National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Rectal Cancer

V.1.2008

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Rectal Cancer Table of Contents
Staging, MS, References

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Table of Contents

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Staging

Manuscript

References

This manuscript is being updated to correspond with the newly updated algorithm.

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To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus

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Summary of the Guidelines updates

Summary of changes in the 1.2008 version of the Rectal Cancer Guidelines from the 2.2007 version include:

REC-2

- In the Workup section, the following was added - "PET scan is not routinely indicated".

REC-4

- For patients with T3, N0 or T any, N1-2 disease, the recommendation for transabdominal resection was clarified with the following indication, "Patients with medical contraindication to combined modality therapy".

REC-5

- The recommendation for bevacizumab in combination with chemotherapy was changed from "+" to "±" for resectable synchronous metastases.

REC-7

- Footnote "v" defining advanced adenoma is new to the page, "Villous polyp, polyp > 1 cm, or high grade dysplasia".

REC-9

- Footnote "y" clarifying the setting for HAI therapy is new to the page, "Should be performed at institutions with experience in both the surgical and medical oncologic aspects of this procedure".

REC-A - Principles of Pathologic Review:

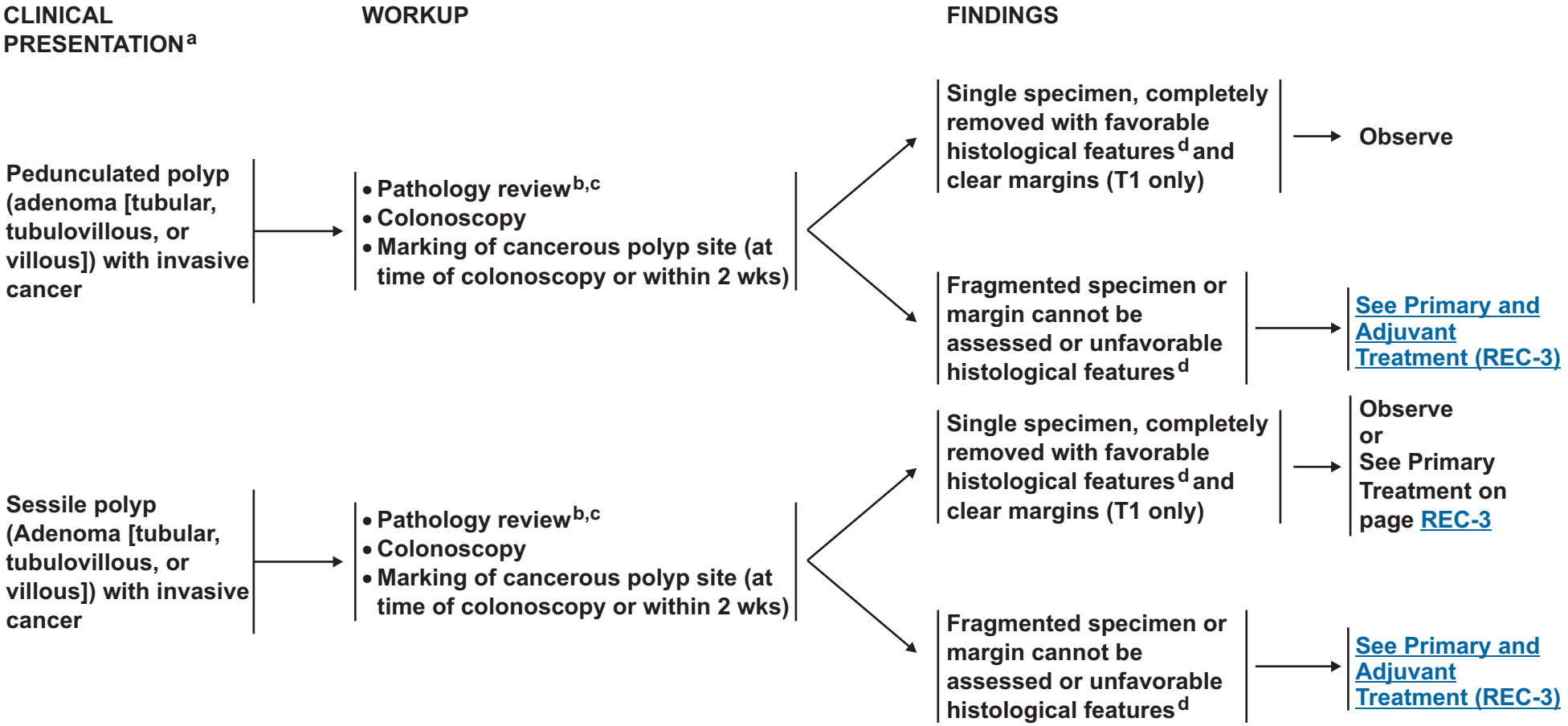
- **REC-A 1 of 3**
  - Bullet 4 under "Endoscopically removed polyps" is new.
  - Comment regarding "Acellular mucin pools" is new under "Pathological stage"
- **REC-A 2 of 3**
  - Under "Lymph node evaluation", the sentences beginning with "For stage II (pN0) colon cancer..." and ending "regardless of the surgical pathology results" are new to the bullet.
  - Under "Sentinel lymph node", the sentences beginning with "While the 6th Edition of the AJCC..." and ending "...invasion of the vessel (lymphatic) wall" are new to the first bullet.

REC-B - Principles of Surgery:

- **REC-B 1 of 3**
  - Treatment of draining lymphatics "by total mesorectal excision"
  - Surgery should be 5-10 weeks following "full dose 5 1/2 wk neoadjuvant chemoradiation"
- **REC-B 2 of 3**
  - The bullet "Plans for a debulking resection (< R0 resection) is not recommended" was added.
  - "All original sites of disease need to be resectable" was added to the bullet "Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy."
  - Ablative techniques "may" be considered "when all known disease is amenable to ablation."

Rectal Cancer

Rectal Cancer Table of Contents
Staging, MS, References



[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, see the NCCN Colorectal Cancer Screening Guidelines.

[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 (REC-A) - Endoscopically removed malignant polyp.

Back to Other Clinical Presentations (Table of Contents)

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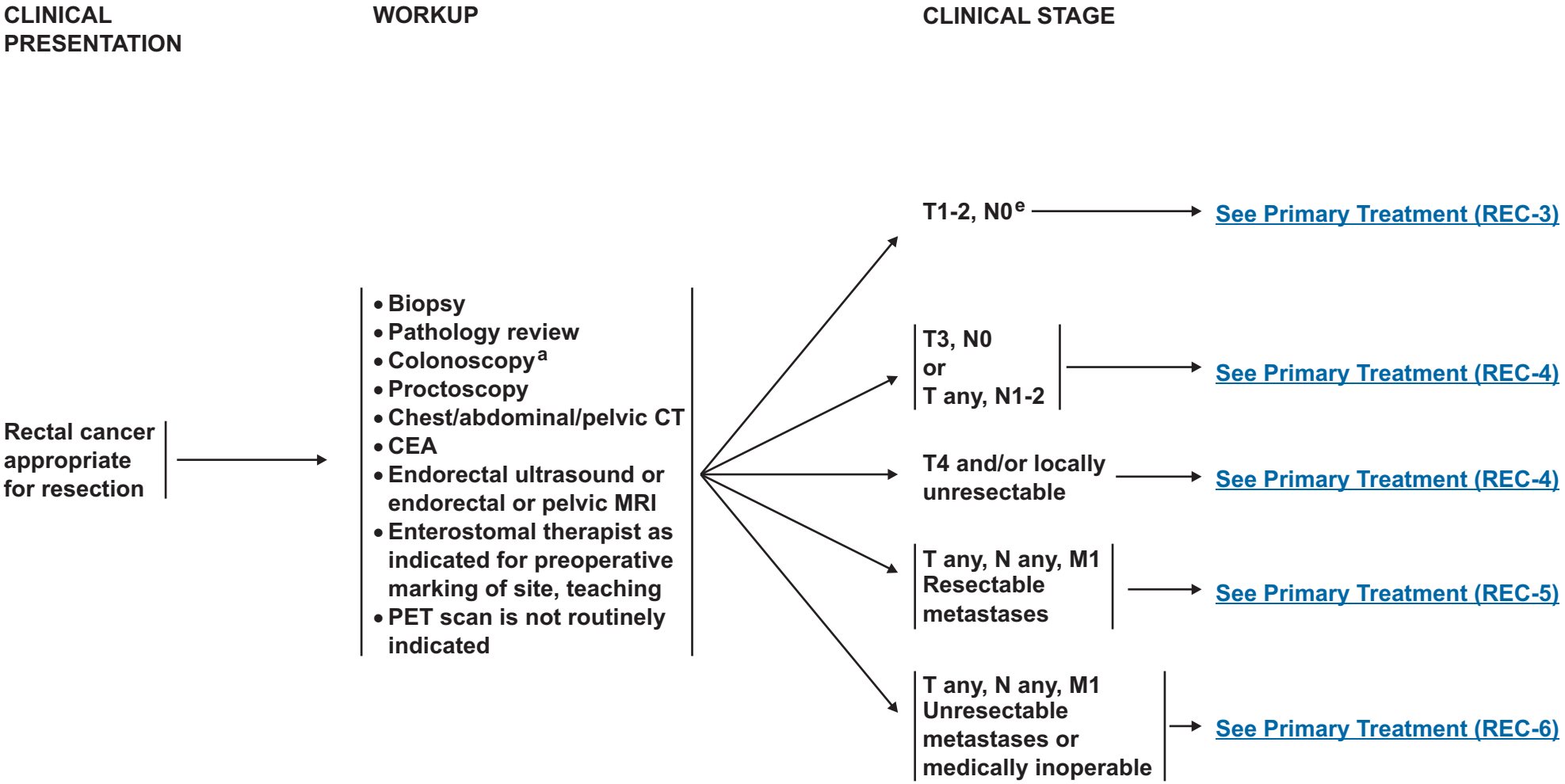
Rectal Cancer

Rectal Cancer Table of Contents
Staging, MS, References



[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, see the NCCN Colorectal Cancer Screening Guidelines.

[e] T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

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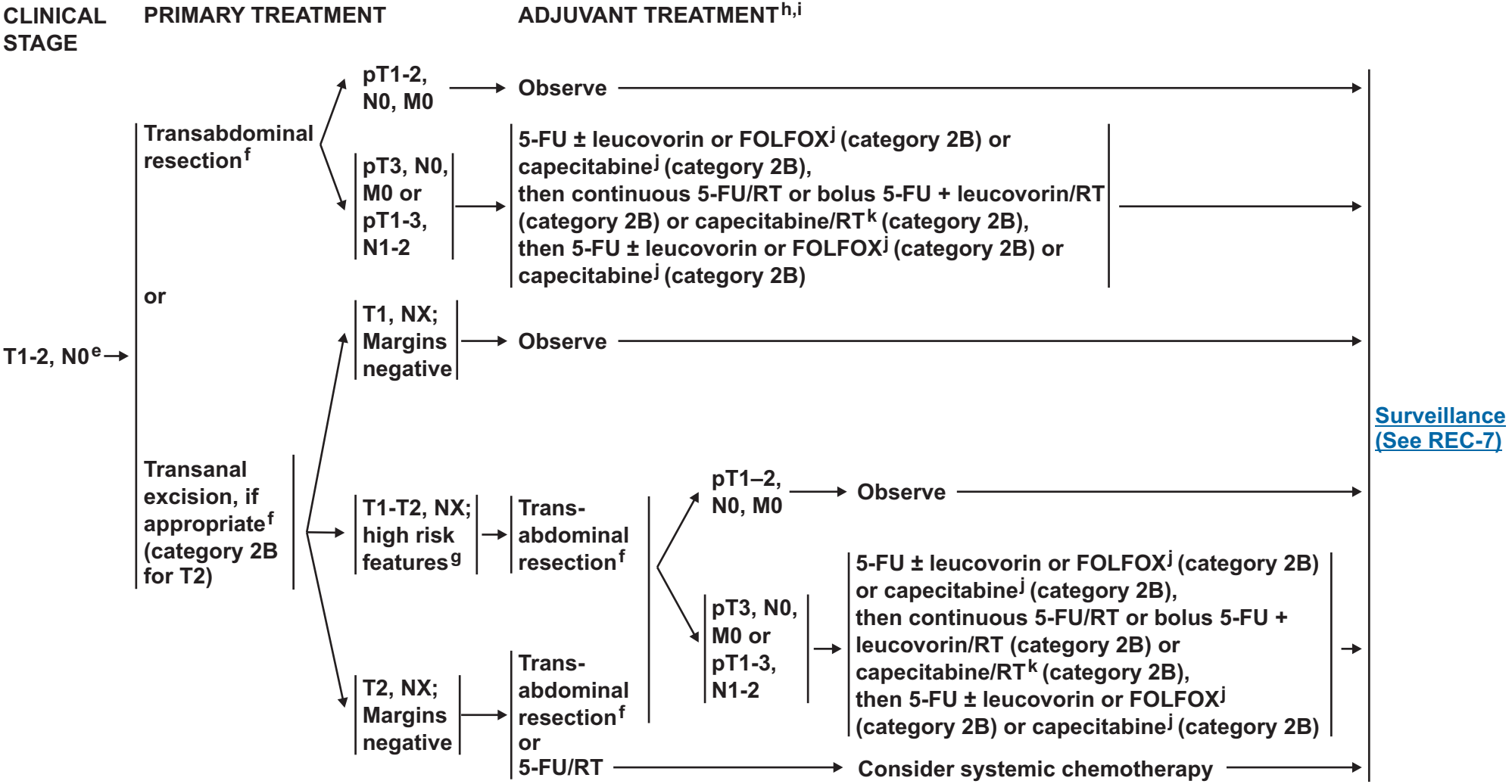
Rectal Cancer

Rectal Cancer Table of Contents
Staging, MS, References



[e] T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

[f] See Principles of Surgery (REC-B).

[g] High risk features include positive margins, lymphovascular invasion and poorly differentiated tumors.

[h] See Principles of Adjuvant Therapy (REC-C).

[i] See Principles of Radiation Therapy (REC-D).

[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 Radiation Oncology Biol Phys 2002;54(2):403-408.

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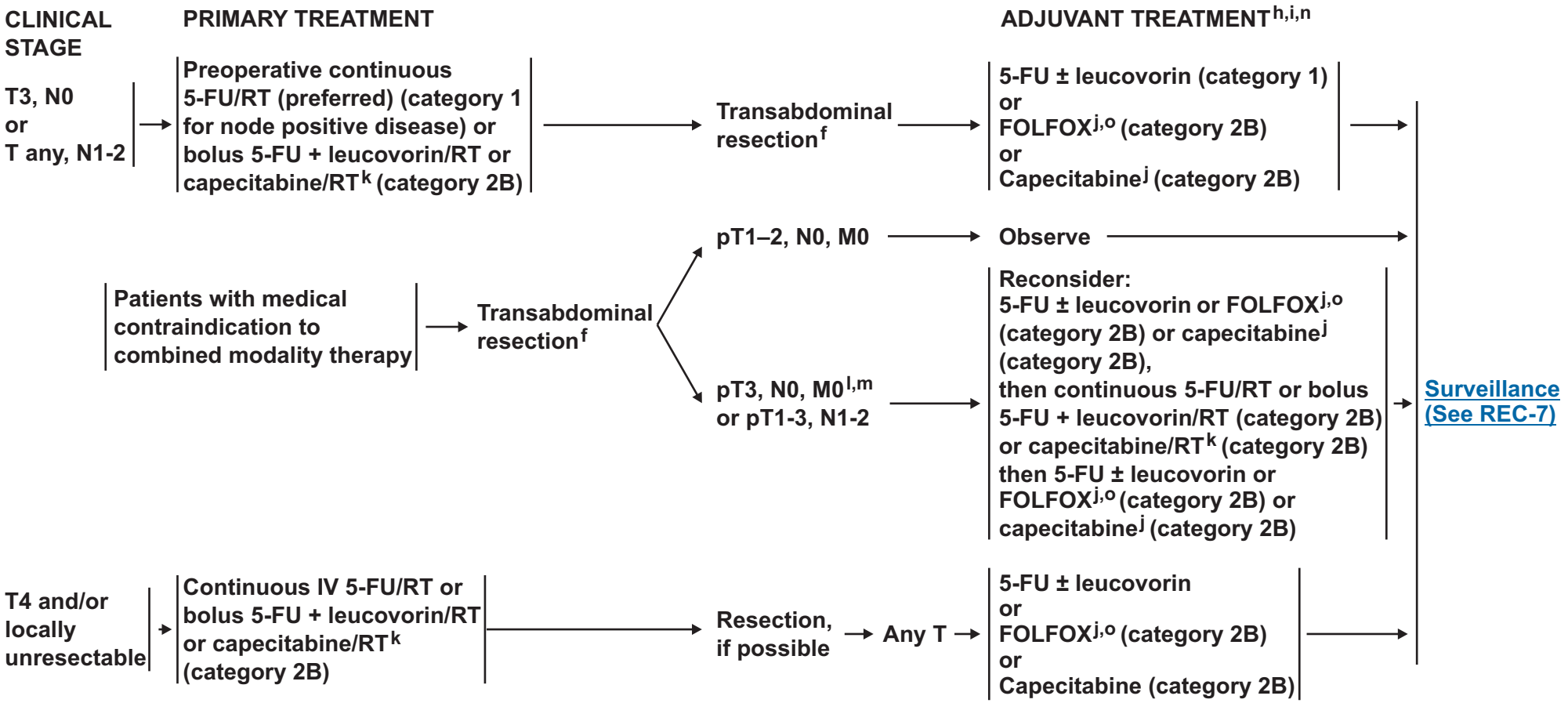
Rectal Cancer

Rectal Cancer Table of Contents
Staging, MS, References



[f] See Principles of Surgery (REC-B).
[h] See Principles of Adjuvant Therapy (REC-C).
[i] See Principles of Radiation Therapy (REC-D).
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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 receive preoperative therapy, regardless of the surgical pathology results.
[o] An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

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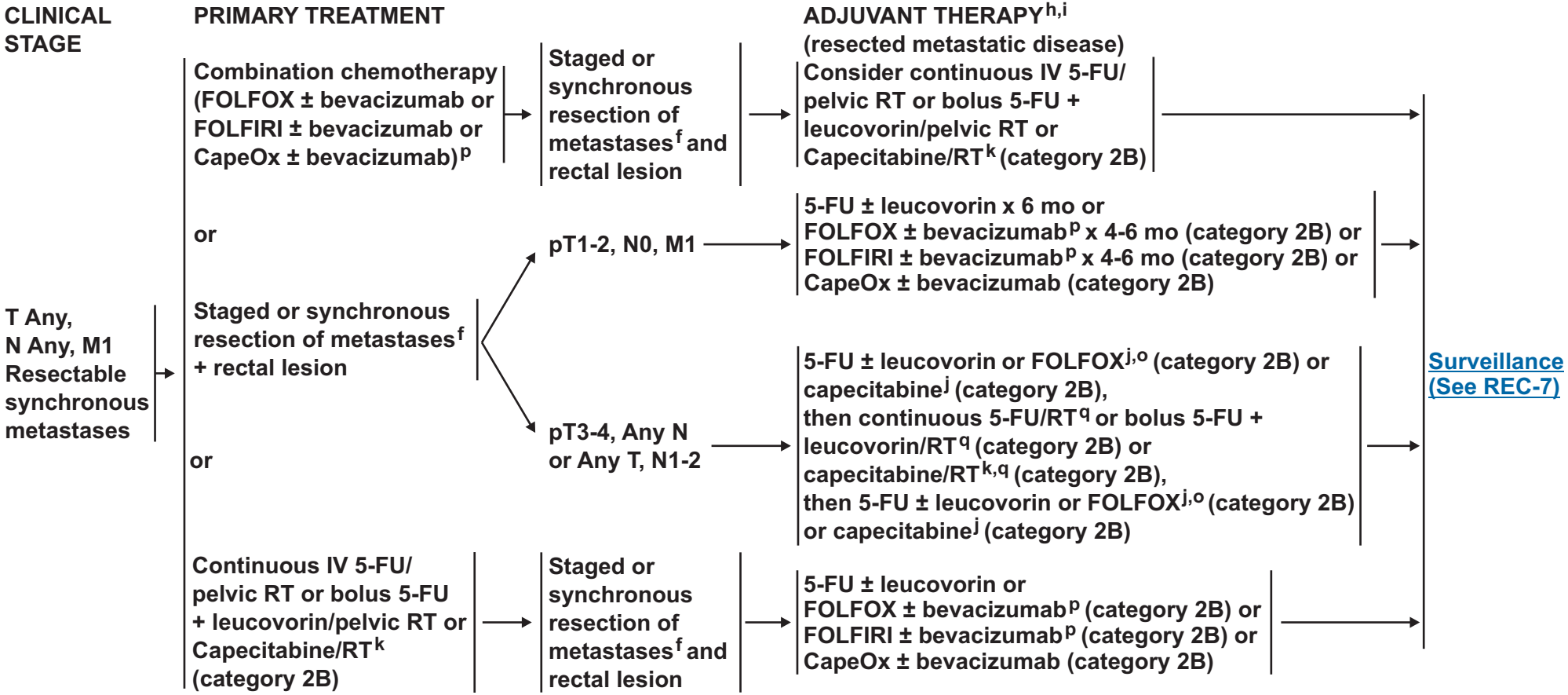
Rectal Cancer

Rectal Cancer Table of Contents
Staging, MS, References



[f] See Principles of Surgery (REC-B).
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[o] An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.
[p] 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 age ≥ 65. The use of bevacizumab may interfere with wound healing.
[q] RT only recommended for patients at relative risk for pelvic recurrence.

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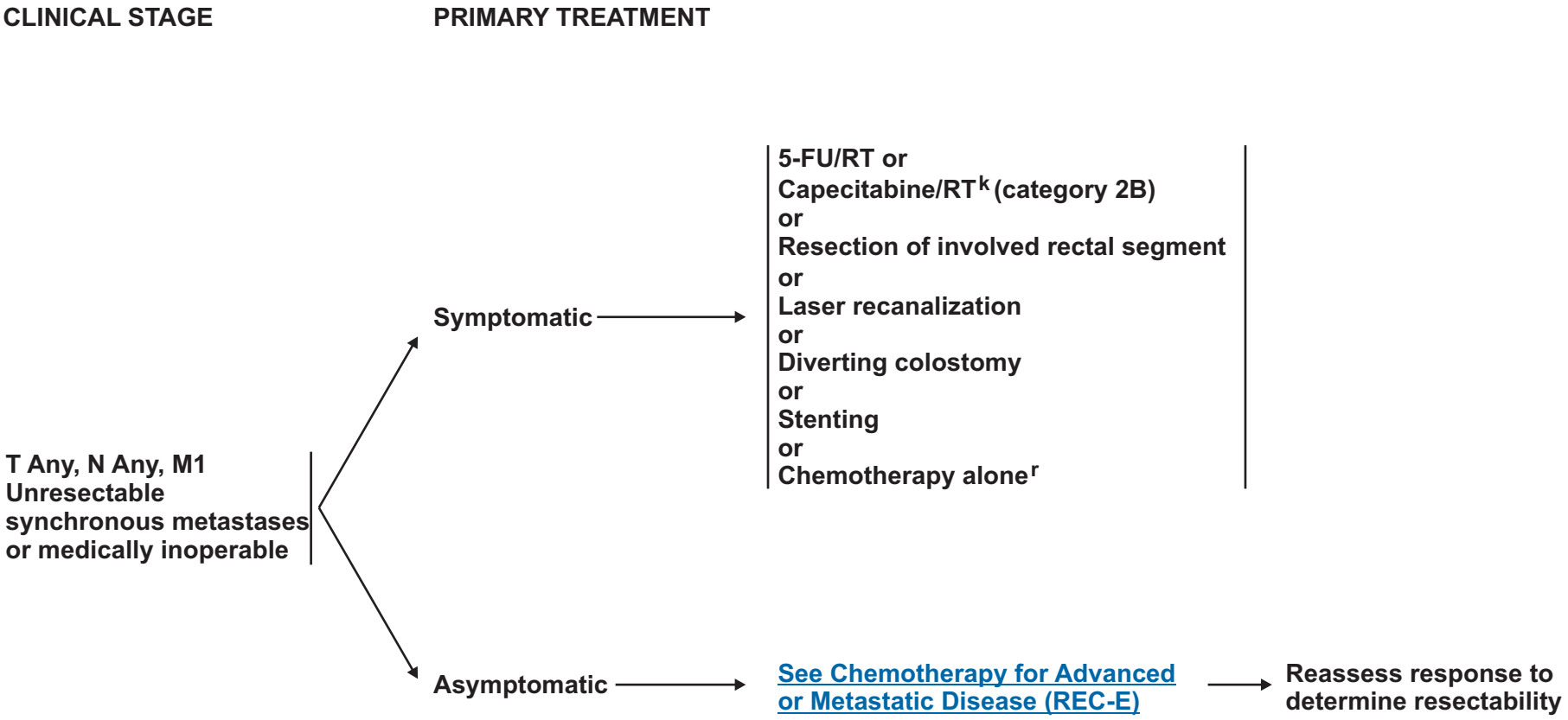
Rectal Cancer



[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 Radiation Oncology Biol Phys 2002;54(2):403-408.

[r] See Chemotherapy for Advanced or Metastatic Disease (REC-E).

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SURVEILLANCE

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA[s] 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[t,u]
- Colonoscopy in 1 y except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3-6 mo
  - If abnormal, repeat in 1 y
  - If advanced adenoma,[v] repeat in 3 y, then every 5 y[w]
- Consider proctoscopy every 6 mo x 5 y for patients status post LAR[x]
- PET scan is not routinely recommended

→ Serial CEA elevation or documented recurrence → See Workup and Treatment (REC-8)

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

[t] 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(33):8512-8519.

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

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

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

[x] 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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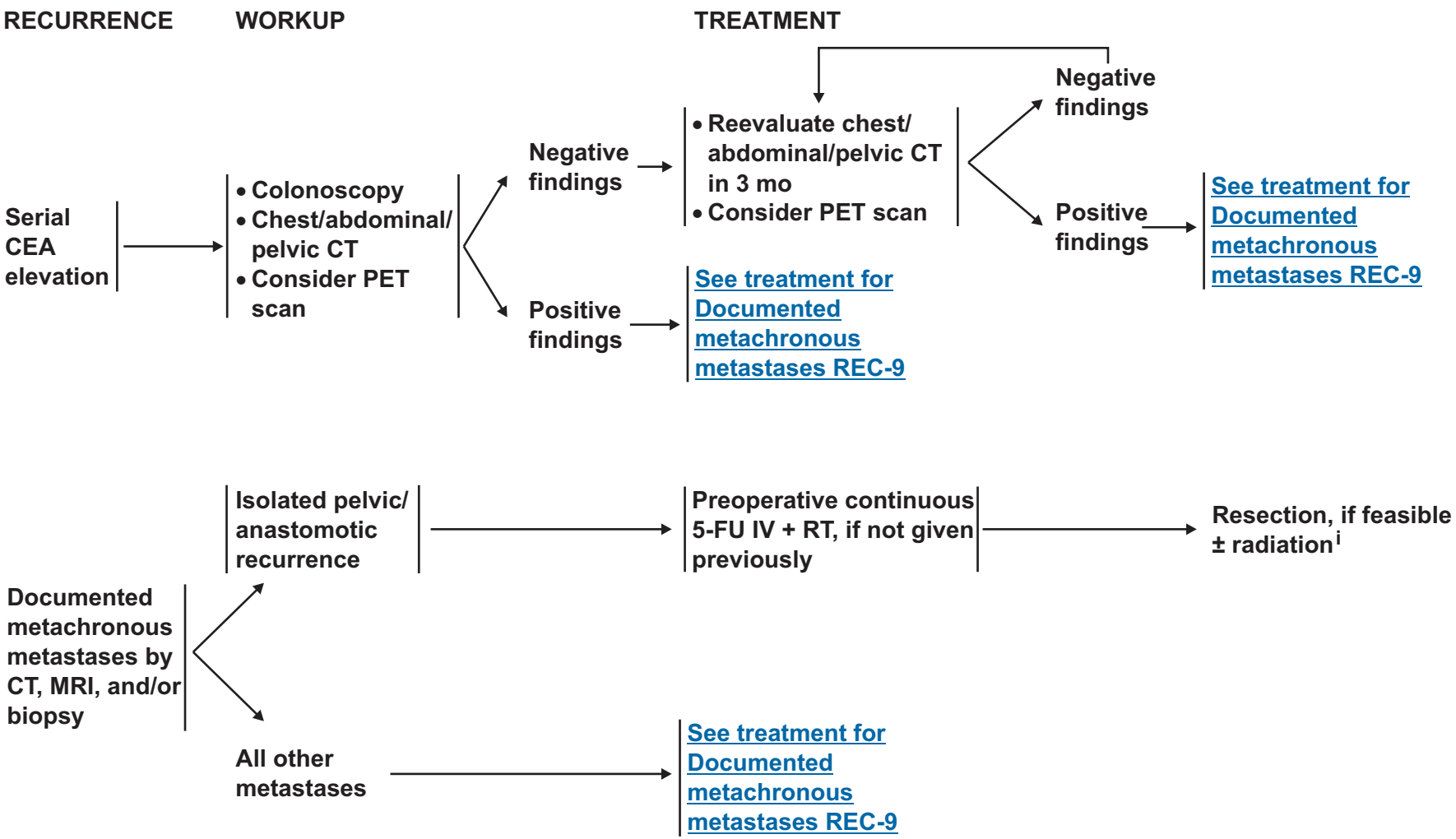
Rectal Cancer

Rectal Cancer Table of Contents
Staging, MS, References



[i] See Principles of Radiation Therapy (REC-D).

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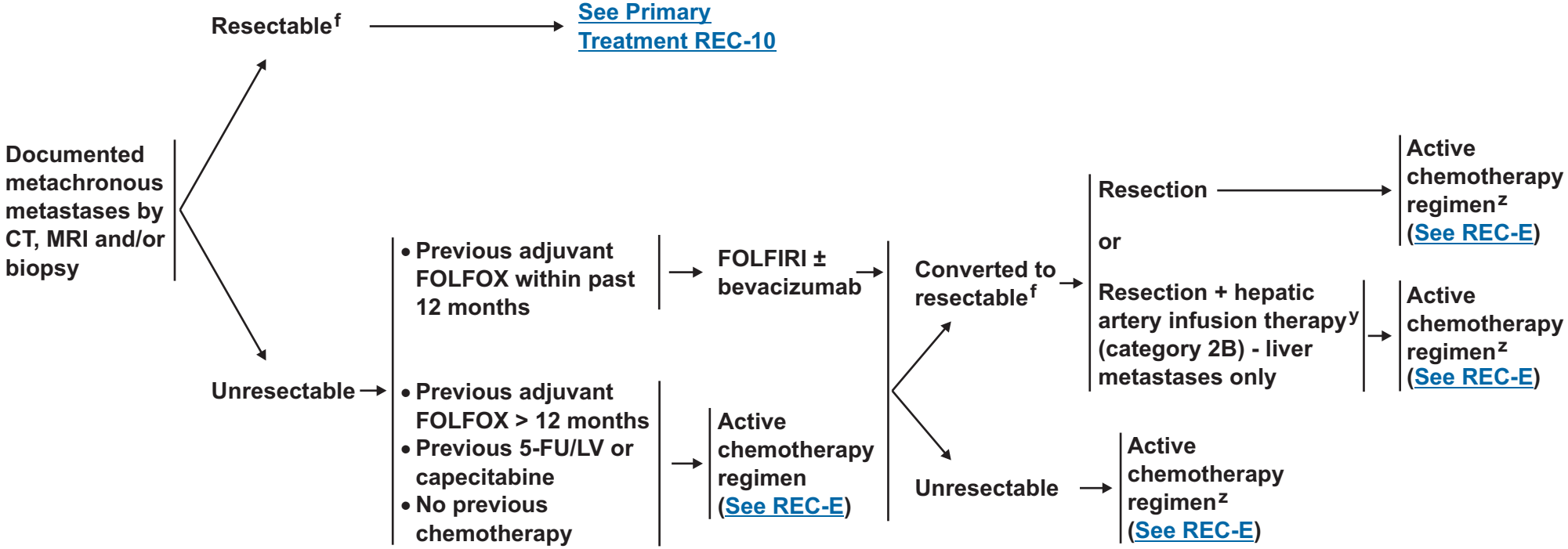
PRIMARY TREATMENT



[f] See Principles of Surgery (REC-B).
[y] Should be performed at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[z] If patient has seen all active chemotherapy regimens, observation is an option.

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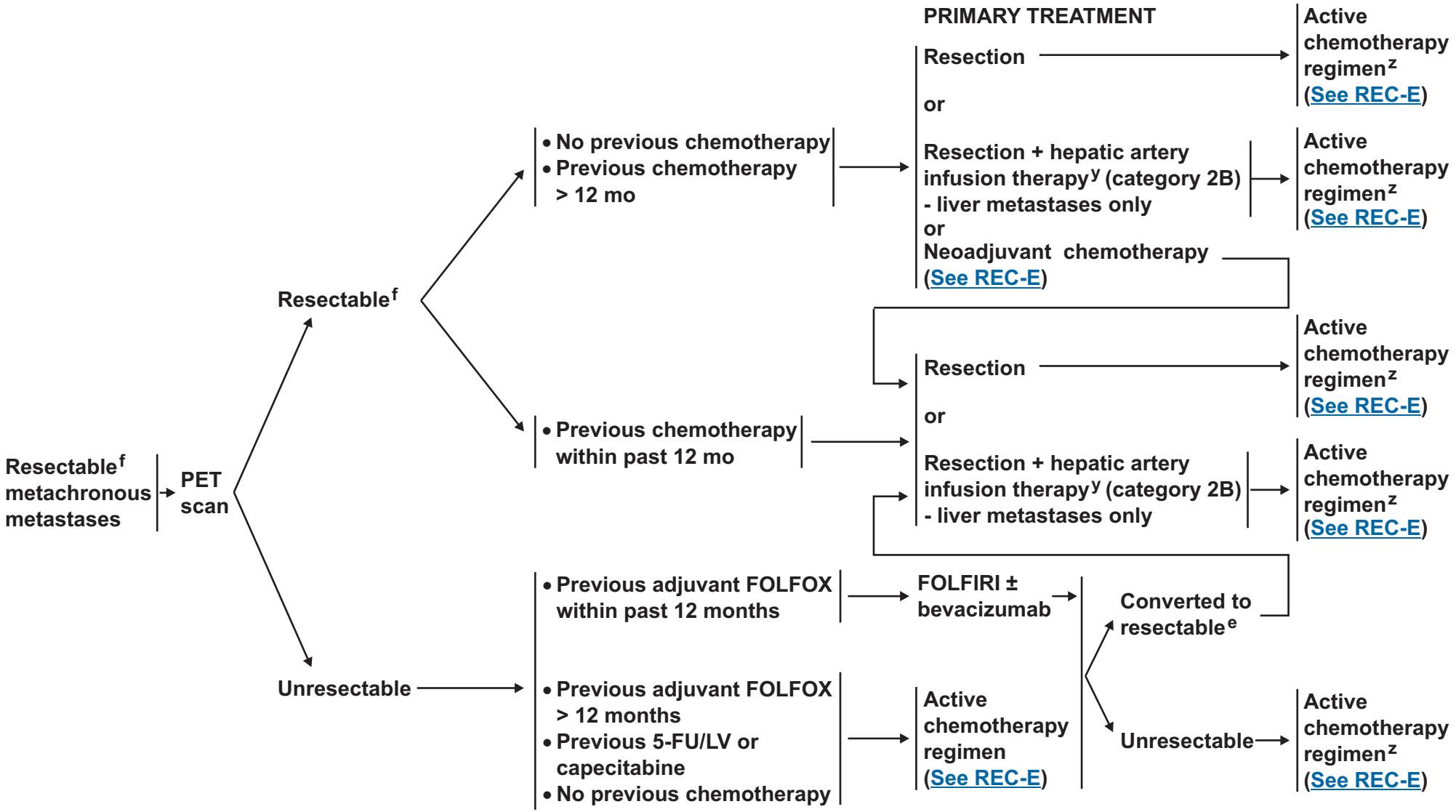
Rectal Cancer

Rectal Cancer Table of Contents
Staging, MS, References



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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 3)

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 histological features grade 1 or 2, no angiolymphatic invasion and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as 1) tumor < 1 mm from the transected margin, 2) tumor < 2 mm from the transected margin, 3) tumor cells present within the diathermy of the transected margin.[1-4]
- Unfavorable histological features grade 3 or 4, or angiolymphatic invasion, or a "positive margin." See above for definition of a positive margin.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcome (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than do polypoid malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable for adverse outcome and endoscopically removed malignant sessile polyps with grade I or II histology, negative margin, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.[3-7]

Transanal excision

- Favorable histopathological features: < 3 cm size, T1 or T2 (use caution in T2 due to high recurrence rate see REC-B), grade I or II, no lymphatic or venous invasion, negative margins.[8,9]
- Unfavorable histopathological features: > 3 cm in size, T1 or T2, with grade III, or lymphovascular invasion, or positive margin.[8-10]

Rectal cancer appropriate for resection

- Histological confirmation of primary malignant rectal neoplasm.

Pathological 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 those 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 (ST-1)

See Lymph node evaluation and sentinel lymph node on page 2 of 3 REC-A

See footnotes on page 3 of 3 REC-A

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PRINCIPLES OF PATHOLOGIC REVIEW (2 of 3)

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, >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 of the patient, gender, tumor grade and tumor site.[16] For stage II (pN0) colon cancer, if less than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs 19, $p < 0.05$, 7 vs 10, $p < 0.001$).[24,25] If 12 lymph nodes is considered the number needed to accurately stage, stage II tumors, then only 20% of cases treated with neoadjuvant therapy had adequate lymph node sampling.[25] To date the number of lymph nodes needed to accurately stage neoadjuvant treated cases is unknown. However, it is not known what is the clinical significance of this in the neoadjuvant setting as postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

Sentinel lymph node and detection of micrometastasis by immunohistochemistry

- Examination of the sentinal lymph node allows an intense histological 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. While studies to date seem promising, there is no uniformity in the definition of what constitutes "true metastatic carcinoma." Confusion arises when isolated tumors cells (ITC) 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 to 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 isolated tumor cells (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 (eg, glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.[30] Hermanek et al[31] proposed isolated tumor cells to 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 while others have failed to show this survival difference. In these studies, ITC were considered micrometastasis.[32-36]
- At the present time the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered investigational and results used with caution in clinical management decisions.[26-28,32-36]

See Malignant polyp, rectal cancer appropriate for resection, and pathological stage on page 1 of 3 REC-A

See footnotes on page 3 of 3 REC-A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF PATHOLOGIC REVIEW (3 of 3) - References

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PRINCIPLES OF SURGERY (1 of 3)

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 be 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 (ie, < 5cm 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 2 of 3 REC-B

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PRINCIPLES OF SURGERY (2 of 3)
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]
- Plan for a debulking resection (less than an R0 resection) is not recommended.
- There should be no unresectable extrahepatic sites of disease.[3,4,5]
- Re-evaluation for resection can be considered in otherwise unresectable patients after neoadjuvant therapy.[6,7] All original sites of disease need to be resectable.
- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.[8]
- Ablative techniques may be considered when all known disease is amenable to ablation.[8]
- The primary tumor must have been resected for cure (R0).
- Re-resection can be considered in selected patients.[9]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[10-13]
- Resectable extrapulmonary metastases do not preclude resection.[14-17]
- The primary tumor must have been resected for cure (R0).
- Re-resection can be considered in selected patients.[18]

See footnotes on page 3 of 3 REC-B

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PRINCIPLES OF SURGERY (3 of 3)
CRITERIA FOR RESECTABILITY OF METASTASES - REFERENCES

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PRINCIPLES OF ADJUVANT THERAPY (1 of 2)

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 receiving preoperative chemotherapy/RT:

- **5-FU 380 mg/m^2/day on days 1-5 ± leucovorin IV 20 mg/m^2 on days 1-5 every 28 days 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 wks x 3 cycles**
  Leucovorin 500 mg/m^2 IV over 2 h once a wk for 6 weeks x 3 cycles[3,4]
  - **A cycle is comprised of 6 wks followed by 2 wks of rest.**

Postoperative adjuvant regimens for patients not receiving 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 one h after the start of the leucovorin infusion, once a wk for 6 wks + leucovorin 500 mg/m^2 IV over 2 h once a wk for 6 wks**
  - **A cycle is comprised of 6 wks followed by 2 wks 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 hours, day 1
    Leucovorin 200 mg/m^2 IV over 2 hours, days 1 and 2
    Followed on days 1 and 2 by 5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours continuous infusion
    Repeat every 2 weeks[5]
  - **mFOLFOX 6**
    Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1
    Leucovorin* 400 mg/m^2 IV over 2 hours, day 1
    5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion**
    Repeat every 2 weeks[6,7]
- **Capecitabine[8] (category 2B)**
  Capecitabine 1250 mg/m^2 twice daily days 1-14 every 3 wks x 24 wks

*Leucovorin dose in Europe is 200 mg/m^2 of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m^2.

**NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

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 wks

See footnotes on page 2 of 2 REC-C

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF ADJUVANT THERAPY (2 of 2)
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PRINCIPLES OF RADIATION THERAPY

- Radiation therapy fields should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures and the inguinal nodes should be included for tumors invading into the distal anal canal.
- Multiple radiation therapy fields should be used (generally a 3 or 4 field technique). Positioning and other techniques to minimize the volume of small bowel in the fields should be encouraged.
- For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.
- Intensity modulated radiotherapy (IMRT) or tomotherapy could be considered when there is a high risk of radiation-related normal tissue toxicity. Care should be taken to assure adequate tumor bed coverage.
- Radiation doses:
  - 45-50 Gy in 25-28 fractions to the pelvis.
  - For resectable cancers, after 45 Gy a tumor bed boost with a 2 cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
  - Small bowel dose should be limited to 45 Gy.
- Intraoperative radiotherapy (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, prior to adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required.
- 5-fluorouracil based chemotherapy should be delivered as continuous infusion or as a bolus daily with radiation.

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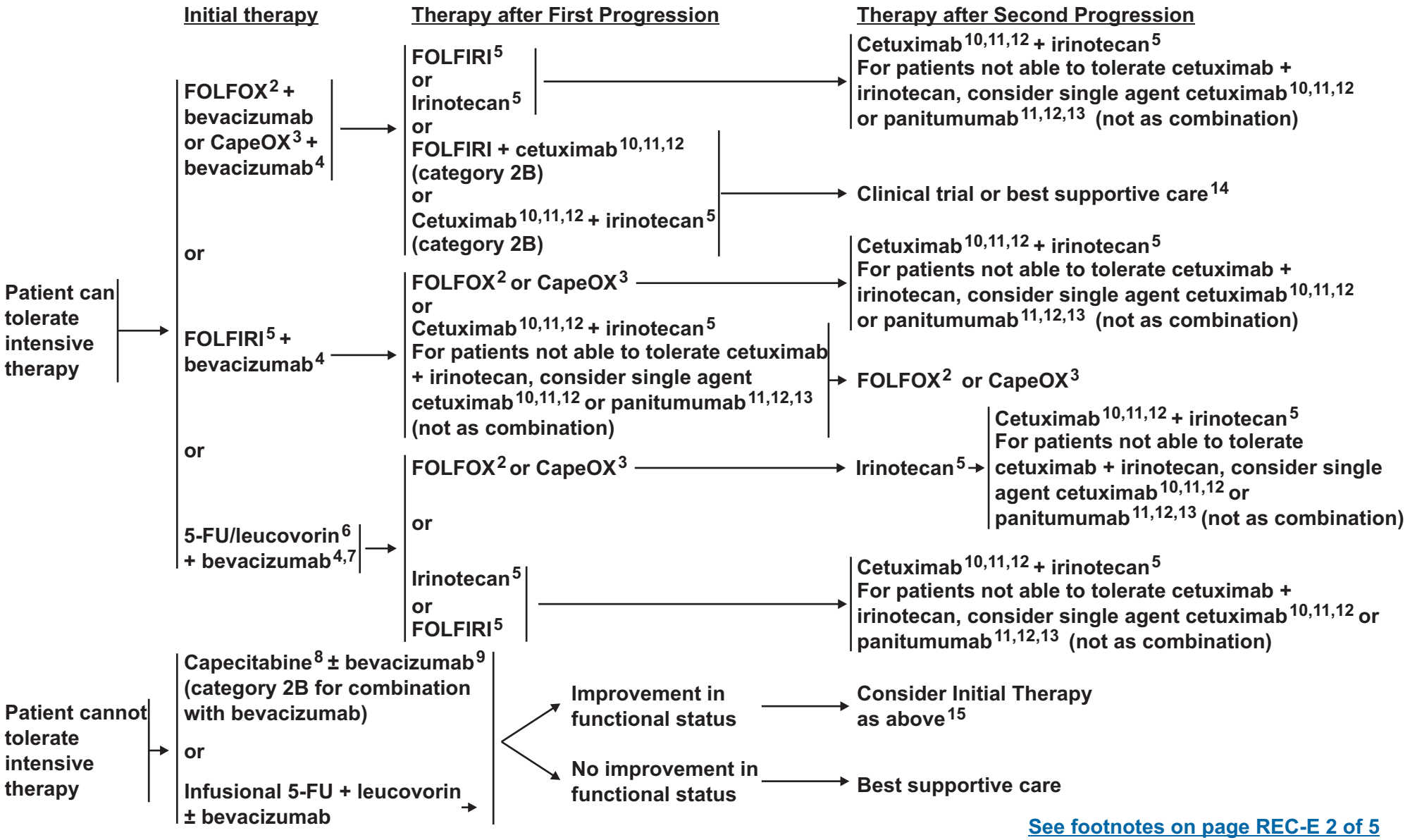
CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:[1] (PAGE 1 of 5)



See footnotes on page REC-E 2 of 5

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 2 of 5)

[1] For chemotherapy references, see Chemotherapy Regimens and References (REC-E pages 3 - 5).

[2] Discontinuation of oxaliplatin is strongly considered from FOLFOX or CapeOX after 3 months of therapy or sooner if significant neurotoxicity develops (> grade 3) with other drugs maintained (fluoropyrimidine + bevacizumab) until time of tumor progression. Oxaliplatin may be reintroduced if it was discontinued previously for neurotoxicity rather than disease progression. Tournigand C, Cervantes A, Figer A, et al. OPTIMOX1: A randomized study of FOLFOX4 or FOLFOX7 with oxaliplatin in a stop-and-go fashion in advanced colorectal cancer - A GERCOR Study. J Clin Oncol 2006;24:394-400. Ca/Mg infusions should not be used to reduce neurotoxicuty because treatment reduces rate of response to FOLFOX.

[3] The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m^2 twice daily for 14 days, repeated every 21 days, is standard. Some data suggest that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large scale randomized trials. For good performance status patients, the 1000 mg/m^2 twice daily dose is the recommended starting dose, with close monitoring in the first cycle for toxicity, and dose adjustments as indicated.

[4] There are no prospective data to support continuation of bevacizumab with a second-line regimen after first progression on a bevacizumab-containing regimen and such use is not routinely recommended. If bevacizumab not used in initial therapy, it may be appropriate to consider if there is no contraindication to therapy. There is an increased risk of stroke and other arterial events especially in age $\geq$ 65. The use of bevacizumab may interfere with wound healing.

[5] Irinotecan should be used with caution and with decreased doses in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established.

[6] Infusional 5-FU is preferred. Bolus regimens of 5-FU are inappropriate as combination regimens with oxaliplatin or irinotecan.

[7] A treatment option for patients not able to tolerate oxaliplatin or irinotecan.

[8] Patients with diminished creatinine clearance may require dose modification of capecitabine.

[9] Routine use of bevacizumab + cetuximab is not recommended in patients with prior bevacizumab progression.

[10] Cetuximab is indicated in combination with irinotecan-based therapy or as single agent therapy for patients who cannot tolerate irinotecan.

[11] EGFR testing has no demonstrated predictive value, and therefore routine EGFR testing is not recommended. No patient should be included or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.

[12] There are no data, nor is there a compelling rationale, to support the use of panitumumab after clinical failure on cetuximab, or the use of cetuximab after clinical failure on panitumumab. As such, the use of one of these agents after therapeutic failure on the other is not recommended.

[13] There are no data to support the combination of panitumumab with chemotherapy.

[14] Single agent or combination therapy with capecitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.

[15] The use of single agent capecitabine as a salvage therapy after failure on a fluoropyrimidine-containing regimen has been shown to be ineffective, and this is therefore not recommended.

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 5)

CHEMOTHERAPY REGIMENS

FOLFOX
FOLFOX 4
Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1
Leucovorin 200 mg/m^2 IV over 2 hours, days 1 and 2
Followed on days 1 and 2 by 5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours continuous infusion
Repeat every 2 weeks[1]

mFOLFOX 6
Oxaliplatin 85 mg/m^2 IV over 2 hours, day 1
Leucovorin* 400 mg/m^2 IV over 2 hours, day 1
5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks[2,3]

CapeOX[3,4]
Oxaliplatin 130 mg/m^2 day 1, Capecitabine 850-1000‡ mg/m^2 twice daily for 14 days
Repeat every 3 weeks

FOLFIRI[5,6]
Irinotecan 180 mg/m^2 IV over 30-120 minutes, day 1
Leucovorin 200 mg/m^2 IV infusion to match duration of irinotecan infusion, days 1 and 2
Followed on days 1 and 2 by 5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours continuous infusion
Repeat every 2 weeks

Irinotecan 180 mg/m^2 IV over 30-120 minutes, day 1
Leucovorin 400* mg/m^2 IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m^2 IV bolus day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Bevacizumab + 5-FU containing regimens:[7,8,9]
Bevacizumab 5 mg/kg IV every 2 weeks +
5-FU and Leucovorin
or FOLFOX[10]
or FOLFIRI
Bevacizumab 7.5 mg/kg IV every 3 weeks + CapeOX[4]

*Leucovorin dose in Europe is 200 mg/m^2 of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

‡The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m^2 twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large scale randomized trials.

See footnotes on page 5 of 5 REC-E

See Additional Chemotherapy Regimens 4 of 5 REC-E

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 4 of 5)

CHEMOTHERAPY REGIMENS

Capecitabine[11]
2000-2500 mg/m^2/day PO in two divided doses, days 1-14, followed by 7 days rest
Repeat every 3 weeks

Bolus or infusional 5-FU/leucovorin
Roswell-Park regimen[12]
Leucovorin 500 mg/m^2 IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m^2 IV bolus 1 hour after start of Leucovorin, days 1, 8, 15, 22, 29, 36
Repeat every 8 weeks

Biweekly[13]
Leucovorin 200 mg/m^2 IV over 2 hours, days 1 and 2
5-FU 400 mg/m^2 IV bolus, then 600 mg/m^2 IV over 22 hours continuous infusion, days 1 and 2
Repeat every 2 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)[14]
Leucovorin 400* mg/m^2 IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m^2 and then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours)† continuous infusion
Repeat every 2 weeks

Weekly
Leucovorin 20 mg/m^2 as a 2 h infusion
5-FU 500 mg/m^2 bolus administered 1 h after LV infusion
Repeat every week[15]
5-FU 2600 mg/m^2 by 24 h infusion plus leucovorin 500 mg/m^2
Repeat every week[16]

Irinotecan[17,18]
Irinotecan 125 mg/m^2 IV over 30-90 minutes, days 1, 8, 15, 22
Repeat every 6 weeks

Irinotecan 300-350 mg/m^2 IV over 30-90 minutes, day 1
Repeat every 3 weeks

Cetuximab ± irinotecan[19]
Cetuximab 400 mg/m^2 1st infusion, then 250 mg/m^2 weekly
or
Cetuximab 500 mg/m^2 every 2 weeks[20]
±
Irinotecan
300-350 mg/m^2 IV every 3 weeks
or
180 mg/m^2 IV every 2 weeks
or
125 mg/m^2 every week for 4 weeks
Every 6 weeks

Panitumumab[21]
Panitumumab 6 mg/kg IV administered over 60 minutes every 2 weeks

*Leucovorin dose in Europe is 200 mg/m^2 of levo-leucovorin. Levo-leucovorin is not available in the United States. The equivalent dose of leucovorin is 400 mg/m^2.

†NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m^2/day NOT 2400 mg/m^2/day over 46 hours) to minimize medication errors.

See footnotes on page 5 of 5 REC-E

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 5 of 5)

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

Staging

Table 1

American Joint Committee on Cancer (AJCC) TNM Staging System for Colorectal Cancer*

Primary Tumor (T)

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ: intraepithelial or invasion of lamina propria†
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into the subserosa, or into nonperitonealized pericolic or perirectal tissues
T4 Tumor directly invades other organs or structures, and/or perforates visceral peritoneum‡

Regional Lymph Nodes (N)§

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage Grouping

Stage	T	N	M	Dukes¶	MAC¶
0	Tis	N0	M0	-	-
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4	N0	M0	B	B3
IIIA	T1-T2	N1	M0	C	C1
IIIB	T3-T4	N1	M0	C	C2/C3
IIIC	Any T	N2	M0	C	C1/C2/C3
IV	Any T	Any N	M1	-	D

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiatied
G4 Undifferentiated

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the *AJCC Cancer Staging Manual*, *Sixth Edition* (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed written permission of Springer-Verlag New York on behalf of the AJCC.

†Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

‡Direct invasion in T4 includes invasion of other segments of the colorectum by way of the serosa; for example, invasion of the sigmoid colon by a carcinoma of the cecum. Tumor that is adherent to other organs or structures, macroscopically, is classified T4. However, if no tumor is present in the adhesion, microscopically, the classification should be pT3. The V and L substaging should be used to identify the presence or absence of vascular or lymphatic invasion.

§A tumor nodule in the pericolorectal adipose tissue of a primary carcinoma without histologic evidence of residual lymph node in the nodule is classified in the pN category as a regional lymph node metastasis if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, it should be classified in the T category and also coded as V1 (microscopic venous invasion) or as V2 (if it was grossly evident), because there is a strong likelihood that it represents venous invasion.

¶Dukes B is a composite of better (T3 N0 M0) and worse (T4 N0 M0) prognostic groups, as is Dukes C (Any TN1 M0 and Any T N2 M0). MAC is the modified Astler-Coller classification.

Note: The y prefix is to be used for those cancers that are classified after pretreatment, whereas the r prefix is to be used for those cancers that have recurred.

Manuscript

This manuscript is being updated to correspond with the newly updated algorithm. Last update 07/31/07

NCCN Categories of Evidence and Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

In 2007 an estimated 41,420 new cases of rectal cancer will occur in the United States (23,840 cases in men; 17,580 cases in women). During the same year, it is estimated that 52,180 people will die from rectal and colon cancer.[1] Although colorectal cancer is ranked as the third most frequently diagnosed cancer in men and women, mortality from rectal cancer has decreased during the past 30 years. This decrease may be due to both 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 clinical experience), that the recommendation is appropriate. The panel unanimously endorses patient participation in a clinical trial 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. The clinical practice guidelines for managing rectal cancer overlap considerably with the NCCN Colon Cancer Guidelines. First-degree relatives of patients with newly diagnosed adenomas[2] or invasive carcinoma[3] are at increased risk for colorectal cancer. Therefore, rectal cancer patients, especially those 50 years or younger, should be counseled regarding their family history as outlined in the NCCN Colorectal Screening Guidelines.

TNM Staging

The NCCN Rectal Cancer Guidelines adhere to the current TNM staging system as included in the 6th edition of the American Joint Committee on Cancer's (AJCC) *Cancer Staging Manual* (Table 1).[4, 5] Stage I rectal cancer is defined as T1-T2, N0, M0. Stage II disease is now subdivided into IIA (if the primary tumor is T3, N0, M0) and IIB (for T4, N0, M0 lesions). Stage III disease is subdivided into IIIA (T1-2, N1, M0), IIIB (T3-4, N1, M0), and IIIC (any T, N2, M0). Stage IV disease is defined as any T, any N, and the presence of one 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 regional lymph nodes. 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] includes the suggestion that the surgeon mark the area of the specimen with the deepest tumor penetration so that the pathologist can directly evaluate the status of the resection margins. The 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. Some of the 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 the cancer; 3) depth of penetration and extension to adjacent structures (T); 4) number of regional lymph nodes evaluated and 5) number of positive regional lymph nodes (N); 6) the presence of distant metastases to other organs, the peritoneum of an abdominal structure, or non-regional lymph nodes (M) and 7) the status of proximal, distal, and circumferential (radial) margins.[5,7] The prefixes "p" and "yp" used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.[8]

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer. Whereas 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 (ie, 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 1-2 mm from the transected margin.[10,11,12,13] Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important since 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]

The AJCC and College of American Pathologists (CAP) recommend evaluation of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancers.[5,6] 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 have reported 14 and >10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.[16,17] The mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs 19, $P<0.05$; 7 vs 10, $P\leq0.0001$).[18,19]

Results of studies evaluating the sentinel node for micrometastatic disease through use of 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.[20,21] 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.[22,23] In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.[24] 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.

Clinical Presentation and Treatment

Management of Polypoid Cancer

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or villous adenoma, physicians should review pathology and consult with the patient.[25] A malignant rectal polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore not considered to be capable of regional nodal metastasis.[5] The panel recommends marking the cancerous polyp site at the time of colonoscopy or within 2 weeks. In patients with invasive cancer and adenoma (tubular, tubulovillous or villous), no additional surgery is required for pedunculated or sessile polyps, if the polyp has been completely resected with favorable histological features.[25] Favorable histological features include lesions of grade 1 or 2, no angiolymphatic invasion and a negative resection margin. However, in addition to the option of observation, the panel includes the option of colectomy in patients with a completely-removed, single-specimen, sessile polyp with favorable histological features and clear margins because it has been reported that patients with sessile polyps have a 10% risk of lymph node metastases.[26] For pedunculated and sessile polyps, unfavorable histopathological features are: grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. It should be noted that there is currently no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as the presence of tumor within 1-2 mm from the transected margin and the presence of tumor cells within the diathermy of the transected margin.[25,27-29] For a pedunculated or sessile polyp with fragmented specimen or margins that cannot be assessed or unfavorable pathology, either a transanal excision or a transabdominal resection is recommended (See section on Surgical Approaches used in the management of rectal cancer appropriate for resection). Results from a preoperative endoscopic ultrasound evaluation may provide additional information to guide choice of surgical approach, although the accuracy of this method to detect residual cancer is limited (see section on Clinical Evaluation/Staging).[30] All patients who have resected polyps should undergo total colonoscopy to rule out other synchronous polyps, as well as appropriate follow-up surveillance endoscopy.[31]

Management of Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge by rigid protoscopy.[32] Some support for this definition comes from the study of Kapiteijn et al.[33] which included a subgroup analysis of the risk of recurrence of rectal cancer based on tumor location. Univariate analyses indicated that local recurrence rates were low for patients who had tumors with an inferior margin of 10.1 cm or more from the anal verge, and that no significant differences between patients in this group receiving radiotherapy and surgery were observed when they were compared to those undergoing surgery alone.

Determination of an optimal treatment plan for an individual patient with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative or palliative), consideration must also be given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence, and preserving genitourinary functions. 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.[34] Furthermore, the risk of pelvic recurrence is higher in patients with rectal cancer compared to those with colon cancer, and locally recurrent rectal cancer has frequently been associated with a poor prognosis.[35,36] Careful patient selection with respect to particular treatment options and the use of sequenced

multimodality therapy for selected patients which 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. Since the clinical stage of the disease is used to direct decisions regarding choice of primary treatment, including surgical intent (eg, curative or palliative) and approaches, and whether to recommend preoperative chemoRT, the implications of either clinically under-staging or over-staging rectal cancer can be substantial.

Patients who present with rectal cancer appropriate for resection require complete staging evaluation, including total colonoscopy and protoscopy to provide a determination of the location of the cancer and to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum, a complete physical examination, including assessment of performance status, to determine operative risk, carcinoembryonic antigen (CEA) determination, and baseline computed tomographic (CT) scans of the chest, abdomen and pelvis. The consensus of the panel is that a positron emission tomography (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 magnetic resonance imaging (MRI), makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.[37] Additional information regarding the extent of disease and the occurrence of distant metastases can be determined preoperatively through CT scans. If available, endorectal ultrasound, 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 demonstrated 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%).[38] Only a very limited number of studies using CT for the purpose of T-staging have been performed, and it is not currently considered to be an optimal method for staging the extent of tumor penetration.[38,39] Accurate assessment of nodal status is one of the greatest challenges in the preoperative staging of rectal cancer. In the meta-analysis of Bipat et al.,[38] the sensitivities and specificities of the 3 imaging modalities for accurately evaluating lymph node involvement were: CT (55% and 74%); endoscopic ultrasound (67% and 78%); and MRI (66% and 76%). Results from another recent meta-analysis of 84 articles, indicated that none of the 3 imaging modalities were significantly superior to another method with respect to an accurate determination of tumor N-stage.[40] Disadvantages of endoscopic ultrasound and MRI include a high degree of operator dependence.[38] 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 prior to radical surgery.[39-41]

Clinical staging is also based on histopathologic examination of the specimen obtained via biopsy or local excision (eg, excised polyps). Endoscopic biopsy specimens of the lesion should undergo careful pathology review for evidence of invasion into the muscularis mucosa. If removal of the rectum is contemplated, early consultation with an enterostomal therapist is recommended for preoperative marking of the site and patient teaching purposes.

Surgical Approaches

A variety of surgical approaches, depending on the location and extent of disease, are used to treat the primary rectal cancer lesion.[42] These methods include local procedures, such as polypectomy, transanal excision and transanal microsurgery, and radical procedures involving an transabdominal resection (eg, low anterior resection [LAR], total mesorectal excision [TME] with coloanal anastomosis or abdominoperineal resection [APR]).

Transanal excision may be appropriate for selected early-stage cancers. Small (<3 cm), well to moderately differentiated T1 tumors that are within 8 cm of the anal verge and limited to less than 30% of the rectal circumference, and for which there is no evidence of nodal involvement (category 2A) can be approached with a full thickness excision with a 3 mm negative margin. An alternative technique to full thickness excision is transanal endoscopic microsurgery. Advantages of a local procedure include minimal morbidity (eg, a sphincter-sparing procedure) and mortality and rapid postoperative recovery.[34,43] If pathologic examination reveals adverse features such as high grade, positive margins, lymphovascular invasion (LVI) or perineural invasion, a more radical resection is recommended.

Patients with rectal cancer who do not meet requirements for local surgery should be treated with a transabdominal resection. Organ-preserving procedures which maintain sphincter function are preferable, but not possible, in all cases. For lesions in the mid to upper rectum, a low anterior resection (LAR), followed by creation of a colorectal anastomosis, is the treatment of choice. Where creation of an anastomosis is not possible, colostomy is required. Laparoscopic surgery is not recommended outside of a clinical trial. For low rectal lesions, abdominoperineal resection (APR) or total mesorectal excision (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" and is designed to spare the autonomic nerves.[34,44] In cases where anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis. An APR involves en bloc resection of the rectosigmoid, the rectum, and the anus, as well as the surrounding mesentery, mesorectum, and perianal soft tissue and necessitates creation of a colostomy.[45] An APR is necessary in cases where 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 section on Neoadjuvant/Adjuvant Therapy, below), tumor location is not altered. Whereas sphincter preservation may become possible in cases where 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.

Neoadjuvant/Adjuvant Therapy

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 (RT), and chemotherapy is recommended for the majority of 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/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. [46,47] 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 (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected). However, one disadvantage of using preoperative RT is the possibility of over-treating early-stage tumors which do not require adjuvant radiation.[47-49] However, improvements in preoperative staging techniques, such as endoscopic ultrasound and CT scans, allow for more accurate staging.

The results of the Swedish Rectal Cancer Trial evaluating the use of RT administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence with this approach compared with surgery alone.[50] However, whereas a number of other studies investigating the effectiveness of preoperative RT or postoperative RT in patients with rectal cancer staged as T1-3 have demonstrated improvements in local control of disease, overall survival was not shown to be significantly affected.[33,51] Preliminary results from a study of patients with stage II/III rectal cancer comparing short course (5 day) preoperative RT to a postoperative approach which included chemoRT in selected patients (ie, those with a positive CRM following resection) and no RT in patients without evidence of residual disease following surgery indicated that patients in the preoperative RT arm had significantly lower local recurrence rates and a 5% absolute improvement in 3-year disease-free survival (DFS) (P=0.03).[52]

A number of randomized trials have evaluated the effectiveness of chemoRT administered either preoperatively following clinical evaluation/staging (eg, T3-4 by endoscopic ultrasound) or postoperatively following pathologic staging of rectal cancer as T3 and/or N1-2. Putative benefits of addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (ie, eradication of micrometastases), whereas preoperative chemoRT also has the potential to increase rates of pathologic complete response and sphincter preservation. In a study of patients with T3/4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative RT alone or preoperative concurrent chemoRT with 5-FU/LV, no difference in overall survival or sphincter preservation was observed in the 2 groups, although patients receiving chemoRT were significantly more likely to exhibit a pathologic complete response (11.4% vs 3.6%; P<0.05) and grade 3/4 toxicity (14.6% vs 2.7%; P<0.05) and less likely to exhibit local recurrence of disease (8.1% vs 16.5%; P<0.05).[53] A large prospective, randomized trial from The German Rectal Cancer Study Group compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer.[47] Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs 13%; P=0.006) 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-T4 resectable rectal cancer demonstrated that use of 5-FU/LV chemotherapy enhanced the tumorocidal effect of RT when the 2 approaches were used concurrently. Significant reductions in tumor size, pTN stage, and lymphatic, vascular and perineural invasion rates were observed with use of combined-modality therapy compared

with use of RT and surgery without chemotherapy.[54,55] 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 preoperatively or postoperatively.[56] Although local recurrence rates were significantly lower in the groups receiving RT followed by chemotherapy, concurrent chemoRT, or concurrent chemoRT plus chemotherapy compared to the group receiving preoperative RT alone, the addition of chemotherapy after concurrent chemoRT did not significantly impact local recurrence rates.

Whereas 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,[47] this conclusion has not been supported by 2 recent meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.[57,58] Other factors to consider when choosing preoperative chemoRT over initial surgery followed by postoperative chemoRT for patients with T3, N0 rectal cancer include the risk of over-treating an inaccurately staged patient when following a preoperative approach, and the decreased adherence associated with postoperative therapy.[47,56]

Although combined-modality therapy has been associated with decreased rates of local recurrence of rectal cancer, it is also associated with increased toxicity (eg, radiation-induced injury, hematologic toxicities, etc.) relative to surgery alone.[9,59] It has been suggested that some patients with disease at lower risk of local recurrence (eg, proximal rectal cancer staged as T3, N0, M0) may be adequately treated with surgery and adjuvant chemotherapy.[9,60,61]

With respect to 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 noninferior to bolus 5-FU plus LV.[60] After a median follow-up of 4 years, neither the rate of local control nor survival differed among 3 different combinations of modulated 5-fluorouracil (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 follow-up of 5.7 years) in which similar outcomes with respect to overall survival and relapse-free survival were observed 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.[62] 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 to bolus 5-FU.[63] Most of the patients in this study had node-positive disease. No phase III randomized data are currently available on the use of capecitabine/RT in rectal cancer, although trials are pending.[64] A limited number of phase I/II studies have demonstrated that chemoRT with capecitabine was well tolerated with no toxicity or mild to moderate toxicity in the majority of patients with stage II/III rectal cancer and produced comparable results to those obtained with continuous infusion of 5-FU and RT.[65-68] Furthermore, results from the study of Smalley et al.[62] indicating that bolus 5-FU is equivalent to infusional 5-FU in concurrent chemoRT for locally advanced rectal cancer provide indirect support for the hypothesis that capecitabine will not be inferior to 5-FU when used in concurrent chemoRT to treat rectal cancer.

Postoperative chemoRT regimens commonly employ a “sandwich” approach – whereby chemotherapy (typically 5-FU based) is administered before and after the chemoRT regimen.[60,62,63] The use of FOLFOX or capecitabine chemotherapy before and after postoperative chemoRT is an extrapolation of the available data in colon cancer.[69,70]

Clinical trials evaluating these agents in the setting of rectal cancer are still pending.

With respect to administration of RT, multiple RT fields should include the tumor or tumor bed with a 2-5 cm margin, presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures and the inguinal nodes should be included for tumors invading into the distal anal canal. Recommended doses of radiation are typically 45-50 Gy, with the exceptions of unresectable cancers where doses higher than 54 Gy may be required, and irradiation of the small bowel where the dose should be limited to 45 Gy. Although not standard routine practice, use of intensity modulated radiotherapy (IMRT) which uses computer-imaging to focus RT to the tumor site and potentially decrease toxicity to normal tissue,[71,72] can be considered. As an additional boost, intraoperative radiotherapy (IORT),[73,74,75] 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 5-10 weeks following completion of therapy prior to performance of surgical resection in order to allow patient recuperation from chemoRT-associated toxicities. Although longer intervals (ie, 10 weeks) from completion of chemoRT to surgery have been shown to be associated with an increase in pathologic complete response rates,[76] 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.[77]

Adjuvant chemotherapy of approximately 6 months duration is recommended for all patients with stage II/III rectal cancer following neoadjuvant chemoRT/surgery regardless of the surgical pathology results, although few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer and its role is not well defined. 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/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 to the group receiving adjuvant chemotherapy alone.[78] However, no benefit of adding 5-FU-based adjuvant chemotherapy to preoperative chemoRT with respect to rate of local recurrence was observed in the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group Trial 22921 (hazard ratio=0.87; 95% CI, 0.72-1.04; P=0.13) when the DFS of patients receiving adjuvant chemotherapy following preoperative RT (+/- 5-FU-based chemotherapy) was compared to DFS of patients who underwent preoperative RT (+/- 5-FU-based chemotherapy) but did not receive adjuvant 5-FU-based chemotherapy.[56] 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.[69,70] 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/III rectal cancer patients following either preoperative or postoperative chemoRT. Early reports indicate that adjuvant FOLFOX can be safely used in this patient population.[79] The ECOG E5204 trial is currently evaluating the effect of postoperative 5-FU/LV plus oxaliplatin with or without bevacizumab on the overall survival of patients with stage II/III rectal cancer treated with preoperative 5-FU-based chemoRT.

Treatment of Nonmetastatic Rectal Cancer

Recommendations for patients with T1 and T2 lesions

Node-negative T1 and T2 lesions are treated with transabdominal resection or transanal excision (category 2B for T2), if appropriate. This recommendation is category 2B for node-negative T2 tumors since local recurrence rates of 11% to 45% have been observed for T2 lesions following local excision alone.[34,80,81] In selected lesions that are staged by endoscopic ultrasound or MRI as T1-2, N0 and without adverse pathologic features (eg, no lymphovascular invasion [LVI] or perineural invasion; size less than 3 cm; well to moderately differentiated), local excision with negative margins may give results comparable to transabdominal resection.[82] 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 these patients who receive adjuvant chemoradiation without additional surgery in order 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). The recommended duration of adjuvant therapy is 6 months. For patients with pathologic evidence of proximal T3, N0, M0 disease with clear margins and favorable prognostic features following resection, the incremental benefit RT likely is small and chemotherapy alone can be considered (category 2B), although 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 or transabdominal resection. Preoperative neoadjuvant chemoRT is the preferred treatment. Upfront surgery should be reserved for patients with medical contraindications to chemoRT or patients with T3, N0 lesions. 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 5-10 weeks following completion of neoadjuvant therapy followed by 6 months of adjuvant chemotherapy (regardless of surgical pathology results) with 5-FU with or without LV (category 1 for T3, N0 or Tany, N1-2 tumors) or FOLFOX (category 2B) or capecitabine (category 2B).

Patients with disease characterized asT3, N0 or T any, N1-2 disease initially treated by transabdominal resection with subsequent pathologic staging of disease as pT1-2, N0, M0 can be followed with observation only. Patients with disease staged as pT3, N0, M0 or pT1-3, N1-2, M0 following initial treatment by transabdominal resection should receive 6 months of adjuvant therapy with 5-FU with or without LV or 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) or 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 following transabdominal resection, the incremental benefit RT is likely is 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 and/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). If possible, resection should be considered following preoperative chemotherapy. Adjuvant therapy for 6 months with either 5-FU with or without LV (category 2A), FOLFOX (category 2B) or capecitabine (category 2B) is indicated regardless of the surgical pathology results.

Treatment of Metastatic Disease

Approximately 50%-60% of patients diagnosed with colorectal cancer will develop colorectal metastases.[83,84] 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%-25% of patients with colorectal cancer present with synchronous liver metastases, although 80%-90% of these patients are initially evaluated to have unresectable metastatic liver disease.[83,85,86,87] Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver as a common site of involvement.[88] There is some evidence to indicate 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=0.008) and more bilobar metastases (P=0.016) when compared with patients diagnosed with metachronous liver metastases.[89]

It has been estimated that over one-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.[90] 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.[85] Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing surgery have been shown to approach 0% in a number of studies.[83,91] 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.[83,92] Recent reports have shown 5-year survival rates following resection of hepatic colorectal metastases exceeding 50%.[93,94] 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.[95]

The criteria for determining patient suitability for resection, or surgical cure, of metastatic disease are evolving, with the emphasis being increasingly placed 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.[96,97] Resectability differs fundamentally from endpoints which focus more on palliative measures of treatment such as response and DFS. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease,[98] since partial liver resection or debulking has not been shown to be beneficial.[84] Approaches used in the surgical treatment of liver metastases include preoperative portal vein embolization for the purpose of increasing the volume and function of the portion of the liver

which will remain postsurgically, hepatic resection performed in 2 stages for bilobar disease, and the use of ablative methods in combination with resection.[96]The panel does not recommend the use of ablative techniques without resection or in patients for whom negative margins can be achieved with resection alone.[99] Resection of liver metastases should not be performed in the presence of unresectable sites of extrahepatic disease, and hepatic intra-arterial embolization should not routinely be used outside of a clinical trial.

Since the majority of patients diagnosed with metastatic colorectal disease are initially classified as unresectable, neoadjuvant chemotherapy is being increasingly employed to downsize colorectal metastases. Potential advantages of this approach include: earlier treatment of micrometastatic disease; determination 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.[85,100] Furthermore, results from a recent study of colorectal cancer patients receiving neoadjuvant 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.[101] It is therefore essential that during treatment with neoadjuvant chemotherapy, frequent evaluations are undertaken and close communication is maintained between medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed which optimizes exposure to the neoadjuvant regimen and facilitates an appropriately-timed surgical intervention.[102]

Certain clinicopathologic factors, such as the presence of extrahepatic metastases and a disease-free interval of < 12 months, have been associated with a poor prognosis in patients with colorectal cancer,[93,94,103-105] although the ability of these factors to predict outcome following resection may be limited.[83] However, decision-making relating to whether to offer neoadjuvant 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 resectable In addition, neoadjuvant chemotherapy may be more beneficial in patients who have not been exposed to prior chemotherapy or who have not received prior chemotherapy in the previous 12 months.

An important benefit of the preoperative approach is the potential to convert patients with initially unresectable metastatic disease to a resectable state. In the study of Pozzo et al, it was reported that neoadjuvant therapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection.[97] Median time to progression was 14.3 months with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the North Central Cancer Treatment Group (NCCTG),[87] 44 patients with unresectable liver metastases were treated with FOLFOX4. Twenty five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study of 1104 initially unresectable patients with colorectal liver disease, 335 patients (23%) were able to undergo primary hepatic resection and 138 patients (12.5%) classified as "good responders" underwent secondary hepatic resection following

neoadjuvant treatment which included oxaliplatin in the majority of cases.[106] The 5-year survival rate for these 138 patients overall was 33%. More recently, 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-containing chemotherapy regimens indicated that 24 patients (3.3%) were able to undergo curative liver resection following treatment.[107] The median overall survival time in this group was 42.4 months.

Recently, the efficacy of bevacizumab in combination with FOLFOX and FOLFIRI (infusional 5-FU, LV, irinotecan) in the treatment of unresectable metastatic disease (see section on Chemotherapy for Advanced or Metastatic Disease) has led to its use in combination with these regimens in the neoadjuvant 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 to the group receiving chemotherapy alone while undergoing major surgery (13% vs 3.4%, respectively; P=0.28).[108] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery, the incidence of wound healing complications in either group of patients was low (1.3% vs 0.5%; P=0.63). The panel recommends at least a 6 week interval (which corresponds to 2 half-lives of the drug[109]) between the last dose of bevacizumab and elective surgery.

Colorectal metastatic disease can also occur in the lung.[110] Most of the treatment recommendations discussed for metastatic colorectal liver disease, with the exception of hepatic arterial infusion (HAI), also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in selected cases.[111] The goal of treatment of most abdominal/peritoneal metastases is palliative, rather than curative. The panel does not recommend cytoreductive resection of disseminated carcinomatosis with or without hyperthermia and intraperitoneal chemotherapy outside of a clinical trial.

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 relative to 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; neoadjuvant combination chemotherapy with a bevacizumab-containing regimen to target metastatic disease; and a surgical approach (ie, 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 neoadjuvant 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 is 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 three times more likely to develop distant metastases than local recurrence of disease after a median follow-up of over 5 years.[56]

Although only limited data exist regarding the efficacy of adjuvant chemotherapy following resection for metastatic colorectal liver or lung disease, administration of a course of an active systemic chemotherapy

regimen for metastatic disease is recommended by the panel for some patients following liver or lung resection who have received preoperative chemoRT or no neoadjuvant therapy following staged or synchronous resection of metastases and rectal lesion in order to increase the likelihood that residual microscopic disease will be eradicated. Postoperative chemoRT is recommended for patients with synchronous metastases who have not received prior chemoRT and who are at higher risk for pelvic recurrence following staged or synchronous resection of metastases and rectal lesion (ie, 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 (HAI) is included in the guidelines as an option for patients with metachronous liver metastases (category 2B). After hepatic resection, administration of floxuridine by HAI in addition to systemic chemotherapy was shown to be superior to systemic chemotherapy alone with respect to survival and time to hepatic progression but not time to extrahepatic progression.[85,112-114] An investigation of the current role of HAI with floxuridine in conjunction with oxaliplatin and capecitabine in the treatment of metastatic colorectal liver disease is underway in the NSABP C-09 trial. Some of the uncertainties regarding patient selection for neoadjuvant chemotherapy are also relevant to the application of HAI.[92] Limitations on the use of HAI therapy include the potential for biliary toxicity[85] and the requirement for specific technical expertise.

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease. Patients with disease recurrence at the anastomotic site are more likely than those with an isolated pelvic recurrence to be cured following re-resection.[115,116] 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.[115]

Recommendations for Treatment of Synchronous Metastases/Resectable

Initial treatment options for patients with stage IV disease (any T, any N, M1) with resectable liver or lung metastases include: 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 combination chemotherapy (eg, FOLFOX, CapeOX, or FOLFIRI regimens with bevacizumab). For the latter 2 groups of patients, surgery should be performed 5-10 weeks following completion of neoadjuvant therapy.

Adjuvant therapy for patients undergoing initial surgery is dependent 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 (eg, disease pathologically staged as pT3-4, Any N or Any T, N1-2) undergo postoperative chemoRT using the “sandwich” approach (ie, chemotherapy followed by concurrent chemoRT followed by chemotherapy for 4-6 months).[62,63] 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 the population of 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 recommended that these patients receive adjuvant chemotherapy with one of the following options: 5-FU with or without LV for 6 months (category 2A); FOLFOX or CapeOX plus bevacizumab for 4-6 months (category 2B); FOLFIRI plus bevacizumab for 4-6 months (category 2B). Adjuvant therapy

recommendations for patients who have received neoadjuvant chemoRT is as described for patients with pT1-2,N0 disease, whereas patients who have undergone neoadjuvant bevacizumab-containing therapy should receive postoperative chemoRT as described above for patients with pT3-4, Any N, or Any T, N1-2 disease.

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. Asymptomatic patients should receive chemotherapy for advanced or metastatic disease.

Recommendations for Treatment of Metachronous Metastases

Upon documentation 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.[117] Two other factors further distinguish the management of metachronous metastatic disease from that of synchronous disease: an evaluation of the chemotherapy history of the patient; and the absence of transabdominal resection. Resectable patients are classified according to whether they have received no previous chemotherapy or prior chemotherapy within or prior to the previous 12 months. For patients who have not received prior chemotherapy and who have resectable metastatic disease, primary treatment options include neoadjuvant chemotherapy followed by resection and additional postoperative chemotherapy; or initial resection followed by chemotherapy. The optimal sequence of therapeutic interventions is less clear for patients who have received prior adjuvant chemotherapy. For patients who exhibit disease recurrence or progression during or within 12 months of chemotherapy, the role of neoadjuvant chemotherapy is less clear. Administration of floxuridine by HAI (category 2B) in addition to systemic chemotherapy through a pump or port implanted during surgery is an option for these patients. Following surgery, adjuvant therapy with an alternative active metastatic chemotherapy regimen can be considered.

Patients determined by cross-sectional imaging or PET scan to have unresectable rectal cancer should receive an active metastatic chemotherapy regimen based on prior chemotherapy history. 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. Patients with chemotherapy-responsive disease who are converted to a resectable stage should undergo resection followed by adjuvant treatment with an active chemotherapy regimen. If metastatic lesions remain unresectable subsequent treatment is dependent, in part, on the performance status (PS) of the patient. Treatment with an active chemotherapy regimen for advanced or metastatic disease is the treatment of choice for patients with PS 0-2. Patients with PS ≥ 3 are given best supportive care. Best supportive care is an option for patients diagnosed with metachronous metastases who have previously received all active chemotherapy regimens in cases of both resectable and unresectable disease.

Isolated pelvic/anastomotic recurrence is optimally managed by preoperative RT and concurrent infusional 5-FU, if full course RT was not given previously. If full course RT was not given previously, additional RT should be considered if it can be safely delivered. Resection should be performed, if possible, although debulking, resulting in gross residual cancer, is discouraged. The panel does not

recommend cytoreductive surgery of disseminated carcinomatosis outside of a clinical trial. Patients with unresectable lesions are treated according to their ability to tolerate therapy.

Chemotherapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colorectal cancer uses various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine; irinotecan, oxaliplatin,,bevacizumab, cetuximab, and panitumumab.[118-133] The putative mechanisms of action of these agents are varied and include interference with DNA replication, and inhibition of the activities of vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) receptors.[83,134-137] The choice of therapy is based on consideration of the type and timing of the prior therapy that has been administered and the differing toxicity profiles of the constituent drugs. Although the specific chemotherapy regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[122] For example, if oxaliplatin, administered as a part of an initial treatment regimen, is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the rest of the treatment regimen would still be considered initial therapy. 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, as well as plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices following first progression of disease should be based, in part, on the prior therapies received by the patient (ie, exposing patient to a range of cytotoxic agents). Further, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, as well as the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient with good tolerance to intensive therapy, the panel recommends a choice of 4 chemotherapy regimens: FOLFOX (eg, FOLFOX4 and mFOLFOX6),[120,131,138-143] CapeOX,[143-145] FOLFIRI,[123,138,142,146] or infusional 5-FU/LV.[125,130,146-148] The panel further recommends that each of these regimens be administered in combination with bevacizumab when used for initial therapy. With respect to the treatment of metastatic disease, the panel consensus is that FOLFOX plus bevacizumab and CapeOX plus bevacizumab can be used interchangeably,[143] and that both of these combination regimens, as well as FOLFIRI plus bevacizumab, represent standards of care for the initial treatment of metastatic colorectal cancer. The infusional 5-FU/LV plus bevacizumab regimen is recommended as initial therapy for patients not able to tolerate oxaliplatin or irinotecan since it has been shown to be associated with lower toxicity but also lower overall survival than these regimens.

Results from several phase II studies have demonstrated that addition of bevacizumab to first-line 5-FU/LV regimens improved overall survival in patients with metastatic colorectal cancer when compared to survival results for patients receiving these regimens without bevacizumab.[149,150] In a combined analysis of the results of several of these trials, addition of bevacizumab to 5-FU/LV-containing regimens was associated with a median survival of 17.9 months versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab.[151] A study of previously untreated patients receiving bevacizumab and irinotecan-5-FU chemotherapy also provided support for the inclusion of bevacizumab in initial therapy.[152] In that pivotal trial a markedly longer survival time was associated with the use of bevacizumab: 20.3 months versus 15.6 months (hazard ratio for

death = 0.66; P<0.001). Addition of bevacizumab to initial therapy with FOLFOX, bolus 5-FU/LV, or CapeOX significantly improved response rate and time to tumor progression in the TREE 1 & 2 studies which evaluated the safety and efficacy of oxaliplatin/fluoropyrimidine regimens (FOLFOX; CapeOX; and bolus 5-FU/LV plus oxaliplatin) with and without bevacizumab.[153,154] Although the final analysis of the TREE studies was a historical comparison of 2 sequential cohorts in a single protocol without randomization of patients to plus/minus bevacizumab treatment arms, addition of bevacizumab was shown to increase response rate by approximately 10% and time to tumor progression by 2 months when results for all patients, regardless of 5-FU backbone regimen, were evaluated. In a pooled analysis of patients enrolled in all 3 treatment arms, median survival time associated with administration of a 5-FU backbone regimen without bevacizumab was 18.2 months (95% CI, 14.5-21.6) and 24.4 months (95% CI, 21.4-26.8) when bevacizumab was added to these regimens. No significant differences in activity between the 3 different 5-FU-based regimens were observed in the TREE study although this analysis was limited by small sample sizes. Nevertheless, the bolus 5-FU/LV regimen may be the least efficacious since overall survival for patients in the 3 arms (without and with bevacizumab) were reported to be 19.2 months and 26.0 months for FOLFOX, 17.2 months and 27.0 months for CapeOX, and 17.9 months and 20.7 months for bolus 5-FU/LV. Although addition of bevacizumab to these regimens was associated with an increase in grade 3-4 hypertension, impaired wound healing, and bowel perforation in each arm, the overall tolerability of these regimens in combination with bevacizumab was considered to be acceptable and an increase in the toxicity of chemotherapy-related events was not observed.[153] Of note, the grade 3-4 toxicity associated with bevacizumab plus oxaliplatin-based chemotherapy in the TREE study was significantly less than that reported in the pivotal study involving IFL (bolus 5-FU, LV, irinotecan) plus bevacizumab. Very recently, results from a head-to-head phase III study comparing CapeOX plus bevacizumab (capecitabine dose 1000 mg/m2 twice daily for 14 days) with FOLFOX plus bevacizumab have been reported. With a median follow-up period of 18.6 months, results from this study support the conclusion that neither regimen is inferior with respect to the other in terms of toxicity or efficacy endpoints when used in the initial treatment of metastatic colorectal cancer.[143] Although the combined analysis of results observed with CapeOX plus bevacizumab and FOLFOX plus bevacizumab showed that the addition of bevacizumab was associated with an increase in progression-free survival (PFS) compared to these regimens without bevacizumab, the significant incremental benefit observed with addition of bevacizumab was more modest than seen in some earlier trials. Results of subset analyses evaluating the benefit of adding bevacizumab to either FOLFOX or CapeOX indicated that bevacizumab was associated with improvements in PFS when added to CapeOX but not FOLFOX, although PFS curves observed for patients receiving either CapeOX plus bevacizumab or FOLFOX plus bevacizumab were nearly identical. The results of the phase III BICC-C study evaluating the effectiveness of 3 irinotecan-containing regimens with and without bevacizumab demonstrated that, for first-line treatment of advanced colorectal cancer, FOLFIRI is superior to a modified IFL regimen or CapIRI (capecitabine plus irinotecan) in terms of efficacy and safety.[155] In that study, a significant increase in PFS was observed for patients receiving first-line FOLFIRI (7.6 months) when compared to PFS results for patients receiving either a modified IFL regimen (5.8 months; P=0.007) or CapIRI (5.7 months; P=0.03). Furthermore, when FOLFIRI was combined with bevacizumab, PFS was shown to increase to 9.0 months. Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and were then switched to the other regimen at the time of disease progression.[138] Similar response rates and PFS times were obtained when these 2 regimens were used as first-line therapy. Further support for this conclusion has come from results of a phase III trial comparing the efficacy and toxicity

of FOLFOX4 and FOLFIRI regimens in previously untreated patients with metastatic colorectal cancer.[142] No differences were observed in response rate, PFS times, and overall survival in the 2 treatment arms. The results of an ongoing phase III study evaluating the effectiveness of FOLFIRI in combination with bevacizumab in the initial treatment of patients with metastatic disease have not yet been reported.[156]

Convincing, albeit indirect, support for inclusion of bevacizumab in combination with chemotherapeutic agents in the initial treatment of advanced or metastatic colorectal cancer comes from results of the randomized phase III study E3200, conducted by Eastern Cooperative Oncology Group (ECOG), which demonstrated that bevacizumab in combination with FOLFOX4 improved survival in bevacizumab-naïve patients with previously-treated advanced colorectal cancer. Median overall survival was 12.9 months for patients receiving FOLFOX4 plus bevacizumab compared to 10.8 months for patients receiving FOLFOX4 alone.[157] Use of single agent bevacizumab is not recommended since it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.[157] Although this study involved patients with previously-treated disease, the results cannot be used to support use of bevacizumab in patients after first or second progression if they have progressed on a bevacizumab-containing regimen.

The risk of stroke and other arterial events is increased in elderly patients receiving bevacizumab. In addition, use of bevacizumab may interfere with wound healing[108,109,153,154] (see Treatment of Metastatic Disease), and gastrointestinal perforation is a relatively rare, but important, side effect of bevacizumab therapy in patients with colorectal cancer.[109,153,154]

With respect to the toxicities associated with capecitabine use, the panel noted that patients with diminished creatinine clearance may accumulate levels of the drug,[153,154,158] that the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV[153,154] and that North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[159] Such toxicities may necessitate modifications in the dosing of capecitabine,[153,154,158,160] and patients on capecitabine should be monitored closely so that dose adjustments can be made at the earliest signs of certain side effects such as hand-foot syndrome. For example, the capecitabine dose was reduced from 1000 mg/m2 twice daily to 850 mg/m2 twice daily on days 1-14 in the TREE studies.[153,154] It is currently not known whether the efficacies of CapeOX plus bevacizumab and FOLFOX plus bevacizumab remain comparable when capecitabine doses are lower than the 1000 mg/m2 twice daily dose used in the study of Cassidy et al.[143]

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[161,162] Irinotecan is metabolized by the enzyme uridine diphosphate-glucuronyl transferease 1A1 (UGT1A1) which is also involved in converting substrates, such as bilirubin, into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGT1A1 can be caused by certain genetic polymorphisms, and can result in conditions associated with accumulation of unconjugated hyperbilirubinemias, such as types I and II of Crigler-Najjar syndrome and Gilbert syndrome. Thus, irinotecan should be used with caution and at decreased dose in patients with Gilbert's disease or elevated serum bilirubin.[163] Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug,[162,164] although severe irinotectan-related toxicity is not experienced by all patients with these polymorphisms.[164] A commercial test is available to detect the UGT1A1*28 allele which is associated with decreased gene expression and, hence, reduced levels of

UGT1A1 expression,[163] and a new warning has been added to the label for Camptosar which indicates that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.[161] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[164] although guidelines for the use of this test in clinical practice have not been established.

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[165] Results of the OPTIMOX1 study demonstrated that a "stop-and-go" approach employing oxaliplatin-free intervals resulted in decreased neurotoxicity but did not affect overall survival in patients receiving FOLFOX as initial therapy for metastatic disease.[166] Therefore, the panel recommends adjustments in the schedule/timing of the administration of this drug as a means of limiting this adverse effect. Discontinuation of oxaliplatin from FOLFOX or CapeOX should be strongly considered after 3 months of therapy or sooner for unacceptable neurotoxicity (eg, > grade 3) with other drugs in the regimen maintained until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy but oxaliplatin can subsequently be reintroduced if stopped to prevent development of neurotoxicity.

The consensus of the panel is that infusional 5-FU regimens appear to be less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with either irinotecan or oxaliplatin. Therefore, the panel no longer recommends using the IFL (irinotecan, bolus 5-FU/LV) regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[155] and FOLFOX in the Intergroup trial[120] at any point in the therapy continuum and it has been removed from the guidelines. 5-FU in combination with irinotecan or oxaliplatin should be administered either via an infusional, weekly or biweekly regimen[130,146,147] or the oral route (i.e. capecitabine).[126]

The recommended therapy after first progression for patients who have received prior 5-FU/LV includes irinotecan as a single agent[124] or in combination with cetuximab.[133] Other options are dependent on the initial treatment regimen and include: FOLFIRI[146] with or without cetuximab for patients who had received a FOLFOX or CapeOX-based regimen for initial therapy. FOLFOX or CapeOX alone is an option for patients who received a FOLFIRI-based regimen as initial treatment. The recommendations regarding use of CapeOX in lieu of FOLFOX after first progression are supported by the results of studies demonstrating comparable efficacies of these 2 agents in initial therapy.[143] Other options to consider after first progression are as follows: FOLFOX for patients receiving 5-FU/LV without oxaliplatin or irinotecan as initial therapy; and single agent cetuximab or panitumumab for patients initially treated with a FOLFOX-based regimen.

Results from a randomized study to evaluate the efficacies of FOLFIRI and FOLFOX6 regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen following first progression showed neither sequence to be significantly superior with respect to PFS or median overall survival.[138] A combined analysis of data from 7 recent phase III clinical trials in advanced colorectal cancer provided support for a correlation between an increase in median survival and administration of all of the 3 cytotoxic agents (ie, 5-FU/LV, oxaliplatin, and irinotecan) at some point in the continuum of care.[167] Furthermore, overall survival was not found to be associated with the order in which these drugs were received. Single agent irinotecan administered after first progression has been shown to significantly improve overall survival relative to best supportive care or infusional 5-FU/LV.[168] In the study of Rougier et al.,[168] median overall survival was

4.2 months for irinotecan versus 2.9 months for 5-FU (P=0.030) whereas Cunningham et al[169] reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive-care group (P-0.001). Furthermore, no significant differences in overall survival were observed in the Intergroup N9841 trial when FOLFOX was compared to irinotecan monotherapy following first progression of metastatic colorectal cancer.[170]

Cetuximab has been studied as both a single agent [133,171] and in combination with irinotecan[133] in the treatment of metastatic colorectal cancer. A partial response rate of 9% was observed when single agent cetuximab was administered in an open-label phase II trial to 57 patients with colorectal cancer refractory to prior irinotecan-containing therapy.[171] Results from a direct comparison of cetuximab monotherapy and the combination regimen of cetuximab and irinotecan in patients who had progressed following initial therapy indicated that response rates were doubled in the group receiving the combination of cetuximab plus irinotecan when compared with patients receiving cetuximab monotherapy (22.9% versus 10.8% [P-0.007]).[133] Therefore, combination therapy with cetuximab and irinotecan is preferable to cetuximab alone as therapy after first progression for patients who can tolerate this combination regimen. Panitumumab, however, has only been studied as a single agent in the setting of metastatic colorectal cancer[132] where respective response rates of 8% versus 0% for panitumumab plus best supportive care versus best supportive care alone were observed. Thus, recommendations for the use of panitumumab in the guidelines are currently restricted to single agent use only. The panel allows that panitumumab can be substituted for cetuximab when either drug is used as a single agent following first or second progression. Although no head-to-head studies comparing cetuximab and panitumumab have been undertaken, this recommendation is supported by the similar response rates observed when each agent was studied as monotherapy. One difference between these 2 agents is that panitumumab is a fully human monoclonal antibody whereas cetuximab is a chimeric monoclonal antibody.[172,173] There are no data to support use of either cetuximab or panitumumab after failure of the other drug and the panel recommends against this practice. Cetuximab in combination with irinotecan is also indicated following progression for patients refractory to irinotecan-based chemotherapy since it has shown activity in this setting.[133] The panel recommends that progression of disease following therapy with a regimen including cetuximab and irinotecan should be followed by either best supportive care or enrollment in a clinical trial. Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[172,173]

EGFR testing of colorectal tumor cells has no demonstrated predictive value in determining likelihood of response to either cetuximab or panitumumab. Data from the BOND study indicated that the intensity of immunohistochemical staining of colorectal tumor cells did not correlate with the response rate to cetuximab.[133] A similar conclusion was drawn with respect to panitumumab.[83,174] Therefore, routine EGFR testing is not recommended, and no patient should be included or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.

With respect to the treatment continuum for metastatic colorectal cancer, there are no data to support the addition of bevacizumab to a regimen following clinical failure of a previous bevacizumab-containing regimen.[157] Therefore, routine use of cetuximab plus bevacizumab in patients who have experienced clinical failure on a bevacizumab-containing regimen is not recommended.

For patients with impaired tolerance to aggressive initial therapy, the guideline recommends single-agent capecitabine,[126,127] or bolus or infusional 5-FU/LV[129,130] with or without bevacizumab (category 2B). Although a comparision of capecitabine plus bevacizumab versus

capecitabine alone as initial therapy for metastatic cancer has not been done, CapeOX plus bevacizumab has been shown to be superior to CapeOX alone in this setting.[153,154] Metastatic cancer patients with no improvement in functional status should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for therapy after first progression as described above.

The panel recommends against the use of capecitabine, mitomycin, or gemcitabine, either as single agents or in combination, as salvage therapy in patients exhibiting disease progression following treatment with a fluoropyrimidine-containing regimen. These agents have not been shown to be effective in this setting, and no objective responses were observed when single agent capecitabine was administered in a phase II study of patients with colorectal cancer resistant to 5-FU.[175]

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 protoscopy to evaluate the rectal anastomosis for local recurrence for patients who have undergone an LAR. Anastomotic recurrence of rectal cancer has a much more favorable prognosis than local recurrence at other locations in the pelvis.[115,116] although the optimal timing for surveillance of the rectal anastomosis is not known.

Following curative-intent surgery, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, identify new metachronous neoplasms at a preinvasive stage, and reassure the patient. Advantages of more intensive follow-up of Stage II and/or Stage III patients have been demonstrated prospectively in several studies[176,177,178] and in three recent meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[179,180-182] Other recent studies impacting on the issue of post-treatment surveillance of colorectal cancer include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials which demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor,[183] and a population-based report indicating increased rates of resectability and survival in patients treated for local recurrence and distant metastases of colorectal cancer, thereby providing support for more intensive post-treatment follow-up in these patients.[184] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.[185,186]

The following panel recommendations for post-treatment surveillance pertain to patients with stage I-III disease who have undergone successful treatment (i.e. no known residual disease): history and physical examination every 3-6 months for 2 years, and then every 6 months for a total of 5 years; a CEA test at baseline and every 3-6 months for 2 years,[187] then every 6 months for the next 5 years for patients with disease staged as T2 or greater[182,187,188]; colonoscopy within 1 year of resection (or 3 to 6 months if not performed preoperatively due to obstructing lesion), repeated in 3 years if the colon is free of polyps followed by colonoscopic surveillance every 5 years, or, if first follow-up colonoscopy is abnormal, repeat colonoscopy after 1 year and, if negative for polyps, repeat colonoscopic surveillance in 3 years and then every 5 years[189]; consideration of protoscopy every 6 months for 5 years to evaluate for local recurrence at the rectal anastomosis for patients who have undergone an LAR; chest, abdominal and pelvic CT scan are recommended annually every 3 years in patients at high risk or recurrence (ie, those with perineural or venous invasion of tumor or poorly differentiated tumors) and may be

considered annually for 3 years for patients with Stage II disease at high risk for recurrence.[182,185] PET scan is not routinely recommended.

Initial follow-up office visits at 3 months intervals for history and physical examination may be more useful for patients diagnosed with Stage III disease, whereas patients with a diagnosis of Stage I disease may not need to be seen as frequently (i.e. can be seen once every 6 months). This principle also applies to CEA testing,[190] which is used primarily to monitor for recurrence of the original disease (see section on Managing an Increasing CEA Level, below), although post-treatment CEA testing is recommended only if the patient is a potential candidate for further intervention.[187] Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps since data show that patients with a history of colorectal cancer have an increased risk of developing second cancers,[191] particularly in the first 2 years following resection. Furthermore, use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original colorectal cancer.[188] CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and the liver. Hence, CT scan is not routinely recommended in patients who are not candidates for potentially curative resection of liver or lung metastases.[182,185] Post-treatment PET scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer to detect recurrence of the original cancer.[185] Furthermore, PET scan is not routinely recommended to detect metastatic disease in the absence of other evidence of such disease.

Managing an Increasing Carcinoembryonic Antigen Level

Managing patients with an elevated CEA level after resection should include colonoscopy, chest, abdominal, and pelvic CT scans, and consideration of a PET scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans are indicated every 3 months if symptoms occur. In addition, PET scan may be used to evaluate for the presence of isolated metastases if CT scan results are negative.[192] The panel does not recommend the use of anti-CEA--radiolabeled scintigraphy.[193] PET scan should be considered before surgical resection for patients with a suspected recurrence or those with documented metastases by CT, MRI and/or biopsy. In the case of local recurrence or resectable organ-confined lesion, curative surgery may be possible. Likewise, isolated lesions in the liver or lung may be resected for cure.

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 T1 or T2 lesions that are node-negative by endorectal ultrasound and who meet carefully defined criteria can be managed with a transanal excision. A transabdominal resection is appropriate for all other rectal lesions. Preoperative chemoRT is preferred for most patients with suspected or proven T3/T4 disease and/or regional node involvement and adjuvant chemotherapy is recommended, although upfront surgery is an option for some of these patients, particularly those with a medical contraindication to chemoRT. 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 (neoadjuvant) or when a response to chemotherapy can convert a patient from an unresectable to resectable state. Another option for these patients is initial treatment with 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, as well as plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy for advanced or metastatic disease includes bevacizumab plus FOLFOX, FOLFIRI, capecitabine or 5-FU/LV. For patients with progressive disease who have received a 5-FU-based regimen or capecitabine as initial therapy, treatment options include chemotherapy consisting of FOLFIRI, CapeOX, FOLFOX or irinotecan alone or, in the case of irinotecan and FOLFIRI, in combination with cetuximab. Monotherapy with either cetuximab or panitumumab is also an option after first or second progression. The panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy.

Disclosures for NCCN Rectal Cancer Guidelines Panel

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