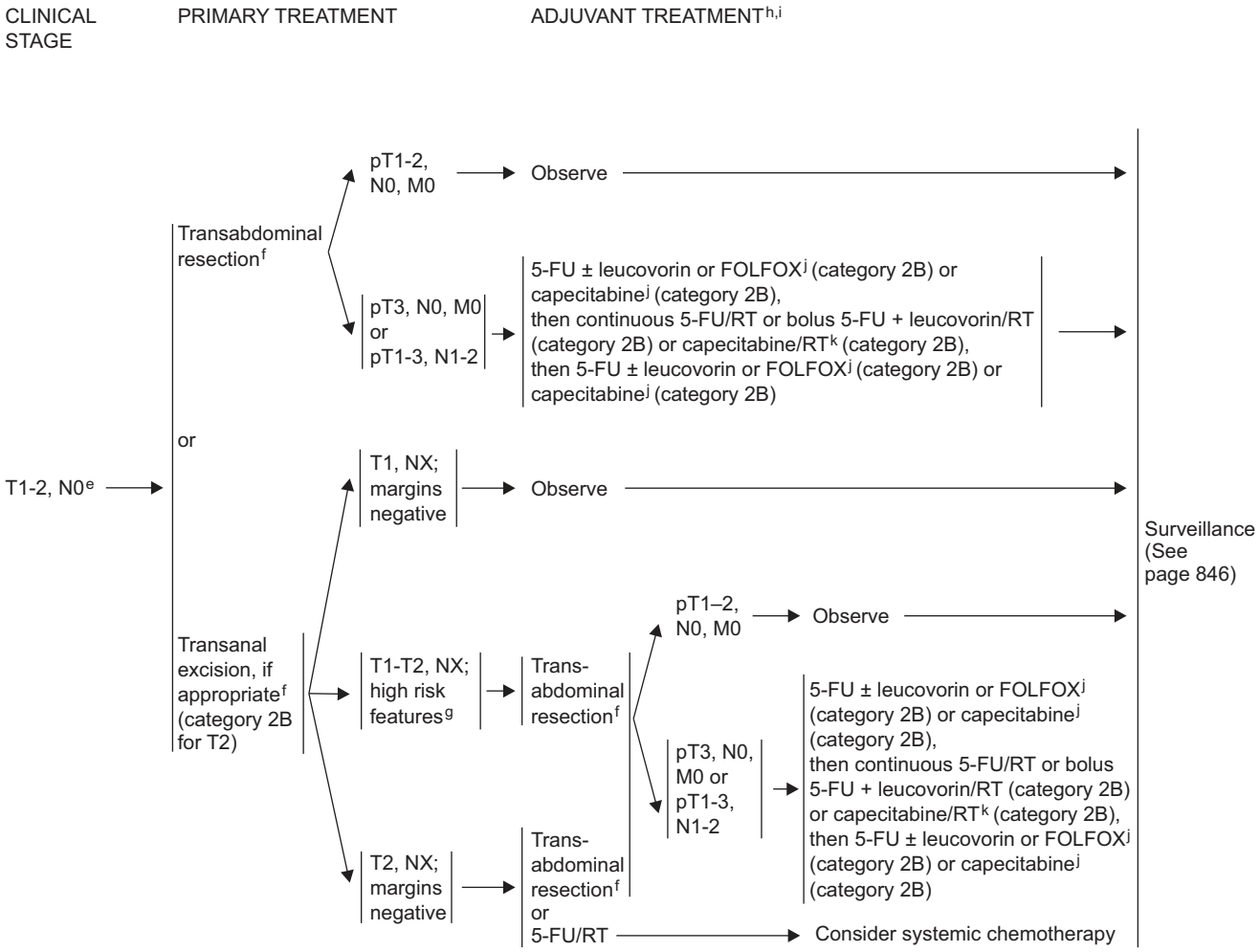


[a] All patients with colon cancer should be counseled for family history. Patients with suspected HNPCC, FAP, and attenuated FAP, see the NCCN Colorectal Cancer Screening Guidelines (to view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org).
[e] T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.



[e] T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.
[f] See Principles of Surgery (pages 851-853).
[g] High risk features include positive margins, lymphovascular invasion, and poorly differentiated tumors.
[h] See Principles of Adjuvant Therapy (pages 854 and 855).
[i] See Principles of Radiation Therapy (page 856).
[j] The use of FOLFOX or capecitabine is an extrapolation from the available data in colon cancer. Trials are still pending in rectal cancer.
[k] Data regarding the use of capecitabine/RT is limited and no phase III randomized data are available. Trials are pending. Kim J-Sang, Kim J-Sung, Cho, M, et al. Preoperative chemoradiation using oral capecitabine in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2002;54:403-408.

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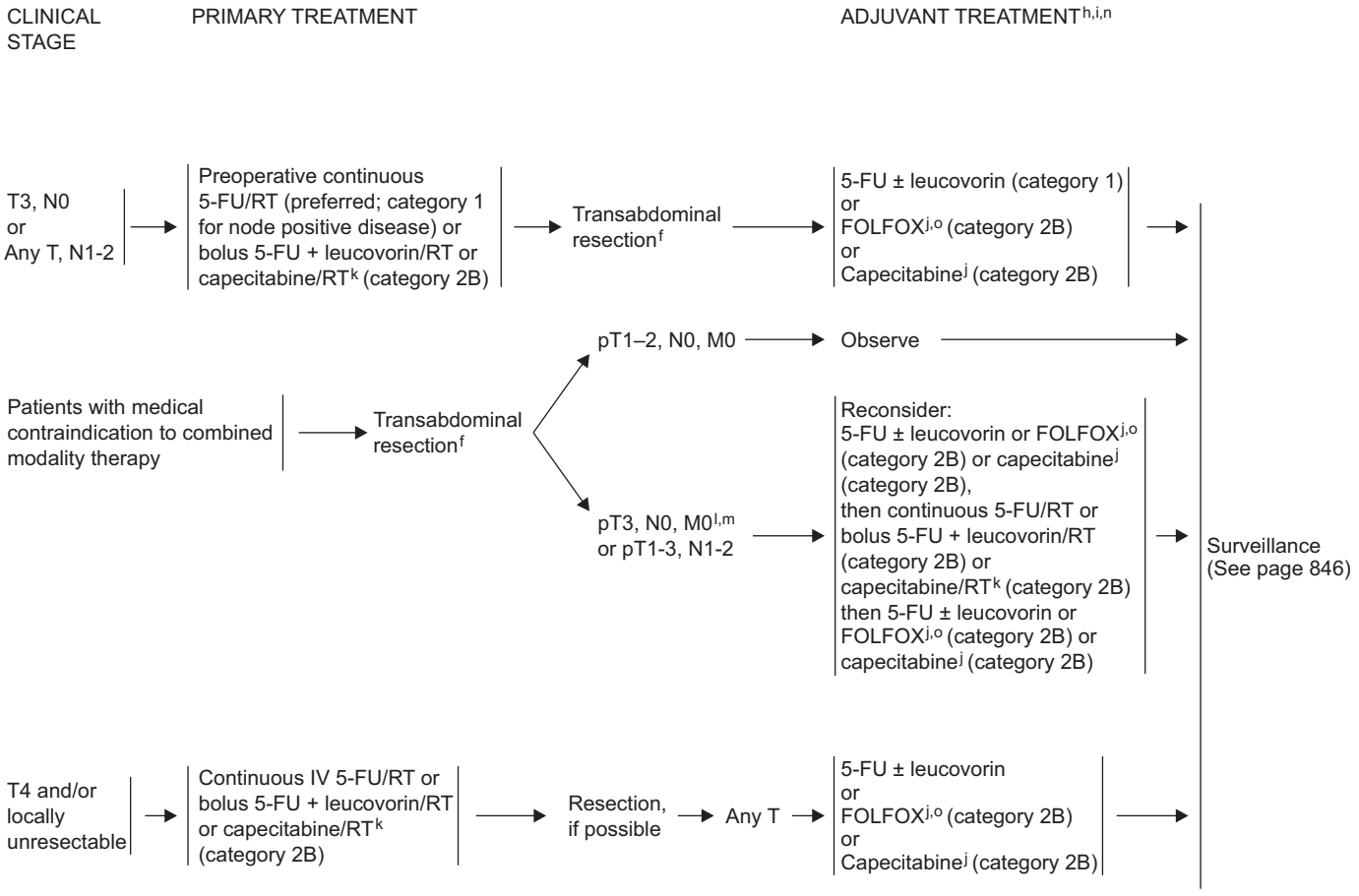

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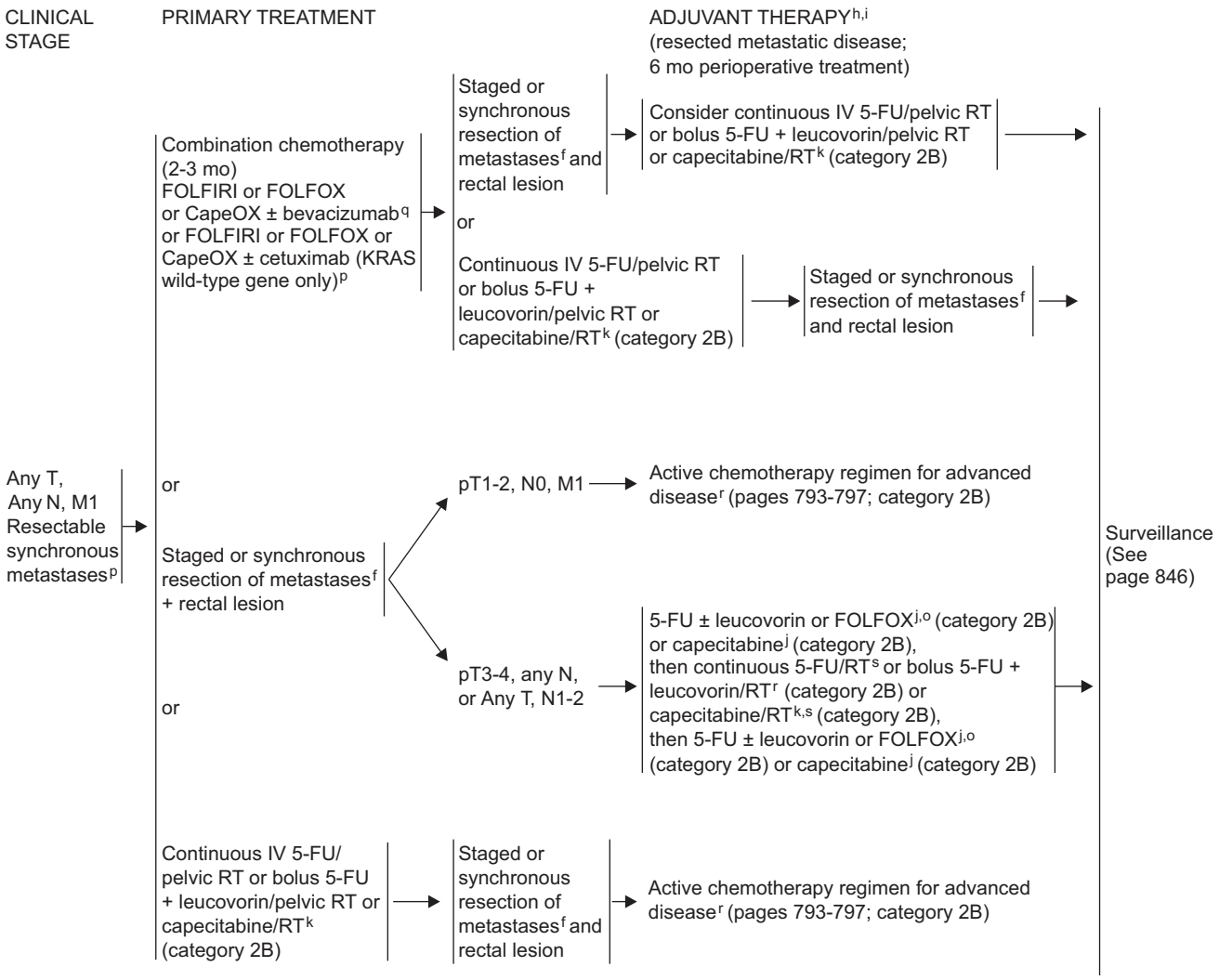
[l] The use of agents other than fluoropyrimidines are not recommended concurrently with RT.
[m] For patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy alone.
[n] Postoperative therapy is indicated in all patients who undergo preoperative therapy, regardless of the surgical pathology results.
[o] An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.



[f] See Principles of Surgery (pages 851-853).
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[o] An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.
[p] Determination of tumor KRAS gene status. See Principles of Pathologic Review: KRAS Mutation Testing (page 849).
[q] The safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6 wk interval between the last dose of bevacizumab and elective surgery. There is an increased risk of stroke and other arterial events especially in patients ≥ 65 years of age. The use of bevacizumab may interfere with wound healing.
[r] FOLFOXIRI is not recommended in this setting.
[s] RT only recommended for patients at relative risk for pelvic recurrence.

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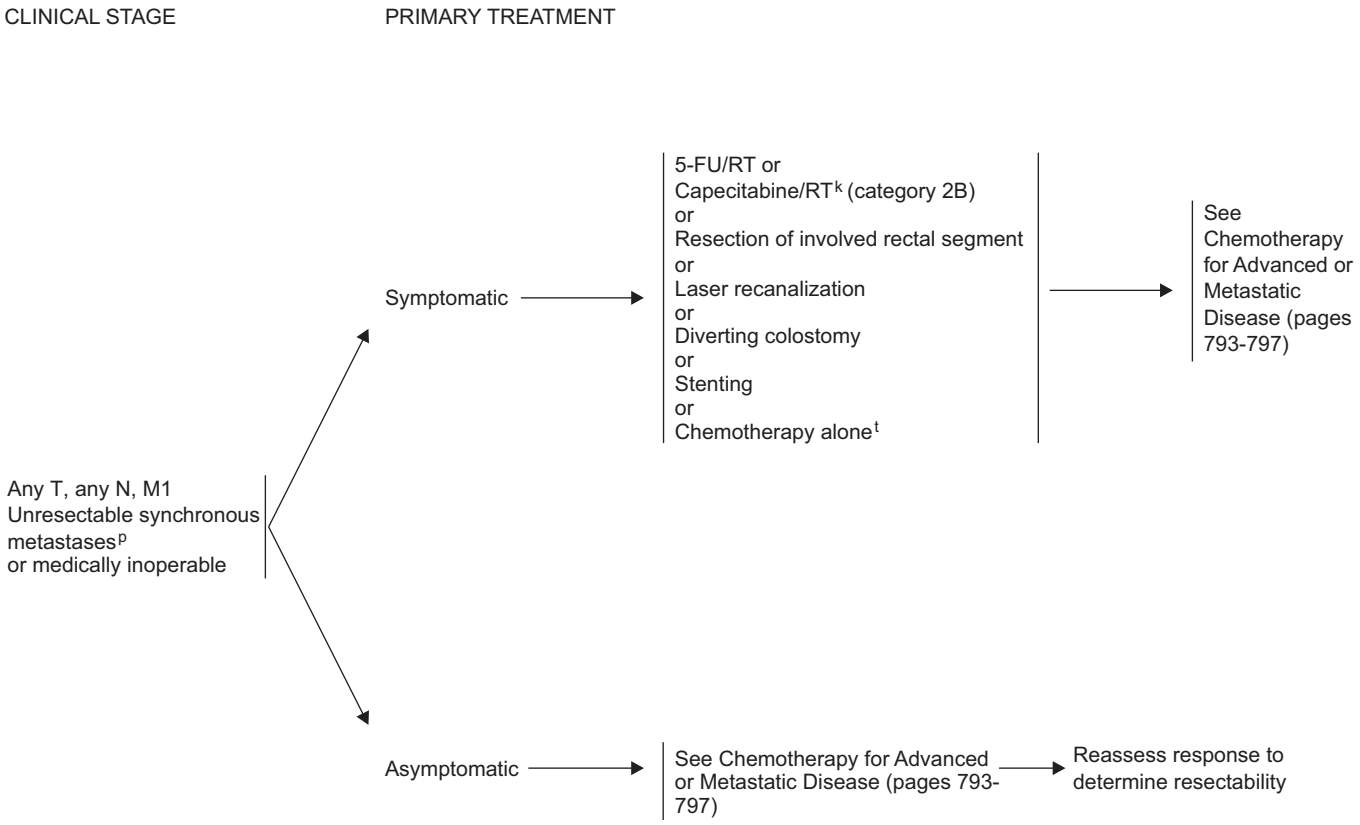

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[p]Determination of tumor KRAS gene status. See Principles of Pathologic Review: KRAS Mutation Testing (page 849)
[t]See Chemotherapy for Advanced or Metastatic Disease (pages 793-797).

SURVEILLANCE

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA[u] 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 x 3 y for patients at high risk for recurrence[v,w]
- Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma,[x] repeat in 3 y, then every 5 y[y]
- Consider proctoscopy every 6 mo x 5 y for patients status post-LAR[z]
- PET scan is not routinely recommended
- See Principles of Survivorship (pages 857 and 858)

→ Serial CEA elevation or documented recurrence → See Workup and Treatment (facing page)

[u] If patient is a potential candidate for resection of isolated metastasis.

[v] Desch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23:8512-8519.

[w] CT scan may be useful for patients at high risk for recurrence (e.g., lymphatic or venous invasion by tumor, or poorly differentiated tumors).

[x] Villous polyp, polyp > 1 cm, or high grade dysplasia.

[y] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865-1871.

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

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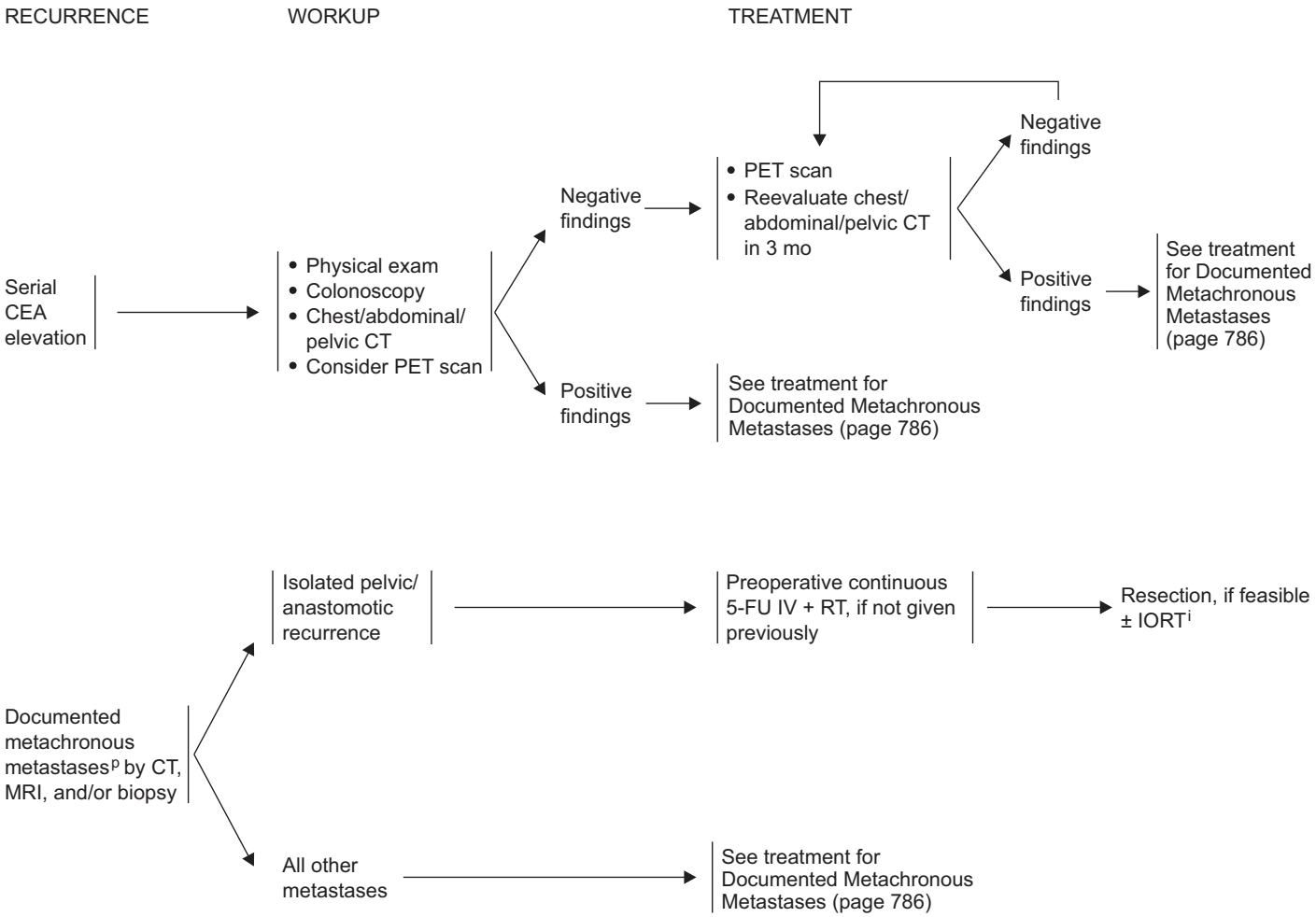

[i] See Principles of Radiation Therapy (page 856).
[p] Determination of tumor KRAS gene status. See Principles of Pathologic Review: KRAS Mutation Testing (page 849).

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 a "malignant polyp."
- Favorable histologic features: grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. No consensus exists regarding 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, or 3) tumor cells present within the diathermy of the transected margin.[1-4]
- Unfavorable histologic features: grade 3 or 4, angiolymphatic invasion, or a "positive margin." See above for definition of a positive margin.
- Controversy exists 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, hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. However, when closely examining 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 or T2 (use caution in T2 because of high recurrence rate; see pages 851-853), grade I or II, no lymphatic or venous invasion, or negative margins.[8,9]
- Unfavorable histopathologic features: > 3 cm in size, T1 or T2, with grade III, lymphovascular invasion, or positive margin.[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 residual tumor in cases treated with neoadjuvant therapy.
  - Number of lymph nodes evaluated and number positive (N). Acellular mucin pools are not considered 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 mm or < 2 mm depending on the publication.[13-14]

  See Staging Table (available online, in these guidelines, at www.nccn.org [ST-1])

Lymph Node Evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.[11,12,15] 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, and > 30.[16-23] 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.[19,22] The number of lymph nodes retrieved can vary with age, gender, tumor grade, and tumor site.[16] For stage II (pN0) colon cancer, if < 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 with surgery alone (13 vs. 19; $P < .05$; 7 vs. 10; $P < .001$).[24,25] If 12 lymph nodes is considered the number needed to accurately identify stage II tumors, then only 20% of cases treated with neoadjuvant therapy had adequate lymph node sampling.[25] To date, the number of lymph nodes needed to accurately stage neoadjuvant-treated cases is unknown. However, the clinical significance of this in the neoadjuvant setting is unknown because postoperative therapy is indicated in all patients who undergo preoperative therapy, regardless of the surgical pathology results.

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PRINCIPLES OF PATHOLOGIC REVIEW (Cont.)

Sentinel lymph node and detection of micrometastasis by immunohistochemistry

- Examination of the sentinal 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. Although studies to date seem promising, there is no uniformity in the definition of what constitutes "true metastatic carcinoma." Confusion arises when isolated tumors cells (ITCs) have been considered micrometastatic disease in contraindication to true micrometastasis (tumor aggregates > 0.2 mm to < 2 mm in size). The significance of detection of single cells by IHC alone is controversial. Some studies have considered these to be micrometastasis; however, “consensus” recommends these be considered ITC and not micrometastatic disease.[26-28] While the 6th edition of the AJCC Cancer Staging[29] manual considers "tumor clusters" < 0.2 mm as ITCs (pN0) and not metastatic carcinoma, some have challenged this. Some investigators believe that size should not effect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (e.g., glandular differentiation, distension of sinus, stromal reaction) should be diagnosed as a lymph node metastasis, regardless of size.[30] Hermanek et al.[31] proposed ITCs be defined as single tumor cells or small clusters (never more than a few cells clumped together) without evidence of extrasinusoidal stromal proliferation or reaction and no contact with or invasion of the vessel (lymphatic) wall.
- 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, ITCs were considered micrometastasis.[32-36]
- Currently, the use of sentinel lymph nodes and detection of cancer cells using IHC alone should be considered investigational, and results used with caution in clinical management decisions.[26-28,32-36]

KRAS Mutation Testing

- Mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to therapy with antibodies targeted to the epidermal growth factor receptor.[37,38]
- Testing for mutations in codons 12 and 13 should be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA – 88) as qualified to perform high complex clinical laboratory (molecular pathology) testing. No specific methodology is recommended (sequencing, hybridization, etc.).
- The testing can be performed on formalin-fixed paraffin embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the KRAS mutations are similar in both specimen types.[39]

Evaluation of Mesorectum (TME)

- The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).[40-42]

See footnotes on page 850

PRINCIPLES OF PATHOLOGIC REVIEW

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Rectal Cancer Version 3:2009

PRINCIPLES OF SURGERY

Transanal excision
- Criteria
  - < 30% circumference of bowel
  - < 3 cm in size
  - Margin clear (> 3 mm)
  - Mobile, nonfixed
  - Within 8 cm of anal verge
  - T1 or T2 (use caution in T2, due to high recurrence rate)
  - Endoscopically removed polyp with cancer or indeterminate pathology
  - No lymphovascular (LVI) or perineural invasion
  - Well to moderately differentiated
  - No evidence of lymphadenopathy on pretreatment imaging
- When the lesion can be adequately identified in the rectum, transanal microsurgery may be used.

Transabdominal resection: abdominoperineal resection or low anterior resection or coloanal anastomosis using total mesorectal excision.
- Management principles
  - The treating surgeon should perform an endoscopy before initiating treatment
  - Removal of primary tumor with adequate margins
  - Laparoscopic surgery is not recommended outside of a clinical trial
  - Treatment of draining lymphatics by total mesorectal excision
  - Restoration of organ integrity, if possible
  - Surgery should occur 5-10 weeks following full-dose 5-1/2 wk 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 (i.e., < 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[1,2]
  - Biopsy or remove clinically suspicious nodes beyond the field of resection if possible
  - Extended resection not indicated in the absence of clinically suspected nodes

See Criteria for Resectability of Metastases on page 852

[1] Gunderson LL, Sargent DJ, Tepper JB, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol 2004;22:1785-1796.
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PRINCIPLES OF SURGERY
CRITERIA FOR RESECTABILITY OF METASTASES

Liver

- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[1,2]
- The primary tumor must have been resected for cure (R0). No unresectable extrahepatic sites of disease should be present.[3-5] Plan for a debulking resection (less than an R0 resection) is not recommended.
- Patients with resectable metastatic disease and primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches using preoperative portal vein embolization or staged liver resections can be considered.
- Hepatic resection is the preferred treatment for resectable liver metastases from colorectal cancer.[6]
- Ablative techniques may be considered alone or in conjunction with resection.[6] All original sites of disease must be amenable to ablation or resection.
- Some institutions use intra-arterial embolization in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, with predominant hepatic metastases (category 3).
- Conformal external beam radiation therapy should not be used unless the patient is symptomatic or in a clinical trial.
- Re-resection can be considered in select patients.[7]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[8-11]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[12-15]
- Reresection can be considered in select patients.[16]
- Ablative techniques can be considered when disease is unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.

Evaluation for conversion to resectable disease

- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.[17-20]
- Diseases with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites must be amenable to resection.[21] Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[22]

PRINCIPLES OF SURGERY
CRITERIA FOR RESECTABILITY OF METASTASES - REFERENCES

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PRINCIPLES OF ADJUVANT THERAPY

Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy. The chemotherapy/RT may be administered either pre- or postoperatively.

Postoperative adjuvant chemotherapy for patients undergoing preoperative chemotherapy/RT:

- 5-FU 380 mg/m^2/d on days 1-5 ± leucovorin IV 20 mg/m^2 on days 1-5 every 28 d x 4 cycles[1,2]
- 5-FU 500 mg/m^2 IV bolus injection 1 h after the start of leucovorin infusion, once a wk for 6 wk x 3 cycles
  Leucovorin 500 mg/m^2 IV over 2 h once a wk for 6 wk x 3 cycles[3,4]
  - A cycle is comprised of 6 wk followed by 2 wk of rest

Postoperative adjuvant regimens for patients not undergoing preoperative therapy:

- 5-FU + leucovorin x 1 cycle, then concurrent chemotherapy/XRT (see below for regimens), then 5-FU/leucovorin x 2 cycles[3,4]
  - 5-FU 500 mg/m^2 IV bolus injection 1 h after the start of the leucovorin infusion, once a wk for 6 wk + leucovorin 500 mg/m^2 IV over 2 h once a wk for 6 wk
  - A cycle consists of 6 wk followed by 2 wk of rest
- 5-FU ± leucovorin x 2 cycles, then concurrent chemotherapy/RT (see below for regimens), then 5-FU ± leucovorin x 2 cycles[1]
  - 5-FU 425 mg/m^2/d and leucovorin 20 mg/m^2/d, days 1-5 and 29-33 before RT. After RT, the regimen is 5-FU 380 mg/m^2/d and leucovorin 20 mg/m^2/d for 5 consecutive days x 2 cycles
- FOLFOX (category 2B)
  - FOLFOX 4
    Oxaliplatin 85 mg/m^2 IV over 2 h, d 1
    Leucovorin 200 mg/m^2 IV over 2 h, d 1 and 2
    Followed on d 1 and 2 by 5-FU 400 mg/m^2 IV bolus,
    then 600 mg/m^2 IV over 22 h continuous infusion
    Repeat every 2 wk[5] to a total of 6 mo perioperative therapy
  - mFOLFOX 6
    Oxaliplatin 85 mg/m^2 IV over 2 h, d 1
    Leucovorin* 400 mg/m^2 IV over 2 h, d 1
    5-FU 400 mg/m^2 IV bolus on d 1, then 1200 mg/m^2/d x 2 days
    (total 2400 mg/m^2 over 46-48 h)† continuous infusion
    Repeat every 2 wk[6,7] to a total of 6 mo perioperative therapy
- Capecitabine[8] (category 2B)
  Capecitabine 1250 mg/m^2 twice daily d 1-14 every 3 wk to a total of 6 mo perioperative therapy

Dosing Schedules for concurrent chemotherapy/RT:

- XRT + continuous infusion 5-FU[9]
  5-FU 225 mg/m^2 over 24 h, 7 d/wk during XRT
- XRT + 5-FU/leucovorin[1]
  5-FU 400 mg/m^2 IV bolus + leucovorin 20 mg/m^2 IV bolus for 4 d during wk 1 and 5 of XRT
- XRT + Capecitabine[10,11] (category 2B)
  Capecitabine 825 mg/m^2 twice daily 5 or 7 d/wk + XRT x 5 wk

*Levo-leucovorin dose is 200 mg/m^2 of levo-leucovorin. The equivalent dose of leucovorin is 400 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24-h units (i.e., 1200 mg/m ^{2}/d NOT 2400 mg/m^2/d over 46 h) to minimize medication errors.

See footnotes on facing page

PRINCIPLES OF ADJUVANT THERAPY
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PRINCIPLES OF RADIATION THERAPY

- RT fields should include the tumor or tumor bed, with a 2- to 5-cm margin, presacral nodes, and internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures. Consider inguinal nodes for tumors invading into the distal anal canal.
- Multiple RT 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.
- Intensity modulated RT (IMRT) or tomotherapy should only be used in the setting of a clinical trial.
- 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 to 9.0 Gy in 3-5 fractions for postoperative radiation.
  - Small bowel dose should be limited to 45 Gy.
- Intraoperative RT (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 to a limited volume could be considered soon after surgery, before adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required.
- 5-FU-based chemotherapy should be delivered as continuous infusion 5 to 7 days with radiation.

Rectal Cancer Version 3:2009

PRINCIPLES OF SURVIVORSHIP
Colorectal Long-term Follow-up Care

Colorectal Cancer Surveillance:
- History and physical every 3-6 mo for 2 y, then every 6 mo for 3 y.
- CEA every 3-6 mo for 2 y, then every 6 mo for 3 y.
- CT scan of abdomen and pelvis annually for 3 y.
- Colonoscopy at 1 y, then as clinically indicated.

Cancer Screening Recommendations:[1]
- Breast Cancer:
  - Periodic self breast exam (SBE) encouraged (optional)
  - Clinical breast exam (CBE) every 1-3 years between ages 20 and 40.
  - Annual mammogram with clinical breast exam beginning at age 40.
  - Women at high risk (> 20% lifetime risk) should get breast MRI and mammogram annually.
  - See NCCN Clinical Practice Guidelines in Oncology: Breast Cancer Screening and Diagnosis.*
- Cervical Cancer:
  - Annual cervical cytology testing with conventional smears or every 2 years with liquid-based cytology for women up to age 30.
  - After age 30, screening may be every 2-3 y if 3 negative/satisfactory annually cervical cytology tests documented.
  - Alternatively, human papilloma virus (HPV) DNA testing for women age 30 and older, combined with cervical cytology.
  - If cervical cytology and HPV DNA testing both negative, testing may be performed every 3 y.
  - Counseling regarding HPV infection.
  - Women older than 70 y with no abnormal testing in past 10 years and 3 normal tests in a row may discontinue screening.
  - Women without a cervix from a total abdominal hysterectomy do not need to be screened.
  - See NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer Screening.*
- Prostate Cancer:
  - Annual prostate-specific antigen (PSA) testing and digital rectal exam (DRE) beginning at age 50.
  - For high-risk men (African-American men and those with a family history of prostate cancer): PSA testing and DRE beginning at age 40.
  - See NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection.*

Management of Late Sequelae of Disease or Treatment:[2-4]
- Chronic diarrhea or incontinence
  - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.
- Oxaliplatin-induced neuropathy
  - Consider the use of analgesics or referral to a pain specialist.
- Bone health after pelvic radiation
  - Consider monitoring of bone density or evaluation for pelvic fractures with pelvic pain if previously received pelvic radiation.
- Sexual dysfunction after pelvic radiation
  - Screen for erectile dysfunction and dyspareunia in those who received pelvic radiation
  - Consider referral to urologist or gynecologist for persistent symptoms.

*To view the most recent version of these guidelines, visit the NCCN Web site at www.nccn.org.

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PRINCIPLES OF SURVIVORSHIP
Colorectal Long-term Follow-up Care

Immunizations:[5]
- Annual trivalent inactivated influenza vaccination
- Pneumococcal vaccination with revaccination as appropriate

Routine Health Monitoring and Screening:
- Cholesterol, blood pressure, and glucose monitoring
- Bone density testing as appropriate
- Routine dental examinations
- Routine sun protection
- Screening for depression as appropriate

Counseling Regarding Healthy Lifestyle and Wellness:[6-9]
- Screening and counseling to maintain a healthy weight
- Screening for physical activity and counseling to adopt a physically active lifestyle (recommended activity: at least 30 min or more of moderate to vigorous physical activity at least 5 d/wk)
- Screening and counseling for alcohol use
- Screening and counseling for tobacco use, with emphasis on smoking cessation
- Counseling regarding healthy diet adoption, with emphasis on plant sources

Prescription for Survivorship and Transfer of Care to Primary Care Physician:[10]
- 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 surveillance recommendations
- Delineate appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist.

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Text continued from p. 839

N1, M0), and IIIC (any T, N2, M0). Stage IV disease is defined as any T, any N, and the presence of 1 or more distant metastases (M1). The difference between N1 and N2 disease is the number of nodes involved; N1 lesions have 1 to 3 positive regional lymph nodes, whereas N2 tumors have 4 or more. In this version of the staging system, smooth metastatic nodules in the pericolic or perirectal fat are considered lymph node metastases and should be included in N staging. Irregularly contoured metastatic nodules in the peritumoral fat are considered vascular invasion. In addition, the 6th edition of the AJCC staging manual[6] suggests that surgeons mark the area of the specimen with the deepest tumor penetration so the pathologist can directly evaluate the status of the resection margins. The surgeon is encouraged to score the completeness of the resection as 1) R0 for complete tumor resection with all margins negative; 2) R1 for incomplete tumor resection with microscopic involvement of a margin; and 3) R2 for incomplete tumor resection with gross residual tumor that was not resected.

Pathology

Pathologic staging information is provided by examination of the surgical specimen (see pages 848–850). Some information that should be detailed in the report of the pathologic evaluation of rectal cancer includes 1) gross description of the tumor and specimen; 2) grade of 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, the peritoneum of an abdominal structure, or non-regional lymph nodes (M); and 7) status of the proximal, distal, and circumferential (radial) margins.[5,7] Prefixes "p" and "yp" denote pathologic staging and pathologic staging after neoadjuvant therapy, respectively.[8]

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.[5] The CRM is the closest radial margin between the deepest penetration of the tumor and the edge of resected soft tissue around the rectum (i.e., the retroperitoneal or subperitoneal aspect of the tumor) 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.[9]

A positive CRM has been defined as tumor within 1 to 2 mm from the transected margin.[10–13] 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, and is an important consideration when post-operative treatment decisions are made.[8,14,15] 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 who had received preoperative therapy compared with those undergoing surgery as initial therapy.[16] Additional components of the pathological evaluation of the surgical specimen after a total mesorectal excision (TME) are described under "Surgical Approaches".

The AJCC and College of American Pathologists (CAP) recommend evaluating a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.[5,6] The number of lymph nodes retrieved can vary with age, gender, and tumor grade or site.[17,18] The extent and quality of surgical resection and pathologic review of the specimen can also have an impact on the node harvest.[19] The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify stage II rectal cancer. 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 reported 14 and more than 10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.[20,21]

Furthermore, the mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated with surgery alone (13 vs. 19, $P < .05$; 7 vs. 10, $P \leq .0001$).[22,23] A recent retrospective analysis of data from patients with T3 or T4 and/or lymph node-positive rectal cancer in the Intergroup 0114 trial showed *lymph node ratio* (LNR), the number of

positive lymph nodes divided by the total number, to be a strong predictor of survival.[24] Nevertheless, the panel does not consider determination of LNR to be a substitute for an adequate lymph node evaluation.

Results of studies evaluating the sentinel node for micrometastatic disease through hematoxylin and eosin (H&E) staining to identify small foci of tumor cells, or identification of particular tumor antigens through immunohistochemical (IHC) analysis, have been reported.[25,26] Although results of some of these studies seem promising, there is no uniformity in the definition of "true" clinically relevant metastatic carcinoma. Some studies have considered detection of single cells by IHC as well as isolated tumor cells (ITC) to be micrometastasis.[27,28] In addition, results of one study demonstrated that, after neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.[29] Presently, the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational, and the results should be used with caution in clinical management decisions.

A sizable body of literature has shown that mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to cetuximab or panitumumab therapy.[30–40] Therefore, the panel strongly recommends genotyping tumor tissue (either primary tumor or metastasis) in all patients with stage IV metastatic colorectal cancer. The recommendation for KRAS testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting but, this early establishment of KRAS status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non-time–sensitive manner. Thus, the patient and provider can discuss the implications of a KRAS mutation, if present, while other treatment options still exist. KRAS mutations are early events in colorectal cancer formation, and a tight correlation exists between mutation status in the primary tumor and metastases.[41,42] For this reason, KRAS genotyping can be done on archived specimens of either the primary tumor or metastasis. Fresh biopsies should not be obtained solely for KRAS genotyping if an archived specimen from either the primary tumor or metastasis is available. The panel recommends that KRAS gene testing be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing (see pages 848–850).

Clinical Presentation and Treatment

Management of Polypoid Cancer

Text describing the management of polypoid cancer is available in the Colon Cancer Guidelines, in this issue, on page 804 or online in these guidelines at www.nccn.org.

Management of Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge by rigid proctoscopy.[50] Some support for this definition comes from the study of Kapiteijn et al.[51] 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 receiving radiotherapy and surgery were seen 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.[52]

Determination of an optimal treatment plan for an individual patient with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (i.e., 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 and 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.[53] 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.[54,55] Careful patient selection for particular treatment options and the use of sequenced multimodality therapy for selected patients that combines chemoradiation (chemoRT) with operative treatment as part of the treatment regimen is recommended.

Clinical Evaluation/Staging: The initial clinical workup of patients with rectal cancer provides important preoperative information on the clinical stage of disease (see page 841). Because the clinical stage of disease is used to direct decisions on primary treatment, including surgical intent (e.g., curative or palliative) and approaches, and whether to recommend preoperative chemoRT, the implications of clinically under- or overstaging rectal cancer can be substantial.

Patients who present with rectal cancer appropriate for resection require complete staging evaluation, including total colonoscopy to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum, rigid proctoscopy to provide a determination of the location of the cancer (i.e., measurement of the distance of the tumor from the anal verge should be performed by the responsible surgeon using rigid proctoscopy), and a complete physical examination, including assessment of performance status to determine operative risk, carcinoembryonic antigen (CEA) and baseline CT scans of the chest, abdomen, and pelvis (see page 841). The panel consensus is that a PET scan is not routinely indicated at baseline in the absence of evidence of synchronous metastatic disease. In addition, the accessibility of rectal cancer to evaluation by certain imaging modalities, such as endoscopic ultrasound and MRI, makes preoperative assessments of tumor penetration depth and presence of local lymph nodal metastases possible.[56]

Additional information regarding the extent of disease and the occurrence of distant metastases can be determined preoperatively through CT scans. Thus, endorectal ultrasound or endorectal or pelvic MRI and CT scans of the chest, abdomen, and pelvis are recommended for the preoperative staging of rectal cancer.

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 propia (94%), although endoscopic ultrasound was found to be more specific than MRI in the evaluation of local tumor invasion (86% vs. 69%).[57] Only a limited number of studies using CT for T-staging have been performed, and it is not currently considered to be an optimal method for staging the extent of tumor penetration.[57,58] Accurate assessment of nodal status is one of the greatest challenges in the preoperative staging of rectal cancer. In the meta-analysis by Bipat et al.,[57] the sensitivities and specificities of the 3 imaging modalities for accurately evaluating lymph node involvement were 55% and 74% for CT, 67% and 78% for endoscopic ultrasound, and 66% and 76% for MRI.

Results from another recent meta-analysis of 84 articles indicated that none of the 3 imaging modalities were significantly superior to another for accurately determining tumor N-stage.[59] Disadvantages of endoscopic ultrasound and MRI include a high degree of operator dependence.[57] 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 the prediction of the CRM before radical surgery.[58–60]

Clinical staging is also based on histopathologic examination of the specimen obtained via biopsy or local excision (e.g., 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 the primary rectal cancer lesion.[61] These methods include local procedures, such as polypectomy, transanal excision and transanal microsurgery, and radical procedures involving a transabdominal resection (e.g., low anterior resection [LAR], TME with coloanal anastomosis, or abdominoperineal resection [APR]; see pages 851–853).

Transanal excision may be appropriate for selected early stage cancers. Small (< 3 cm), well to moderately differentiated tumors that are within 8 cm of the anal verge, limited to less than 30% of the rectal circumference, and for which no evidence of nodal involvement (category 2A) is seen can be approached with transanal excision with negative margins. Transanal endoscopic microsurgery (TEM) can facilitate excision of small tumors through the anus that are located higher up in the rectum. Both transanal excision and TEM involve a full thick-

ness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (> 3 mm) deep and mucosal margins are required. Tumor fragmentation should be avoided. The excised specimen should be oriented and pinned before fixation and brought to the pathologist by the surgeon (i.e., to facilitate an oriented histopathologic evaluation of the specimen).

Advantages of a local procedure include minimal morbidity (e.g., a sphincter-sparing procedure) and mortality and rapid postoperative recovery.[53,62] If pathologic examination reveals adverse features such as high grade, positive margins, lymphovascular invasion (LVI), or perineural invasion, 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.[62]

Limitations of a transanal excision include the absence of pathologic staging of nodal involvement. Further, there is evidence to indicate that lymph node micrometastases are both more common in early rectal lesions and unlikely to be identified by endorectal ultrasound.[63] These observations may underlie the findings of a recent retrospective study of 282 patients undergoing either transanal excision or radical resection for T1 rectal cancer from 1985 through 2004, which showed respective local recurrence rates of 13.2% and 2.7% for these 2 groups.[64]

Patients with rectal cancer who do not meet requirements for local surgery should be treated with transabdominal resection. Organ-preserving procedures that maintain sphincter function are preferable but not possible in all cases. For lesions in the mid to upper rectum, an LAR extended 4 to 5 cm below the distal edge of tumor, followed by creation of a colorectal anastomosis, is the treatment of choice. Where creation of an anastomosis is not possible, colostomy is required.

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer are limited.[65,66] In the CLASICC trial comparing laparoscopically-assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.[65] No significant differences in local recurrence, disease-free survival (DFS), or overall survival were seen between the 2 groups of patients with rectal cancer based on surgical approach. However, factors that may confound conclusions drawn from randomized studies comparing open surgery with laparoscopically-assisted surgery for colorectal cancer have been described,[67] and laparoscopic surgery for rectal cancer is not recommended by the panel outside of a clinical trial.

For low rectal lesions, APR or TME with coloanal anastomosis is required. 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.[53,68] In cases in which anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis. Pathologists play a key role in evaluating the surgical specimen after TME, which includes a macroscopic assessment of both external appearance/completeness and the CRM (see pages 848–850).[69,70] Detailed descriptions of how the quality of the mesorectal specimens should be scored were provided in the Dutch Rectal Cancer Trial and those guidelines are endorsed by the NCCN panel.[70]

An APR involves en bloc resection of the rectosigmoid, rectum, and anus, as well as the surrounding mesentery, mesorectum, and perianal soft tissue and necessitates creation of a colostomy.[71] An APR is necessary in cases in which a margin-negative resection of the tumor would result in loss of anal sphincter function resulting in incontinence. Although preoperative chemoRT may result in tumor downsizing and a decrease in tumor bulk (see following section), tumor location is not altered. Although sphincter preservation may become possible in cases in which initial tumor bulk prevented consideration of such surgery but exposure to the tumor is improved by chemoRT, an APR should be performed when tumor directly involves the anal sphincter or the levator muscles.

Recent comparisons of the outcomes of patients undergoing an APR versus a LAR in the treatment of rectal cancer have shown those treated with an APR to have worse local control and overall survival.[72,73] Whether these differences can be attributed to the surgical procedure alone, patient- and tumor-related characteristics, or some combination of these factors is presently unclear. However, results from a recent retrospective study of 3633 patients with T3 or 4 rectal cancer tumors included in 5 large European trials suggest an association between the APR procedure itself and the increased risks for recurrence and death.[73]

The lymphatic drainage regions of rectal tumors are influenced by their position in the rectum. More distal tumors are more likely to be characterized by upward and lateral lymphatic drainage, whereas the likelihood of only upward mesorectal drainage is much higher for more proximal tumors.[74] The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.[75] The panel does not recommend extension of nodal dissection beyond the field of resection (e.g., into the distribution of iliac lymph nodes) unless these nodes are clinically suspicious.

Neoadjuvant/Adjuvant Therapy: Neoadjuvant/adjuvant therapy of rectal cancer often includes locoregional treatment due to the relatively high risk of locoregional recurrence. This risk is associated with the close proximity of the rectum to pelvic structures and organs, the absence of a serosa surrounding the rectum, and technical difficulties associated with obtaining wide surgical margins at resection. In contrast, adjuvant treatment of colon cancer is more focused on preventing distant metastases since this disease is characterized by lower rates of local recurrence.

Combined-modality therapy consisting of surgery, radiation therapy (RT), and chemotherapy is recommended for most patients with stage II (node-negative disease with tumor penetration through the muscle wall) or stage III rectal cancer (node-positive disease without distant metastasis). Use of perioperative pelvic RT in the treatment of patients with stage II to III rectal cancer continues to evolve. Concurrent fluoropyrimidine-based chemotherapy is recommended with radiation.

Ionizing radiation to the pelvis provides local tumoricidal therapy. Putative advantages to preoperative radiation are related to both tumor response and normal tissue.[76,77] Reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (i.e., the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected). One disadvantage of using preoperative RT is the possibility of over-treating early stage tumors that do not require adjuvant radiation.[77–79] Improvements in preoperative staging techniques, such as endoscopic ultrasound and CT scans, allow for more accurate staging, although the risk of overstaging disease has not been eliminated.[80]

The results of the Swedish Rectal Cancer Trial evaluating the use of short course (5-day) RT administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence compared with surgery alone.[81] However, although a number of other studies investigating the effectiveness of preoperative or postoperative RT in patients with rectal cancer staged as T1 to 3 have shown improvements in local control of disease, overall survival was not shown to be significantly affected.[51,82,83] A multicenter, randomized study of 1350 patients with stage II to III rectal cancer compared short-course preoperative RT with a postoperative approach that included chemoRT in selected patients (i.e., those with a positive CRM after resection) and no RT in patients without evidence of residual disease after surgery. The study indicated that patients in the preoperative RT arm had significantly lower local recurrence rates and a 6% absolute improvement in 3-year DFS ($P = .03$).[84] No difference in overall survival has been observed between the 2 arms. Currently, however, short-course RT for the treatment of rectal cancer is not widely practiced in the United States.

A number of randomized trials evaluated the effectiveness of chemoRT administered either preoperatively after clinical evaluation and staging (e.g., T3-4 by endoscopic ultrasound) or postoperatively after pathologic staging of rectal cancer as T3 and/or N1 or 2. Putative benefits of addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (i.e., 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 or 4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative RT alone or preoperative concurrent chemoRT and 5-fluorouracil (5-FU)/leucovorin (LV), no difference in overall survival or sphincter preservation was seen, although patients receiving chemoRT were significantly more likely to exhibit a pathologic complete

response (11.4% vs. 3.6%; $P < .05$) and grade 3 to 4 toxicity (14.6% vs. 2.7%; $P < .05$) and less likely to exhibit local recurrence of disease (8.1% vs. 16.5%; $P < .05$).[85] These conclusions have been supported in a recent systematic review which included 4 randomized controlled trials.[86]

A large prospective, randomized trial from The German Rectal Cancer Study Group compared preoperative versus postoperative chemoRT in the treatment of clinical stage II or III rectal cancer.[77] 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, although overall survival was similar in the 2 groups. Preliminary results of a phase III trial that included an evaluation of the addition of chemotherapy to preoperative RT in patients with T3 or T4 resectable rectal cancer showed that 5-FU/LV chemotherapy enhanced the tumorocidal effect of RT when used concurrently. Significant reductions in tumor size, pTN stage, and lymphatic, vascular, and perineural invasion rates were seen with combined-modality therapy compared with RT and surgery without chemotherapy.[87,88] More mature results from this trial, 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.[89] Although local recurrence rates were significantly lower in the groups receiving RT followed by chemotherapy, concurrent chemoRT, or concurrent chemoRT plus chemotherapy compared with 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 with ypT0-2 showed significant benefit in DFS and overall survival from adjuvant chemotherapy.[90] These findings may indicate that patients are more likely to benefit from adjuvant therapy if their disease can be downstaged using chemoRT. Although reports from at least one of these studies has indicated that preoperative chemoRT is associated with increased rates of sphincter preservation in rectal cancer patients,[77] this conclusion was not supported by 2 recent meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.[91,92]

Combined-modality therapy has been associated with decreased rates of local recurrence for rectal cancer but with increased toxicity (e.g., radiation-induced injury, hematologic toxicities) relative to surgery alone.[9,93] It has been suggested that some patients with disease at lower risk of local recurrence (e.g., 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.[9,94,95] Nevertheless, results from a recent retrospective analysis showed the risk of locoregional recurrence to be significantly higher in patients with pT3N0 rectal cancer who did not undergo RT.[96] In addition, 22% of 188 patients clinically staged with T3N0 rectal cancer using either esophageal ultrasound or MRI who subsequently received preoperative chemoRT had positive lymph nodes after pathologic review of the surgical specimens, according to results of a recent retrospective multicenter study.[80]

Regarding the type of chemotherapy administered concurrently with RT, results from the Intergroup 0114 trial showed bolus 5-FU as part of adjuvant therapy for rectal cancer to be non-inferior to bolus 5-FU plus LV.[94] After a median follow-up of 4 years, neither the rate of local control nor survival differed among 3 different combinations of modulated 5-FU chemotherapy. The equivalence of bolus 5-FU/LV and infusional 5-FU in concurrent chemoRT for rectal cancer is supported by the results of a phase III trial (median followup, 5.7 years) in which similar outcomes in overall and relapse-free survival were seen when a continuous infusion of 5-FU or bolus 5-FU plus LV was administered concurrently with postoperative RT, although hematologic toxicity was greater in the group of patients receiving bolus 5-FU.[97] However, results from an earlier trial from the North Central Cancer Treatment Group (NCCTG) showed that postoperative administration of continuous infusion 5-FU during pelvic irradiation was associated with longer overall survival when compared with bolus 5-FU.[98] Most of the patients in this study had node-positive disease.

Postoperative chemoRT regimens commonly employ a "sandwich" approach whereby chemotherapy (typically 5-FU based) is administered before

and after the chemoRT regimen.[94,97,98] The use of FOLFOX or capecitabine chemotherapy before and after postoperative chemoRT is an extrapolation of the available data in colon cancer.[99,100]

During administration of RT, multiple RT fields should include the tumor or tumor bed with a 2- to 5-cm margin, presacral nodes, and internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures, and clinicians should also consider inclusion of the inguinal nodes for tumors invading into the distal anal canal. Recommended doses of radiation are typically 45 to 50 Gy, with the exceptions of unresectable cancers for which doses higher than 54 Gy may be required and irradiation of the small bowel for which the dose should be limited to 45 Gy. Intensity-modulated radiotherapy which uses computer-imaging to focus RT to the tumor site and potentially decrease toxicity to normal tissue,[101–103] should be used in the context of a clinical trial only. As an additional boost, intraoperative radiotherapy,[104–106] which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment, should be considered preoperatively for patients with T4 tumors or recurrent cancers to facilitate resection.

Coordination of preoperative therapy, surgery, and adjuvant chemotherapy is important. For patients treated with preoperative chemoRT, the panel recommends an interval of 5 to 10 weeks after completion of full-dose 5.5-week chemoRT and before performance of 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,[107–109] it is unclear whether this is associated with clinical benefit. Nevertheless, when longer intervals are clinically necessary, they do not appear to increase the blood loss, time associated with surgery, or positive margin rate.[110]

Adjuvant chemotherapy for approximately 4 months is recommended for all patients with stage II or III rectal cancer after neoadjuvant chemoRT/surgery regardless of the surgical pathology results. However, few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well defined. Evaluation of adjuvant chemotherapy with 5-FU/LV alone versus postoperative RT followed by adjuvant chemotherapy with 5-FU/LV in patients with stage II to III rectal cancer in the National Surgical Breast and Bowel Project (NSABP) R-02 trial showed a significant decrease in local recurrence rate in the group receiving adjuvant chemotherapy after RT compared with the group receiving adjuvant chemotherapy alone.[111] However, no benefit of adding 5-FU–based adjuvant chemotherapy to preoperative chemoRT with respect to rate of local recurrence was observed in the EORTC Radiotherapy Group trial 22921 (hazard ratio = 0.87; 95% CI, 0.72–1.04; P = .13) when the DFS of patients receiving adjuvant chemotherapy after preoperative RT (with or without 5-FU–based chemotherapy) was compared with DFS of patients who underwent preoperative RT (with or without 5-FU–based chemotherapy) but did not receive adjuvant 5-FU–based chemotherapy.[89] However, patients responding to preoperative chemoRT had a survival benefit with adjuvant chemotherapy.

Most of the support for use of FOLFOX or capecitabine as adjuvant chemotherapy in rectal cancer is an extrapolation from the data available for colon cancer.[99,100] The phase III ECOG E3201 trial is investigating the effect of adding either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) to 5-FU/LV–based adjuvant chemotherapy administered to stage II to III rectal cancer patients after either preoperative or postoperative chemoRT. Early reports indicate that adjuvant FOLFOX can be safely used in this patient population.[112] Nevertheless, the duration of treatment with adjuvant FOLFOX in rectal cancer is still unclear.[113,114]

In the MOSAIC trial, patients with stage II or III colon cancer were treated with 6 months of adjuvant FOLFOX. Some justification for a shorter course of adjuvant FOLFOX in rectal cancer (i.e., 4 months) can be provided when preoperative chemoRT is administered. In addition, the NSABP-07 trial showed similar DFS benefits to those reported in the MOSAIC trial with only 9 cycles of an oxaliplatin-containing adjuvant regimen.[114] A summary of ongoing clinical trials in early-stage rectal cancer has been presented.[115]

Treatment of Nonmetastatic Rectal Cancer: *Recommendations for Patients With T1 and T2 Lesions:* Node-negative T1 and T2 lesions are treated using transabdominal resection or transanal excision (cat-

egory 2B for T2), if appropriate (see page 842). This recommendation is category 2B for node-negative T2 tumors because local recurrence rates of 11% to 45% have been observed for T2 lesions after local excision alone.[53,116,117] In selected lesions that are staged using endoscopic ultrasound or MRI as T1 to 2, N0 and without adverse pathologic features (e.g., no LVI or perineural invasion, < 3 cm, well to moderately differentiated), local excision with negative margins may give results comparable to transabdominal resection.[118] No additional therapy is recommended for patients with well-differentiated T1 cancers. If pathology review after local excision reveals a poorly differentiated histology, positive margins, or LVI, then a transabdominal re-resection should be performed. T2 cancers excised with negative margins and no poor prognostic factors should be treated with transabdominal resection or adjuvant 5-FU/RT. Systemic chemotherapy should be considered as an adjuvant treatment for those patients who receive adjuvant chemoRT without additional surgery to avoid the risk of undertreatment as the lymph node status is unknown.

For patients with T1 to T2 lesions not amenable to local excision, a transabdominal resection is required. No adjuvant therapy is indicated for patients with pathologic findings of T1 or T2 lesions. Patients with pathologic lymph node-negative T3 lesions (pT3, N0, M0) or pathologic lymph node-positive lesions (pT1-3, N1-2) should receive a "sandwich regimen" consisting of adjuvant chemotherapy with 5-FU with or without LV or FOLFOX (category 2B) or capecitabine (category 2B), followed by concurrent 5-FU/RT (continuous infusion [category 2A] or bolus infusion along with LV [category 2B]) or capecitabine/RT (category 2B), then 5-FU with or without LV or FOLFOX (category 2B) or capecitabine (category 2B; see pages 854 and 855, and 856). The panel recommends postoperative therapy for a total duration of 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. However, most patients are not likely to be part of this subset.

Recommendations for Patients with T3 Lesions and Lesions with Nodal Involvement: Patients clinically staged as having resectable T3, N0 or any T, N1-2 lesions should initially be treated with preoperative combined-modality therapy (see pages 843, 854 and 855, and 856). Upfront surgery should be reserved for patients with medical contraindications to chemoRT. Preoperative continuous infusional 5-FU/RT is the preferred treatment option (category 1 for node positive disease). Alternative regimens include bolus 5-FU/LV/RT (category 2A) or capecitabine/RT (category 2B). Patients who receive preoperative radiotherapy should undergo transabdominal resection 5 to 10 weeks after completion of neoadjuvant therapy. The panel recommends approximately 6 months total duration of pre- and postoperative chemotherapy (regardless of surgical pathology results) with 5-FU with or without LV (category 1 for T3, N0 or any T, N1-2 tumors), FOLFOX (category 2B), or capecitabine (category 2B).

Patients with disease characterized as T3, N0 or any T, N1-2 disease initially treated by transabdominal resection with subsequent pathologic staging of disease as pT1-2, N0, M0 can be followed up with observation only. Patients with disease staged as pT3, N0, M0 or pT1-3, N1-2, M0 after initial treatment by transabdominal resection should receive approximately 6 months postoperative chemotherapy with 5-FU with or without LV, FOLFOX (category 2B), or capecitabine (category 2B), followed by concurrent 5-FU/RT (5-FU as continuous infusion [category 2A] or bolus infusion with LV [category 2B]) or capecitabine/RT (category 2B), then 5-FU with or without LV (category 2A), FOLFOX (category 2B), or capecitabine (category 2B). For some patients with pathologic evidence of proximal T3, N0, M0 disease with clear margins and favorable prognostic features after transabdominal resection, the incremental benefit of RT is probably small, and chemotherapy alone can be considered, although this subset of patients is small.

Recommendations for Patients with T4 Lesions and/or Locally Unresectable Disease: Patients with T4 or locally unresectable disease are treated with preoperative continuous infusional 5-FU/RT (category 2A) or bolus 5-FU with LV/RT (category 2A) or capecitabine/RT (category 2B; see pages 843, 854 and 855, and 856). If possible, resection should be considered after preoperative chemoRT. Adjuvant therapy to complete 6 months with either 5-FU with or without LV (category 2A), FOLFOX (category 2B), or capecitabine (category 2B) is recommended regardless of the surgical pathology results.

Treatment of Metastatic Disease: Approximately 50% to 60% of patients diagnosed with colorectal cancer will develop colorectal metastases.[119,120] Patients with stage IV (any T, any N, M1) colorectal cancer or recurrent disease can present with synchronous liver or lung metastases or abdominal peritoneal metastases. Approximately 15% to 25% of patients with colorectal cancer present with synchronous liver metastases, although 80% to 90% of these patients are initially evaluated to have unresectable metastatic liver disease.[119,121–123] Metastatic disease more frequently develops metachronously after treatment for colorectal cancer, with the liver as a common site of involvement.[124] Some evidence is available that indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal disease that develops metachronously. In one retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (P = .008) and bilobar metastases (P = .016) compared with patients diagnosed with metachronous liver metastases.[125] For patients presenting with synchronous metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver.[126]

It has been estimated that over half of patients who die of colorectal cancer have liver metastases at autopsy and that metastatic liver disease is the cause of death in the majority of these patients.[127] Results from reviews of autopsy reports of patients dying from colorectal cancer showed that the liver was the only site of metastatic disease in one third of patients.[121] Furthermore, in a number of studies, 5-year survival rates for patients with metastatic liver disease not undergoing surgery have been quite low.[119,128] However, studies of selected patients undergoing surgery to remove colorectal liver metastases have demonstrated that cure is possible in this population and should be the goal for many patients with colorectal metastatic liver disease.[119,129]

Recent reports have shown 5-year survival rates following resection of hepatic colorectal metastases exceeding 50%.[130,131] Therefore, decisions relating to patient suitability, or potential suitability, and subsequent selection for metastatic colorectal surgery are critical junctures in the management of metastatic colorectal liver disease.[132]

The criteria for determining patient suitability for resection or surgical cure of metastatic disease are evolving, and the emphasis is increasingly on the likelihood of achieving negative surgical margins while maintaining adequate liver reserve, as opposed to other criteria, such as the number of liver metastases present.[133–136] Resectability differs fundamentally from end points that focus more on palliative measures such as response and DFS. Instead, the resectability end point is focused on the potential of surgery to cure the disease,[137] since partial liver resection or debulking has not been shown to be beneficial.[120,135] Approaches used in the surgical treatment of liver metastases include simultaneous resections of colorectal cancer and synchronous liver metastases,[138] preoperative portal vein embolization for the purpose of increasing the volume and function of the portion of the liver which will remain postsurgically,[139] and hepatic resection performed in 2 stages for bilobar disease.[140]

Resection is the standard of care for local treatment of metastatic disease that is initially resectable or converted to a potentially curable status after chemotherapy.[141] However, some patients in this group who cannot undergo resection due to comorbidity, location of the metastatic lesions (i.e., adjacent to a major hepatic vein or the vena cava), or an estimate of inadequate liver volume after resection may be candidates for ablation therapy.[142] A number of retrospective studies have compared radiofrequency ablation (RFA) and liver resection in the treatment of liver metastases,[143–145] although RFA has not been well studied in this setting. Most of these studies have shown RFA to be inferior to resection with respect to rates of local recurrence and 5-year overall survival.[141] Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are due to patient selection bias, technologic limitations of RFA, or a combination is currently unclear.[144] Nevertheless, the panel does not consider RFA to be a substitute for resection in patients with completely resectable disease. In addition, resection or RFA (either alone or in combination with resection) should be reserved for patients with disease that is completely amenable to local therapy. Use of surgery, RFA, or the combination for "debulking procedures" with a goal of less than complete resection or ablation of all known sites of disease is not recommended.

The panel's consensus is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (i.e., with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status.

Most patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease. For those with liver-limited unresectable disease, however, preoperative chemotherapy is increasingly used to downsize colorectal metastases and convert them to a resectable status (i.e., conversion chemotherapy); it has also been administered to patients with metastatic disease considered to be resectable (i.e., neoadjuvant therapy). Potential advantages include earlier treatment of micrometastatic disease, determination of responsiveness to chemotherapy (which can be prognostic and help plan postoperative therapy), and avoidance of local therapy in those who progress early. Potential disadvantages include chemotherapy-induced liver injury and missing the "window of opportunity" for resection through the possibility of either disease progression or achievement of a complete response, thereby making it difficult to identify areas for resection.[121,146]

Furthermore, results from a recent study of colorectal cancer patients receiving preoperative chemotherapy indicated that cancer cells were still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.[147] It is therefore essential that during treatment with preoperative chemotherapy, frequent evaluations are undertaken and close communication is maintained among medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.[148] When preoperative chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation should be planned 2 months after initiation of preoperative chemotherapy, and that patients who continue to receive preoperative chemotherapy undergo surgical re-evaluation every 2 months thereafter.[149–152]

Certain clinicopathologic factors, such as the presence of extrahepatic metastases and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with colorectal cancer,[130,131,153–155] although the ability of these factors to predict outcome after resection may be limited.[119] However, the decision whether to offer preoperative chemotherapy begins with an initial evaluation of the degree of resectability of metastatic disease. Benefits of initial surgery in patients with clearly resectable disease characterized by generally favorable prognostic characteristics may outweigh the benefits of downsizing the disease with neoadjuvant chemotherapy. Alternatively, preoperative chemotherapy would be more appropriate in patients with borderline resectable or initially unresectable but potentially convertible after response to chemotherapy. In addition, preoperative chemotherapy may be more beneficial in patients who have not been exposed to prior chemotherapy or who have not received chemotherapy in the previous 12 months.

The most important benefit of the preoperative approach is the potential to convert patients with initially unresectable metastatic disease to a resectable state. The study by Pozzo et al.[134] reported that preoperative therapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of patients with initially unresectable liver metastases to undergo liver resection. Median time to progression was 14.3 months, and all these patients were alive at a median follow-up time of 19 months. In a NCCTG phase II study,[123] 44 patients with unresectable liver metastases were treated with FOLFOX4. Twenty five patients (60%) had tumor reduction and 17 (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy.

In another study of 1439 initially unresectable patients with colorectal liver disease, 1104 patients were treated with chemotherapy and 335 (23%) were able to undergo primary hepatic resection. Of the 1104 patients receiving chemotherapy, 138 patients (12.5%) classified as "good responders" underwent secondary hepatic resection after preoperative chemotherapy, which included oxaliplatin in most cases.[156] The 5-year survival rate for these 138 patients overall was 33%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-con-

taining chemotherapy regimens indicated that 24 patients (3.3%) were able to undergo curative liver resection after treatment.[157] The median overall survival time in this group was 42.4 months.

The choice of chemotherapy regimen in the preoperative setting depends on a number of factors, including whether the patient has resectable or potentially convertible metastatic disease and the response rates and safety/toxicity issues associated with the regimens. Although the benefits of pre- or postoperative chemotherapy for patients with liver metastases have not yet been fully validated in randomized clinical trials, a recent EORTC phase III study evaluating use of perioperative FOLFOX4 (6 cycles before and 6 cycles after surgery) for patients with initially resectable liver metastases demonstrated absolute improvements in 3-year progression-free survival of 8.1% (P = .041) and 9.2% (P = .025) for all eligible and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[158] The partial response rate after preoperative FOLFOX was 40% and operative mortality was less than 1% in both treatment groups.

There have been recent reports of randomized clinical trials evaluating preoperative FOLFIRI or FOLFOX as conversion therapies in combination with anti-epidermal growth factor receptors (EGFR) inhibitors.[159,160] However, a number of randomized studies have investigated the efficacy and safety of FOLFOX, CapeOX, or FOLFIRI with and without bevacizumab or cetuximab in the first-line treatment of patients with metastatic colorectal cancer (see "Chemotherapy for Advanced or Metastatic Disease"). In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials.[161,162] Significantly improved rates of response and overall survival were reported for patients in the FOLFOXIRI arm of one of the studies,[162] but not in the other.[161]

The efficacy of bevacizumab in combination with FOLFOX and FOLFIRI (infusional 5-FU, LV, irinotecan) in the treatment of unresectable metastatic disease (see "Chemotherapy for Advanced or Metastatic Disease") has led to its use in combination with these regimens in the preoperative setting, although the safety of administering bevacizumab pre- or postoperatively in combination with 5-FU–based regimens has not been adequately evaluated. A retrospective evaluation of data from 2 randomized trials of 1132 patients receiving chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen when this population was compared with the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively; P = .28).[163] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered before surgery, the incidence of wound healing complications in either group of patients was low (1.3% vs. 0.5%; P = .63).

The panel recommends at least a 6-week interval (which corresponds to 2 half-lives of the drug[164]) between the last dose of bevacizumab and elective surgery. Further support for this recommendation comes from results of a single-center, non-randomized phase II trial of patients with potentially resectable liver metastases that showed no increase in bleeding or wound complications when the bevacizumab component of CapeOX plus bevacizumab therapy was stopped 5 weeks before surgery (i.e., bevacizumab excluded from the sixth cycle of therapy).[165] In addition, no significant differences in bleeding, wound, or hepatic complications were observed in a retrospective trial evaluating effects of preoperative bevacizumab stopped 8 weeks or prior compared to more than 8 weeks before resection of liver colorectal metastases for patients receiving oxaliplatin- or irinotecan-containing regimens.[166]

Other reported risks associated with the preoperative approach include the potential for development of liver steatosis or steatohepatitis when oxaliplatin- or irinotecan-containing chemotherapeutic regimens are administered.[148] To limit the development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable and usually not more than 3 to 4 months following initiation of preoperative treatment.

As mentioned previously, colorectal metastatic disease can also occur in the lung.[167] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic

disease have been performed in selected cases.[168] The goal of treatment of most abdominal/peritoneal metastases is palliative, rather than curative.

It is important to note that some of the treatment approaches for patients diagnosed with rectal cancer and potentially resectable synchronous lung or liver metastases differ from those for patients diagnosed with stage IV colon cancer characterized as potentially resectable metastatic disease. In particular, initial treatment options for potentially resectable rectal cancer include preoperative chemoRT directed toward treatment of the primary cancer; preoperative combination chemotherapy regimen plus a biologic agent to target metastatic disease; and a surgical approach (i.e., staged or synchronous resection of metastases and rectal lesion). Advantages of an initial chemoRT approach include a possible decreased risk of pelvic failure following surgery, although preoperative pelvic RT may decrease tolerance to systemic bevacizumab-containing adjuvant regimens, thereby limiting subsequent treatment of systemic disease. However, data to guide decisions regarding optimal treatment approaches in this population of patients are very limited. Of note, patients with stage II/III rectal cancer enrolled in a large randomized trial evaluating the effect of adding chemotherapy to preoperative RT were found to be 3 times more likely to develop distant metastases than local recurrence of disease after a median follow-up of more than 5 years.[89]

Only limited data exist regarding the efficacy of adjuvant chemotherapy following resection for metastatic colorectal liver or lung disease. Nevertheless, the panel recommends administration of a course of an active systemic chemotherapy regimen for metastatic disease for some patients following liver or lung resection who have received preoperative chemoRT or no preoperative therapy after staged or synchronous resection of metastases and rectal lesion to increase the likelihood that residual microscopic disease will be eradicated for a total perioperative treatment time of approximately 6 months. Postoperative chemoRT is recommended for patients with synchronous metastases who have not received prior chemoRT and who are at higher risk for pelvic recurrence after staged or synchronous resection of metastases and rectal lesion (i.e., patients with disease staged as pT3-4, any N, or any T,N1-2).

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent administration of chemotherapy directed to the liver metastases through the hepatic artery (i.e., hepatic arterial infusion [HAI]) is listed in the guidelines as an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine (with dexamethasone and with or without LV) by HAI in addition to systemic chemotherapy was shown to be superior to systemic chemotherapy alone with respect to 2-year survival and time to progression of hepatic disease.[169,170] However, the difference in survival between the 2 arms was not significant at later follow-up periods.[169,171] A number of other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy was compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy.[169] Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.[129] However, limitations of HAI therapy include the potential for biliary toxicity[169] and the requirement for specific technical expertise. The consensus of the panel is that HAI therapy should be considered only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Finally, a number of liver-directed therapies are available for the treatment of unresectable metastatic disease in highly select patients, although their role in the treatment of colorectal metastases is controversial. These therapies include arterial radioembolization with yttrium-90 microspheres,[172,173] arterial chemoembolization,[173] and conformal radiation therapy.[174] Use of intra-arterial embolization is a category 3 recommendation for select patients with predominant hepatic metastases, and conformal external beam radiation therapy is not recommended unless the patient is symptomatic or it is used in a clinical trial. (See "Workup and Management of Synchronous Metastatic Disease" and "Workup and Management of Metachronous Metastatic Disease").

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease. In a single-center study at The University of Texas M. D. Anderson Cancer Center, rates of 5-year local recurrence were reported to be low (i.e., 5-year

locoregional control rate of 91%) for patients with rectal cancer treated with surgery and either RT or chemoRT, and 78% of recurrences occurred in the low pelvic and presacral regions.[175] Patients with disease recurrence at the anastomotic site are more likely than those with an isolated pelvic recurrence to be cured following re-resection.[176,177] 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 by continuous infusion concurrent with RT enabled the majority of patients (77%) to undergo re-resection with curative intent.[176]

Recommendations for Treatment of Synchronous Metastases/Resectable Disease: As part of the pre-treatment work-up, the panel recommends tumor KRAS gene status testing for all patients with metastatic colorectal cancer at the time of diagnosis of metastatic disease (see previous discussion of KRAS testing). Initial treatment options for patients with stage IV disease (any T, any N, M1) and resectable liver or lung metastases include combination chemotherapy for 2 to 3 months (e.g., FOLFOX, CapeOX, or FOLFIRI regimens with or without bevacizumab or cetuximab for KRAS wild-type tumors only); staged or synchronous resection of metastases and rectal lesion; treatment with continuous infusional 5-FU/pelvic RT (category 2A) or bolus 5-FU with LV/pelvic RT (category 2A) or capecitabine/RT (category 2B); or 2 to 3 months of upfront combination chemotherapy with FOLFOX, CapeOX, or FOLFIRI regimens with or without bevacizumab or cetuximab (KRAS wild-type tumors only) followed by chemoRT (see pages 793–797, 844, and 856). The impetus for inclusion of the latter option is upfront systemic treatment with a goal of early eradication of micrometastases followed by consolidating chemoRT for local control of disease prior to surgery (see page 844). For the 3 groups of patients receiving neoadjuvant therapy, surgery should be performed 5 to 10 weeks following completion of such treatment.

Adjuvant therapy for patients undergoing initial surgery depends on pathologic staging of disease. For patients undergoing initial surgical treatment, the panel recommends that those at higher risk for pelvic failure relative to systemic disease (e.g., disease pathologically staged as pT3-4, any N or any T, N1-2) undergo postoperative chemoRT using the "sandwich" approach (i.e., chemotherapy followed by concurrent chemoRT followed by chemotherapy for 6 months total duration).[97,98] The panel acknowledged that not all patients with rectal cancer and resectable liver or lung metastases need to be treated with chemoRT. For example, in patients with pT1-2, N0 disease, the competing risk of distant metastases is considered to be higher than that of locoregional recurrence. Therefore, the panel recommends that these patients receive an active adjuvant chemotherapy regimen (for 6 months) as described on pages 793–797, with the exception of FOLFOXIRI.

Adjuvant therapy recommendations for patients who have received neoadjuvant chemoRT only is as described for patients with pT1-2, N0 disease (except total duration of pre- plus postoperative chemotherapy should be 6 months), whereas patients who have undergone preoperative bevacizumab- or cetuximab (KRAS wild-type tumors only) -containing therapy should receive postoperative chemoRT as described previously for patients with pT3-4, any N, or any T, N1-2 disease (except total duration of pre- plus postoperative chemotherapy should be 6 months). Those patients undergoing preoperative bevacizumab- or cetuximab-containing therapy followed by preoperative chemoRT should not receive postoperative chemotherapy (see page 844).

Recommendations for Treatment of Synchronous Metastases/Unresectable Disease: Patients with any unresectable or medically inoperable metastases are treated according to whether they are symptomatic or asymptomatic. Symptomatic patients are treated with chemotherapy alone or combined modality therapy with 5-FU/RT or capecitabine/RT (category 2B), resection of the involved rectal segment or laser canalization or diverting colostomy or stenting (see page 845). Primary treatment should be followed by an active chemotherapy regimen for metastatic disease (see pages 793–797).

For patients with asymptomatic liver or lung disease that is deemed to be unresectable, the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (e.g., choice of FOLFIRI, FOLFOX, or CapeOX chemotherapy with or without bevacizumab or cetuximab [KRAS wild-type tumors only], or the same chemotherapy regimens with or without cetuximab [KRAS wild-type tumors only], or FOLFOXIRI [category 2B for FOLFOXIRI]) to attempt to render these patients candi-

dates for resection (see pages 793–797). Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease,[178] and these patients should be re-evaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing such therapy.

Primary treatment of unresectable synchronous liver or lung metastases by palliative surgery to remove the primary tumor should be considered only if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding. It should be noted that symptomatic improvement in the primary is often seen with first-line systemic chemotherapy, even within the first 1 to 2 weeks, and routine palliate resection of a synchronous primary lesion should not be done in the absence of overt, serious symptoms.[126] Complications from the primary lesion are uncommon in these circumstances, and its removal delays initiation of systemic chemotherapy. An intact primary is not a contraindication to bevacizumab use. The risk of gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, as large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare (see section on "Chemotherapy for Advanced or Metastatic Disease" in the NCCN Colon Cancer Guidelines).

Ablative therapy of metastatic disease, either alone or in combination with resection, can also be considered when all measurable metastatic disease can be treated (see "Principles of the Management of Metastatic Disease"). Post-treatment follow-up for patients classified as stage IV and no evidence of disease (NED) is described in the section on "Post-Treatment Surveillance."

Patients with unresectable metastatic disease not responding to preoperative therapy should receive chemotherapy for advanced or metastatic disease as outlined on pages 793–797 with treatment selection based, in part, on whether the patient is or is not an appropriate candidate for intensive therapy.

There was no panel consensus regarding the use of liver-directed therapies such as arterial radioembolization therapy and arterial chemoembolization therapy. For select patients with chemotherapy resistant/refractory disease characterized by predominant liver metastases and no obvious systemic disease, use of these interventions was supported by some panel members but not others (category 3). The consensus of the panel is that conformal external radiation therapy should not be used unless the patient is symptomatic or it is administered in the context of a clinical trial.

Recommendations for Treatment of Metachronous Metastases: Routine use of PET to monitor for disease recurrence is not recommended. It should be noted that the CT that accompanies a "PET/CT" is a non-contrast CT and thus not of ideal quality for routine surveillance. On documentation on dedicated contrast-enhanced CT or MRI of metachronous metastases in which disease is or may become potentially resectable, characterization of the extent of disease by PET scan is recommended. PET is used at this juncture to promptly characterize the extent of metastatic disease, and to identify possible sites of extrahepatic disease which could preclude surgery (see pages 786, 793–797, and 847).[179] As with other first identifications of metastatic disease, a tumor sample (metastases or original primary) should be sent for KRAS genotyping to define whether anti-EGFR agents can be considered in the list of potential options for this patient (see previous discussion of KRAS testing). Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases (see pages 786 and 847).

The management of metachronous metastatic disease is further distinguished from that of synchronous disease by also including an evaluation of the chemotherapy history of the patient, and by the absence of transabdominal resection. Resectable patients are classified according to whether they have received no previous chemotherapy or chemotherapy within or prior to the previous 12 months (see page 787). For patients who have not received prior chemotherapy and who have resectable metastatic disease, primary treatment options include initial resection followed by chemotherapy with an active chemotherapy regimen (see pages 793–797) for 6 months or neoadjuvant chemotherapy for 2 to 3 months followed by resection and additional postoperative chemotherapy for a total duration of pre- plus postoperative chemotherapy for up to 6 months based on response to the neoadjuvant regimen; observation is also an option for patients without a response to neoadjuvant therapy. For example,

the same chemotherapy regimen used in the neoadjuvant setting should be repeated postoperatively for patients with a preoperative disease response to such therapy. However either an alternative active chemotherapy regimen (see pages 793–797) or observation is an option in the postoperative setting for patients not responding to neoadjuvant therapy.

Patients determined by cross-sectional imaging or PET scan to have unresectable (including those considered to potentially convertible or unconvertible) disease should receive an active chemotherapy regimen based on prior chemotherapy history (see pages 786, 787, and 793–797). Specifically, patients exhibiting disease progression on FOLFOX administered within the previous 12 months should be switched to a FOLFIRI regimen with the option of inclusion of bevacizumab or cetuximab (KRAS wild type only). Patients potentially convertible to resectability should be re-evaluated for disease conversion to a resectable status every 2 months; those with chemotherapy-responsive disease who are converted to a resectable state should undergo resection followed by postoperative therapy as described above for patients with resectable disease and a history of previous chemotherapy. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) or continuous IV 5-FU infusion remains at option at centers with experience with the surgical and medical oncologic aspects of this procedure.

Patients with unresectable metastatic disease not responding to preoperative therapy should receive chemotherapy for advanced or metastatic disease as outlined on pages 793–797, with treatment selection based, in part, on whether the patient is or is not an appropriate candidate for intensive therapy. Patients receiving palliative chemotherapy should be monitored with CT or MRI scans approximately every 2 to 3 months. PET scans are not recommended for routine monitoring of the progression of metastatic disease.

Isolated pelvic/anastomotic recurrence is optimally managed by preoperative RT and concurrent infusional 5-FU, if full course RT was not given previously. Resection followed by the option of IORT should be considered if it can be safely delivered (see page 847).[180] However, debulking, resulting in gross residual cancer, is discouraged. Patients with unresectable lesions are treated according to their ability to tolerate therapy. The treatment goal for most abdominal/peritoneal metastases is palliative rather than curative. The panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery (i.e., peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy[181,182] to be investigational and does not endorse such therapy outside of a clinical trial. However, the panel recognizes the need for randomized clinical trials to address the risks and benefits associated with each of these modalities.

Chemotherapy for Advanced or Metastatic Disease: The continuum of care approach to the management of patients with metastatic rectal cancer is the same as described for patients with metastatic colon cancer. Please refer to the corresponding section in the Colon Cancer Guidelines.

Post-Treatment Surveillance

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 (see page 846). Anastomotic recurrence of rectal cancer has a much more favorable prognosis than local recurrence at other locations in the pelvis,[176,177] although the optimal timing for surveillance of the rectal anastomosis is not known.

Additional information on Post-treatement Surveillance is available in the Colon Cancer Guidelines, on page 820 in this issue or online in these guidelines at www.nccn.org.

Post-treatment surveillance also includes a survivorship care plan involving disease preventive measures such as immunizations against influenza and pneumococcal infections at prescribed intervals and regular dental care, and early disease detection through periodic screening for second primary cancers (e.g., breast, cervical, or prostrate cancers) and routine health monitoring to screen for comorbid conditions including psychosocial distress associated with colorectal cancer and its treatment (see pages 857 and 858).

Other recommendations include monitoring for late sequelae of rectal cancer or the treatment of rectal cancer, such as chronic diarrhea or incontinence (e.g., patients with stoma);[199] persistent neuropathy (a well known side effect of oxaliplatin treatment);[99] pelvic pain or pelvic fractures; and urogenital dys-

function after resection or pelvic irradiation.[200–203] Specific management interventions to address these side effects are described on pages 857 and 858 and in a recent review.[204]

There is also evidence to indicate that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy body mass index, 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 body mass index of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[205] In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, DFS was found to be directly dependent on how much exercise these patients received.[206] Furthermore, a diet consisting of more fruits, vegetables, poultry and fish, and less red meat, as well as diets 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.[207] A discussion of lifestyle characteristics that may be associated with a decreased risk of colorectal cancer recurrence 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.

Managing an Increasing CEA Level

The approach to managing an increased CEA level for patients with rectal cancer is the same as that described for patients with colon cancer. It is available in the colon cancer guidelines in this issue (page 822) or in these guidelines online at www.nccn.org.

Summary

The NCCN Rectal Cancer Guidelines 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 lesions that are node-negative by 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 the majority of patients with suspected or proven T3/T4 disease and/or regional node involvement and adjuvant chemotherapy is recommended. Patients with recurrent localized disease should be considered for resection with or without radiotherapy.

A patient with metastatic disease in the liver or lung should be considered for surgical resection if he or she is a candidate for surgery and if complete resection (R0) or ablation can be achieved. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease (i.e., neoadjuvant therapy) or when a response to chemotherapy may convert a patient from an unresectable to resectable state (i.e., conversion therapy). Other options for patients with resectable synchronous metastases are initial treatment with chemoRT or chemotherapy with or without a bevacizumab or cetuximab (KRAS wild type tumor only) followed by consolidating chemoRT. Resection should be followed by adjuvant therapy based on prior therapy received. The recommended post-treatment surveillance program for rectal cancer patients includes serial CEA determinations, as well as periodic chest, abdominal and pelvic CT scans, and periodic evaluations by colonoscopy and proctoscopy.

Recommendations for patients with previously untreated disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or metastatic disease depend on whether or not the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOX, and FOLFOXIRI (category 2B). Addition of a biologic agent (e.g., bevacizumab or cetuximab) is either recommended, or listed as an option, in combination with some of these regimens, depending on available data. Chemotherapy options for patients with progressive disease are dependent on the choice of

initial therapy. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

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nccn.org.

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Reference 208 is cited in the section on "Managing an Increasing CEA Level" and is available in these guidelines online at www.nccn.org.

Individual Disclosures of the NCCN Rectal Cancer Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
J. Pablo Arnoletti, MD	OSI Pharmaceuticals, Inc.	None	None	None	5/19/08
Al B. Benson III, MD	Abbott Laboratories; Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Enzon Pharmaceuticals; Genentech, Inc.; General Electric; Genomic Health, Inc.; ImClone Systems Incorporated; National Cancer Institute; Novartis Pharmaceuticals Corporation; Onyx Pharmaceuticals, Inc.; Pfizer Inc.; Roche Laboratories, Inc.; sanofi-aventis U.S.; and Taiho Parmaceuticals Co., Ltd.	Abbott Laboratories; Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bayer HealthCare; Bristol-Myers Squibb Company; Eli Lilly and Company; Enzon Pharmaceuticals; Genentech, Inc.; General Electric; Genomic Health, Inc.; ImClone Systems Incorporated; National Cancer Institute; Novartis Pharmaceuticals Corporation;Onyx Pharmaceuticals, Inc.; Pfizer Inc.; Roche Laboratories, Inc.; sanofi-aventis U.S.; and Taiho Parmaceuticals Co., Ltd.	None	None	7/20/09
Yi-Jen Chen, MD, PhD	None	None	None	None	7/1/09
Michael A. Choti, MD	Ipsen	Genentech, Inc.; and sanofi-aventis U.S.	None	None	7/27/08
Harry S. Cooper, MD	None	None	None	None	7/7/09
Anne M. Covey, MD	None	None	None	None	7/2/09
Raza A. Dilawari, MD	None	Eisai Inc.; Pfizer Inc.; and Schering-Plough Corporation	None	None	7/27/08
Dayna S. Early, MD	None	None	None	None	7/23/08
Paul F. Engstrom, MD	None	None	None	None	7/2/09
Peter C. Enzinger, MD	Genentech, Inc.; ImClone Systems Incorporated; Pfizer Inc.; and sanofi-aventis U.S.	Roche Laboratories, Inc.; and sanofi-aventis U.S.	None	None	7/12/09
Marwan G. Fakih, MD	Bristol-Myers Squibb Company; and sanofi-aventis U.S.	ImClone Systems Incorporated; and sanofi-aventis U.S.	None	None	7/1/09
James W. Fleshman, Jr., MD	Covidien AG; ACOSOG; Applied Medical; and SurgRX, Inc.	None	None	None	6/2/08
Charles S. Fuchs, MD	Amgen Inc.; AstraZeneca Pharmaceuticals LP; Genentech, Inc.; ImClone Systems Incorporated; and Roche Laboratories, Inc.	AstraZeneca Pharmaceuticals LP; Genentech, Inc.; and Roche Laboratories, Inc.	None	None	7/22/09
Jean L. Grem, MD	None	Adherex Technologies Inc.; and Amgen Inc.; and Bristol-Myers Squibb Company	None	None	9/7/08
Krystyna Kiel, MD	None	None	None	None	5/7/08
James A. Knol, MD	None	None	None	None	7/28/08
Lucille A. Leong, MD	None	None	None	None	6/25/08
Edward Lin, MD	None	None	None	None	1/2/09
Mary F. Mulcahy, MD	sanofi-aventis U.S.	None	None	None	4/28/08
Sujata Rao, MD	None	Amgen Inc.; Genentech, Inc.; and sanofi-aventis U.S.	None	None	5/15/08
Eric Rohren, MD, PhD	None	None	None	None	7/1/09
Leonard Saltz, MD	Abbott Laboratories; Amgen Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; Celgene Corporation; Genentech, Inc.; Genomic Health, Inc.; Genzyme Corporation; ImClone Systems Incorporated; Merck & Co., Inc.; Alchemia; Delcath; Pfizer Inc.; Roche Laboratories, Inc.; Taiho Parmaceuticals Co., Ltd.; and YM BioScience Inc.	Abbott Laboratories; Celgene Corporation; Exelixis Inc.; Genentech, Inc.; and ImClone Systems Incorporated	None	None	7/1/09
David Shibata, MD	None	None	None	None	7/1/09
John M. Skibber, MD	None	None	None	None	9/9/08
Constantinos T. Sofocleous, MD, PhD, FSIR	National Cancer Institute	None	None	None	11/7/08
James Thomas, MD, PhD	None	None	None	None	7/1/09
Alan P. Venook, MD	Amgen Inc.; Bayer HealthCare; Genentech, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	Amgen Inc.; Genentech, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	None	7/28/09
Christopher Willett, MD	None	None	None	None	9/24/08

The NCCN guidelines staff have no conflicts to disclose.