



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Rectal Cancer

Version 1.2012

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Rectal Cancer

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Clinical Presentations and Primary Treatment:

- [Pedunculated polyp with invasive cancer \(REC-1\)](#)
- [Sessile polyp with invasive cancer \(REC-1\)](#)
- [Rectal cancer appropriate for resection \(REC-2\)](#)
 - ▶ [T1-2, N0: Primary and Adjuvant Treatment \(REC-3\)](#)
 - ▶ [T3, N0 or T any, N1-2: Primary and Adjuvant Treatment \(REC-4\)](#)
 - ▶ [T4 and/or locally unresectable: Primary and Adjuvant Treatment \(REC-4\)](#)
 - ▶ [T any, N any, M1: Resectable Metastases Treatment \(REC-5\)](#)
 - ▶ [T any, N any, M1: Unresectable Metastases or Medically Inoperable Treatment \(REC-6\)](#)

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

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](#)

The NCCN Guidelines™ are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2011.



Summary of changes in the 1.2012 version of the Rectal Cancer Guidelines from the 4.2011 version include:

General: In regard to intravenous therapy, continuous changed to infusional throughout the Guidelines.

REC-1

- Footnote “e” added to this page: Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. [See Principles of Pathologic Review \(REC-A\)](#) - Endoscopically removed malignant polyp.

REC-2

- Endorectal MRI removed as a recommended test in the workup of a patient with rectal cancer appropriate for resection.

REC-3

- Preferred designation added to continuous 5-FU/RT and capecitabine/RT as compared to bolus 5-FU/RT.
- Footnote “k” modified by deleting the last sentence, “Trials are still pending in rectal cancer.” (also applies to REC-4 and REC-5)
- Previous footnote “k” deleted: “Data regarding the use of capecitabine/RT are 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.” (also applies to REC-4, REC-5, and REC-6)

REC-4

- Preoperative capecitabine/RT changed from a category 2A to a category 1 designation and preferred as compared to bolus 5-FU/RT.
- Category 1 and preferred for infusional 5-FU/RT and capecitabine/RT applies to stage II and stage III disease (previously only stage III disease).

REC-5

- FOLFOX + cetuximab removed as a treatment option.
- Preferred designation added to continuous 5-FU/RT and capecitabine/RT as compared to bolus 5-FU/RT.
- Adjuvant therapy recommendations following staged or synchronous resection of metastases + rectal lesion: Active chemotherapy regimen for advanced disease (REC-E) changed to adjuvant therapy for stage III disease (REC-4).

REC-8

- Isolated pelvic/anastomotic recurrence, potentially resectable: “if not given previously” removed from preoperative 5-FU + RT and referral to the Principles of Radiation Therapy added for further guidance.

REC-9

- Response changed to “No progression” and No response changed to “Progression”.
- Adjuvant therapy recommendations following resection and no previous chemotherapy: Active chemotherapy regimen for advanced disease (REC-E) changed to adjuvant therapy for stage III disease (REC-4).

REC-A 4 of 6

- Lymph node evaluation, bullet 1: early stage replaced stage II.

REC-A 5 of 6

- BRAF Testing, second bullet: The following sentence was added: Allele-specific PCR is another acceptable method for detecting BRAF V600E mutation.

REC-B 1 of 3

- Transabdominal Resection, Management Principles: Sub-bullet 3 deleted “Laparoscopic surgery is not recommended outside the setting of a clinical trial” and replaced with “Laparoscopic surgery is preferred in the setting of a clinical trial” with the following footnote “Long term outcomes from laparoscopic surgery have not been reported. Current clinical trials are exploring open versus laparoscopic approach.”



Summary of changes in the 1.2012 version of the Rectal Cancer Guidelines from the 4.2011 version include:

[REC-C 1 of 2](#)

- **First paragraph modifications: 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.~~ A total of *approximately 6* months of perioperative treatment is preferred.**
- **Recommendations combined for postoperative adjuvant therapy (previously divided based on whether patient received preoperative chemotherapy/RT).**
- **Adjuvant postoperative chemotherapy: All regimens clarified “to a total of 6 mo perioperative therapy.”**
- **Adjuvant postoperative chemotherapy: FLOX regimen added with supporting reference: Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007;25:2198-2204.**
- **Adjuvant postoperative chemotherapy: Mayo clinic regimen deleted: Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. J Clin Oncol 1996;14:2274-2279.**
- **Concurrent chemotherapy/RT: Capecitabine/RT changed from a category 2B recommendation to a category 2A recommendation.**

[REC-D](#)

- **Bullet 4 modified - Intensity modulated radiotherapy (IMRT) should only be used in the setting of a clinical trial *or in unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy.***
- **Bullet 6 modified: 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 *and/or brachytherapy* to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.**
- **Bullet 10 removed the second sentence: All male patients should be evaluated for erectile dysfunction and considered for early treatment intervention if necessary.**

[REC-E 1 of 7](#)

- **Patient appropriate for intensive therapy: FOLFOX + cetuximab removed as a treatment option for initial therapy of advanced or metastatic disease.**

[REC-E 2 of 7](#)

- **Patient not appropriate for intensive therapy: Capecitabine ± bevacizumab added as a treatment option for initial therapy of advanced or metastatic disease.**

[REC-E 4 of 7](#) through [REC-E 7 of 7](#)

- **Chemotherapy regimen dosing and references expanded and updated.**



Summary of changes in the 1.2012 version of the Rectal Cancer Guidelines from the 4.2011 version include:

REC-F

Cancer Surveillance. Previous bullets deleted and the following added:

- See [REC-7](#).
- Long term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning is not recommended beyond 5 years.

Management of Late Sequelae of Disease or Treatment: The following bullets added:

Urogenital Dysfunction after Resection and/or Pelvic Radiation^{6,7}

- ▶ Screen for sexual dysfunction, erectile dysfunction, dyspareunia, and vaginal dryness
- ▶ Screen for urinary incontinence, frequency, and urgency
- ▶ Consider referral to urologist or gynecologist for persistent symptoms.

Cancer Screening Recommendations. Previous bullets deleted and the following added:

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

- **Breast Cancer:** See the [NCCN Breast Cancer Screening Guidelines](#)
- **Cervical Cancer:** See the [NCCN Cervical Cancer Screening Guidelines](#)
- **Prostate Cancer:** See the [NCCN Prostate Early Detection Guidelines](#)

Counseling Regarding Healthy Lifestyle and Wellness. Previous bullets deleted and the following added:

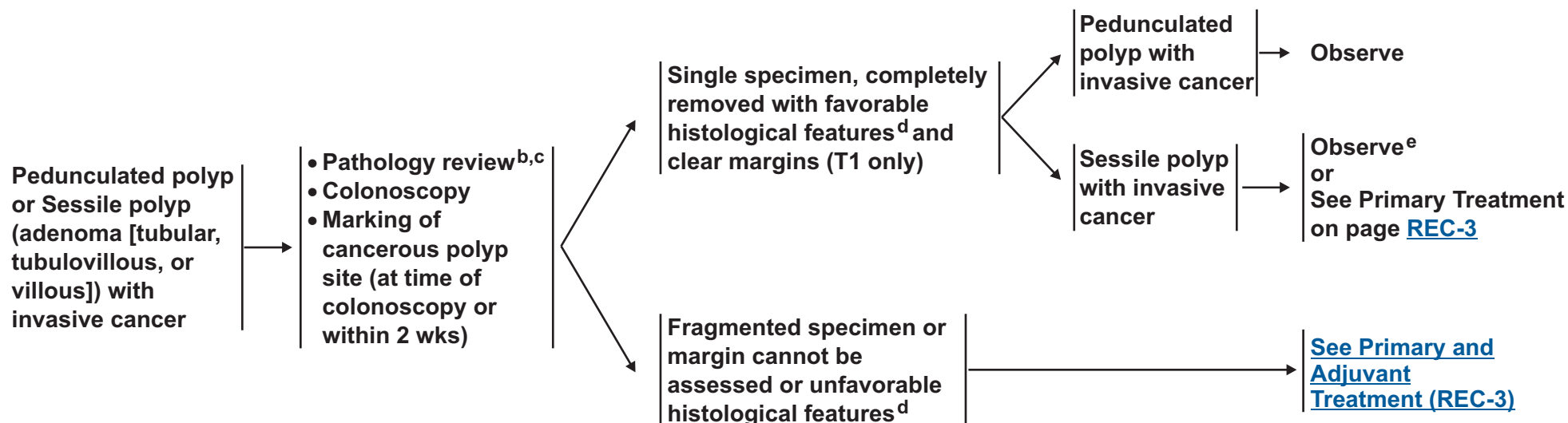
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (At least 30 minutes of moderate intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (i.e. ostomy, neuropathy).
- Consume a healthy diet with emphasis on plant sources.
- Limit alcohol consumption.
- Smoking cessation counseling as appropriate.
- Additional health monitoring and immunizations should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.



CLINICAL PRESENTATION^a

WORKUP

FINDINGS



^aAll patients with rectal 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](#).

^bConfirm the presence of invasive cancer (pT1). pT1s has no biological potential to metastasize.

^cIt 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.

^eObservation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. [See Principles of Pathologic Review \(REC-A\)](#) - Endoscopically removed malignant polyp.

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.



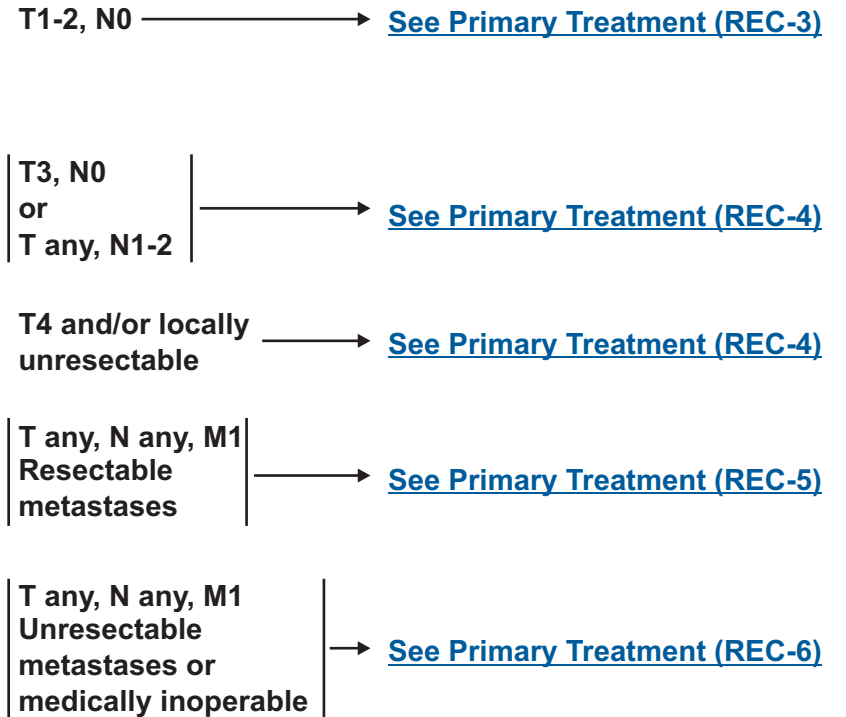
**CLINICAL
PRESENTATION^a**

WORKUP

CLINICAL STAGE

Rectal cancer
appropriate
for resection

- Biopsy
- Pathology review
- Colonoscopy
- Rigid proctoscopy
- Chest/abdominal/pelvic CT
- CEA
- Endorectal ultrasound or pelvic MRI
- Enterostomal therapist as indicated for preoperative marking of site, teaching
- PET-CT scan is not routinely indicated



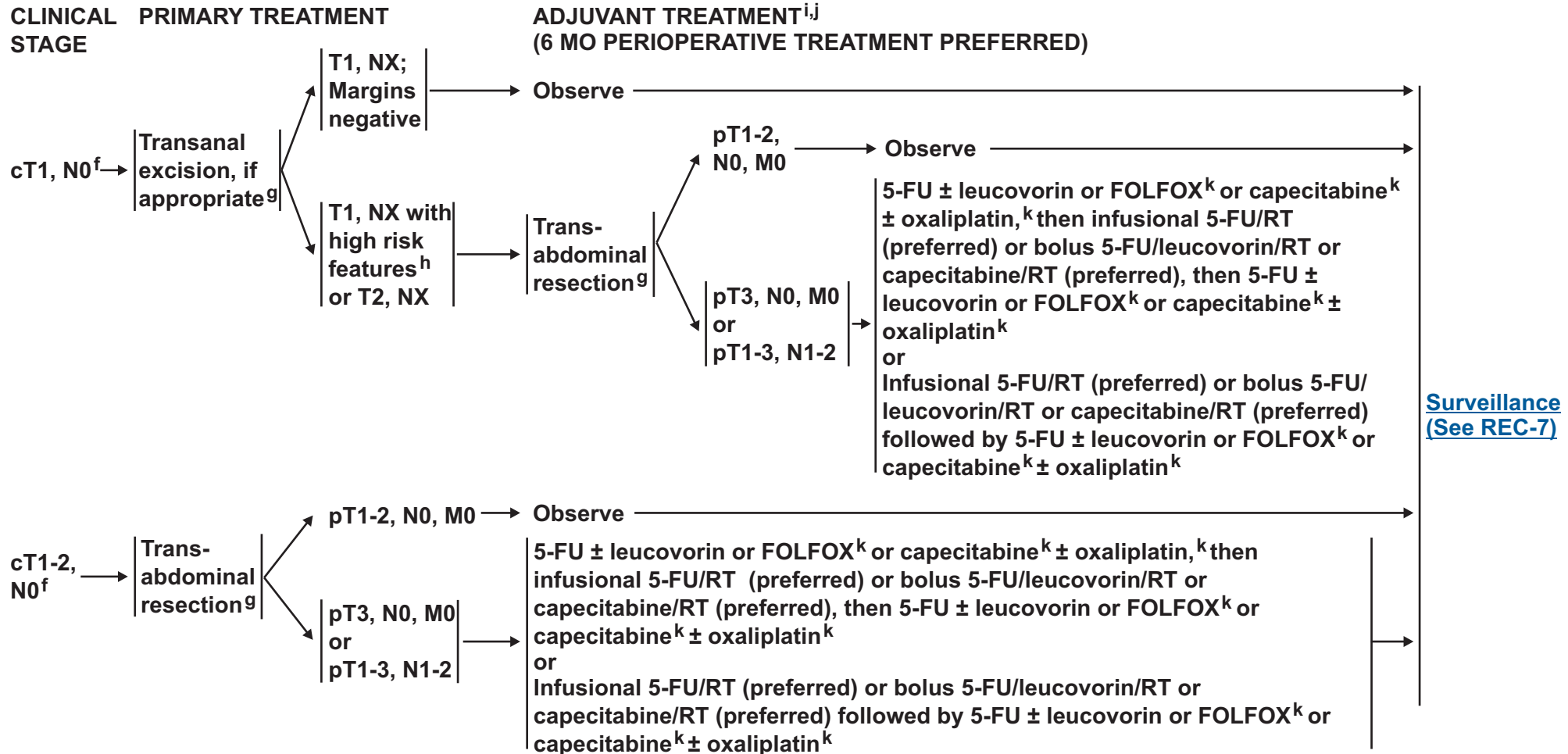
^aAll patients with rectal cancer should be counseled for family history. Patients with suspected hereditary non-polyposis colon cancer (HNPCC), familial adenomatous polyposis (FAP) and attenuated FAP, see the [NCCN Colorectal Cancer Screening Guidelines](#).

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Rectal Cancer



^fT1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

^gSee [Principles of Surgery \(REC-B\)](#).

^hHigh risk features include positive margins, lymphovascular invasion and poorly differentiated tumors.

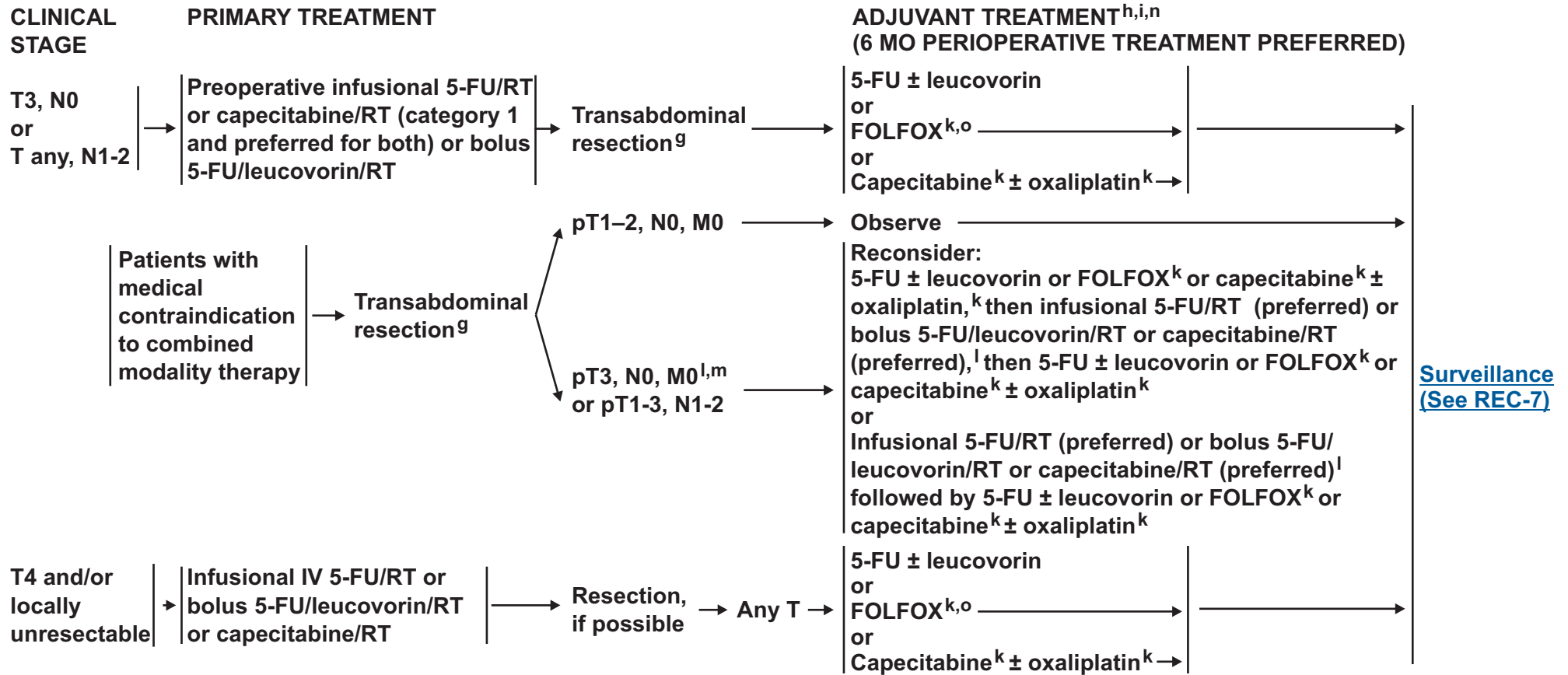
ⁱSee [Principles of Adjuvant Therapy \(REC-C\)](#).

^jSee [Principles of Radiation Therapy \(REC-D\)](#).

^kThe use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer.

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^gSee Principles of Surgery (REC-B).

ⁱSee Principles of Adjuvant Therapy (REC-C).

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

^kThe use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer.

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

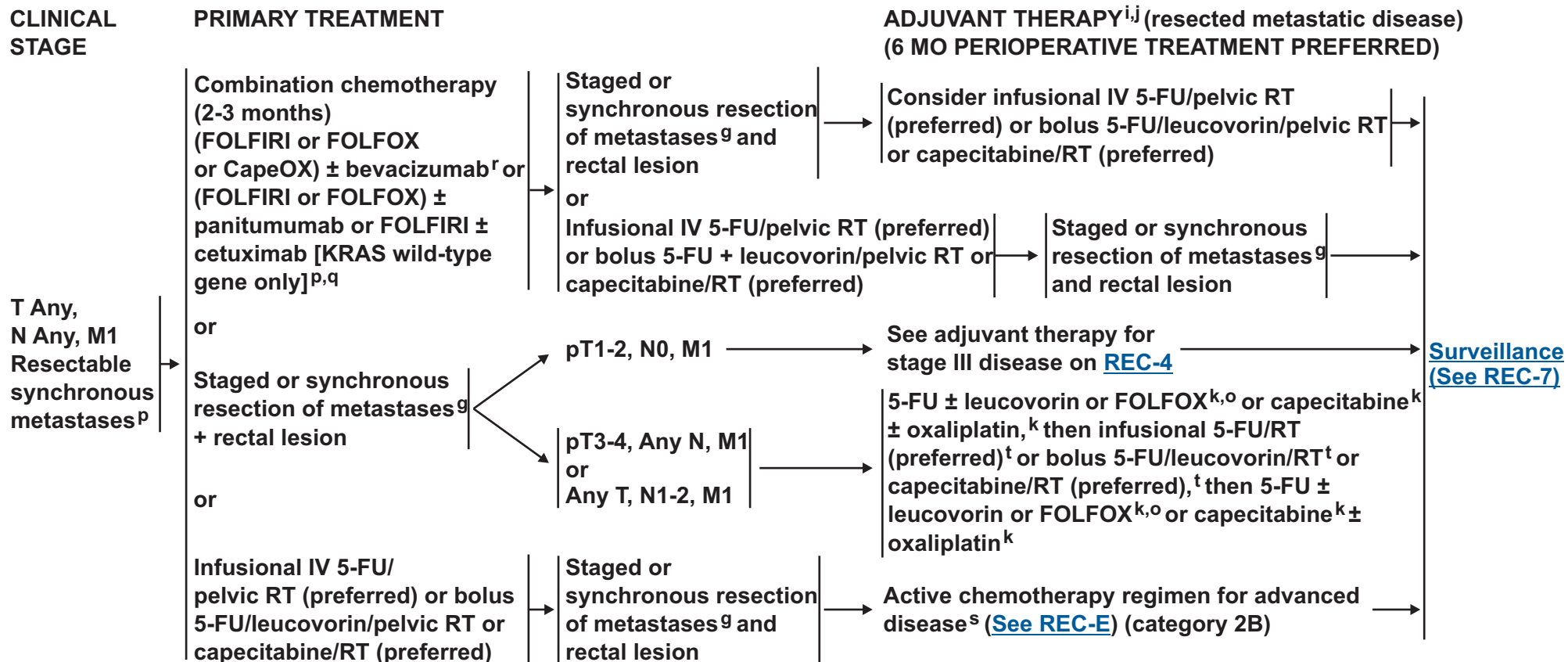
^mFor patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy alone.

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

^oAn ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

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^gSee Principles of Surgery (REC-B).

ⁱSee Principles of Adjuvant Therapy (REC-C).

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

^kThe use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer.

^oAn ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

^pDetermination of tumor KRAS (if KRAS non-mutated, consider BRAF testing).

[See Principles of Pathologic Review \(REC-A 5 of 6\)](#) - KRAS and BRAF Mutation Testing.

^qPatients with a V600E BRAF mutation appear to have a poorer prognosis. Retrospective subset analyses suggest potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status.

^rThe 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.

^sFOLFOXIRI is not recommended in this setting.

^tRT only recommended for patients at increased risk for pelvic recurrence.

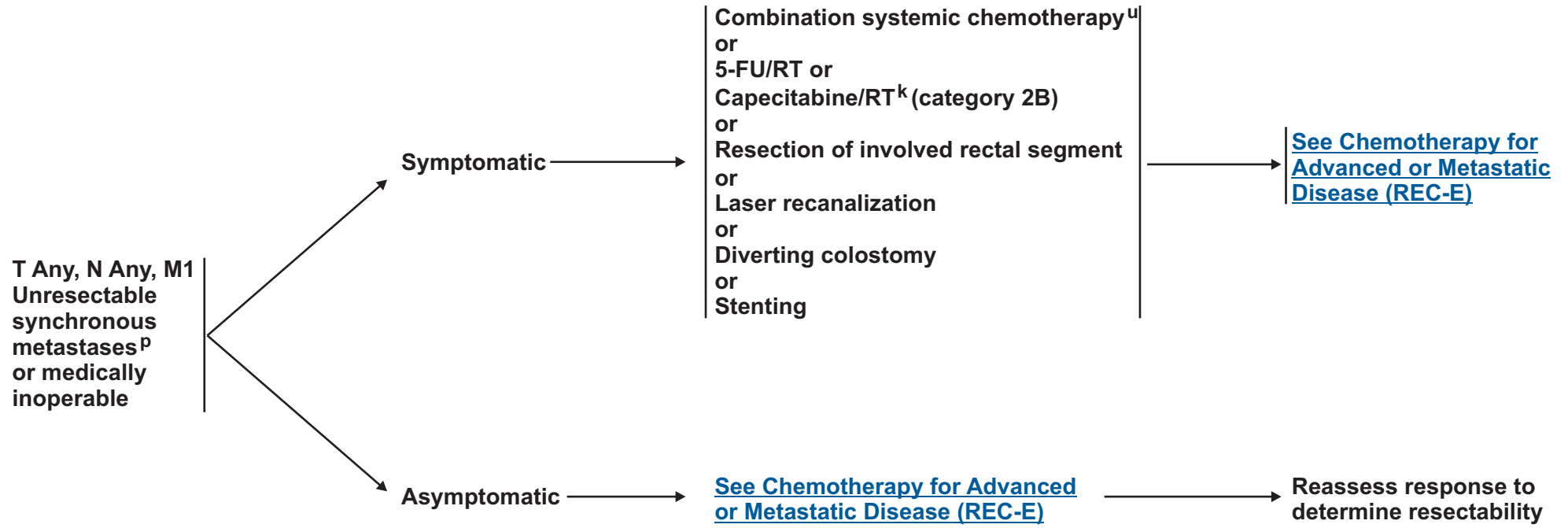
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CLINICAL STAGE

PRIMARY TREATMENT



^PDetermination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). [See Principles of Pathologic Review \(REC-A 5 of 6\)](#) - KRAS and BRAF Mutation Testing.

^U[See Chemotherapy for Advanced or Metastatic Disease \(REC-E\)](#).

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SURVEILLANCE^w

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

Serial CEA elevation or documented recurrence

[See Workup and Treatment \(REC-8\)](#)

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

^wDesch 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.

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

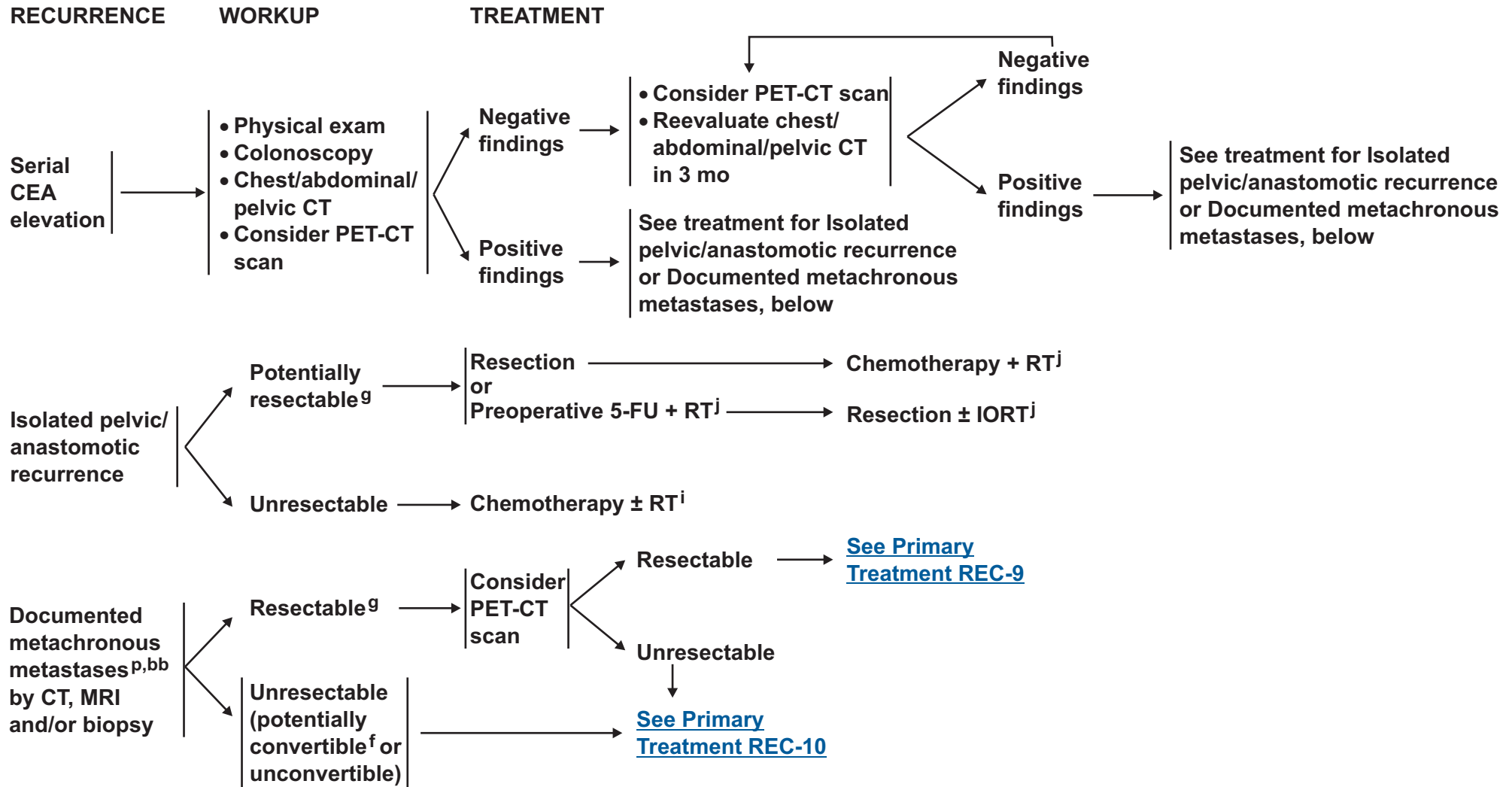
^yVillous polyp, polyp > 1 cm, or high grade dysplasia.

^zRex 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.

^{aa}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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^gSee Principles of Surgery (REC-B).

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

^pDetermination of tumor KRAS (if KRAS non-mutated, consider BRAF testing). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.

^{bb}Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

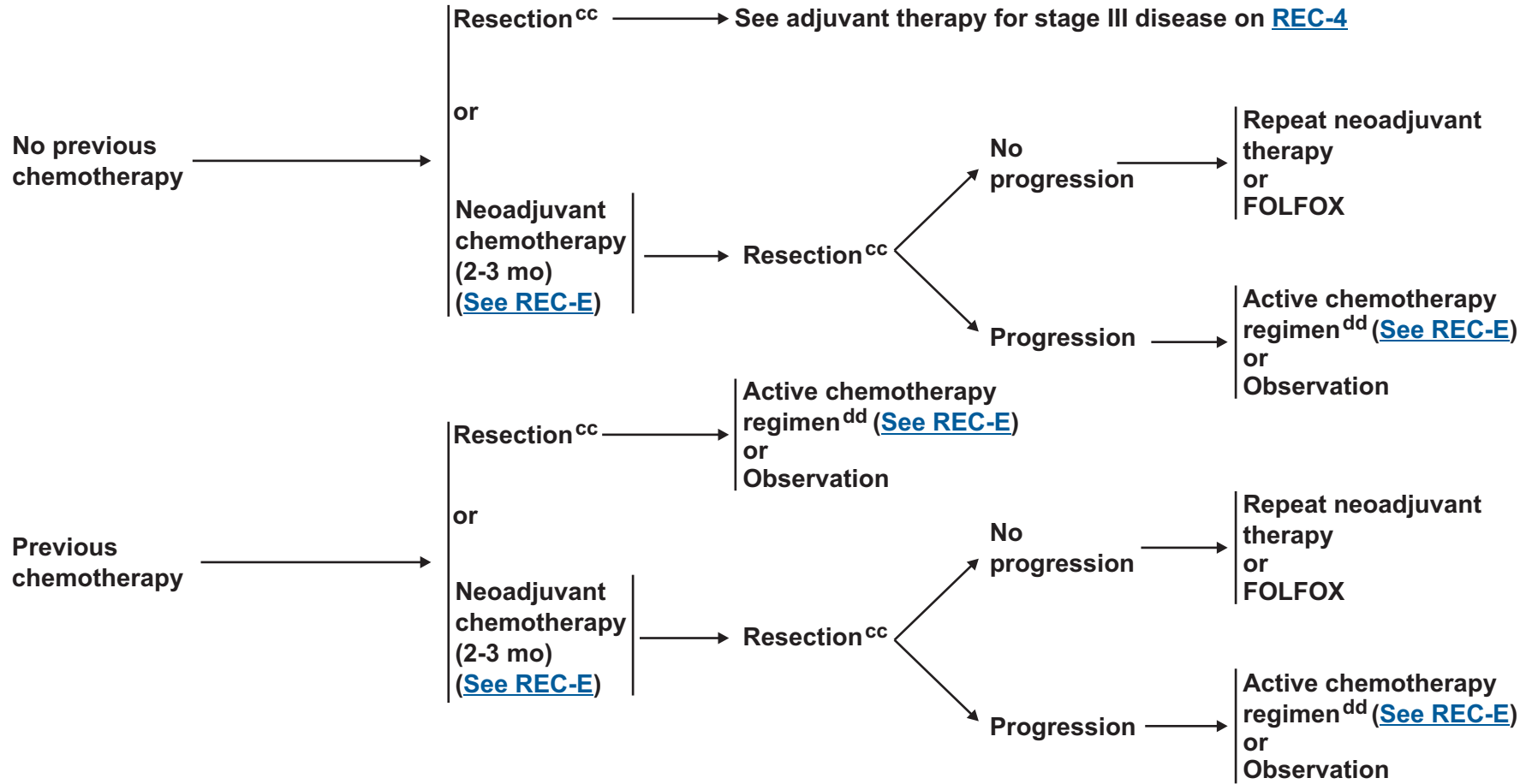
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**RESECTABLE
METACHRONOUS METASTASES**

PRIMARY TREATMENT



^{cc}Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

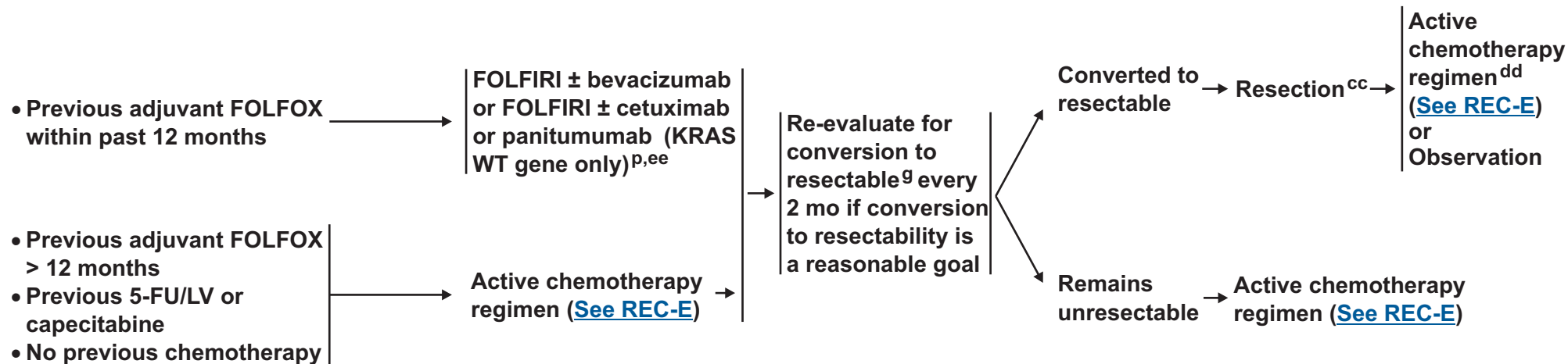
^{dd}Perioperative therapy should be considered for up to a total of 6 months.

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**UNRESECTABLE
METACHRONOUS METASTASES**

PRIMARY TREATMENT



^gSee Principles of Surgery (REC-B).

^pDetermination of tumor KRAS (if KRAS non-mutated, consider BRAF testing. See Principles of Pathologic Review (REC-A 5 of 6) - KRAS and BRAF Mutation Testing.

^{cc}Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

^{dd}Perioperative therapy should be considered for up to a total of 6 months.

^{ee}Patients with a V600E BRAF mutation appear to have a poorer prognosis. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after patient has progressed on first-line therapy.

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 6)

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, grade I or II, no lymphatic or venous invasion, negative margins.^{8,9}
- Unfavorable histopathological features: > 3 cm in size, T1, with grade III, or lymphovascular invasion, or positive margin.⁸⁻¹⁰

Rectal cancer appropriate for resection

- Histological confirmation of primary malignant rectal neoplasm.

[See Pathological stage on page 2 of 6 REC-A](#)

[See Lymph node evaluation on page 4 of 6 REC-A](#)

[See KRAS and BRAF Mutation Testing page 5 of 6 REC-A](#)

[See references on page 6 of 6 REC-A](#)

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**PRINCIPLES OF PATHOLOGIC REVIEW (2 of 6)****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** ¹³⁻¹⁴ [See Staging \(ST-1\)](#)
- ▶ **Circumferential resection margin** ¹³⁻¹⁷
- ▶ **Neoadjuvant treatment effect** ^{15,16,18,19}
- ▶ **Lymphovascular invasion** ^{15,16,20}
- ▶ **Perineural invasion** ²¹⁻²³
- ▶ **Extra nodal tumor deposits** ²⁴⁻²⁵

• **Circumferential resection margin - A positive CRM is defined as tumor ≤ 1 mm from the margin. This assessment includes both tumor within a lymph node as well as direct tumor extension, however, if CRM positivity is based solely on intranodal tumor this should be so stated in the pathology report. A positive CRM is a more powerful predictor of local recurrence in patients treated with neoadjuvant therapy. A positive CRM secondary to lymph node metastasis in some studies has been associated with lower recurrence rates than by direct extension.** ¹³⁻¹⁷

• **Neoadjuvant treatment effect - The most recent College of American Pathologists Guidelines on examination specimens of the rectum and the 7th Edition of the AJCC Staging Manual require commenting on treatment effect after neoadjuvant therapy. The minimum requirement is:**

- ▶ **Treatment effect present.**
- ▶ **No definitive response identified.**

The system used to grade tumor response is modified from Ryan R, et al. *Histopathology* 2005;47:141-146.

- ▶ **0 (complete response) - no viable cancer cells.**
- ▶ **1 (moderate response) - single cells or small groups of cancer cells.**
- ▶ **2 (minimal response) - residual cancer outgrown by fibrosis.**
- ▶ **3 (poor response) - minimal or no tumor kill; extensive residual cancer.**

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

[See Pathological stage continued on page 3 of 6 REC-A](#)

[See Endoscopically removed malignant polyp, rectal cancer appropriate for resection on page 1 of 6 REC-A](#)

[See Lymph node evaluation on page 4 of 6 REC-A](#)

[See KRAS and BRAF Mutation Testing page 5 of 6 REC-A](#)

[See references on page 6 of 6 REC-A](#)

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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 6)

Pathological stage (continued)

- **Perineural invasion** - The presence of perineural invasion is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer specific and overall disease-free survival. For stage II rectal cancer, those with PNI have a significantly worse 5 year disease-free survival compared to those without PNI 29% vs 82% (p=0.0005). In stage III rectal cancer, those with PNI have a significantly worse prognosis.²¹⁻²³
- **Extra nodal tumor deposits** - Irregular discrete tumor deposits in pericolic or perirectal fat from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered extra nodal tumor deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular or, more rarely, perineural invasion. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report.
In the 7th AJCC staging manual, extra nodal deposits are staged as pN1c. In stage II rectal cancer, the presence of extranodal tumor deposits worsens T any disease to that of stage III rectal cancer. pN0 cancer with extra nodal tumor deposits has a 50% 5 year survival while pN0 cancer without extra nodal tumor deposits has an 80% 5 year survival (p < 0.001).²⁴⁻²⁵

[See Endoscopically removed malignant polyp, rectal cancer appropriate for resection on page 1 of 6 REC-A](#)

[See Pathological stage on page 2 of 6 REC-A](#)

[See Lymph node evaluation on page 4 of 6 REC-A](#)

[See KRAS and BRAF Mutation Testing page 5 of 6 REC-A](#)

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Note: All recommendations are category 2A unless otherwise indicated.

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**PRINCIPLES OF PATHOLOGIC REVIEW (4 of 6)****Lymph node evaluation**

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately identify early stage colorectal cancers.^{11,12,26} The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, >30.²⁶⁻³⁴ Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and > 10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.^{30,33} The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade and tumor site.²⁷ For stage II (pN0) colon cancer, if 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, $p < 0.001$).^{35,36} If 12 lymph nodes is considered the number needed to accurately stage, stage II tumors, then only 20% of cases treated with neoadjuvant therapy had adequate lymph node sampling.³⁶ To date the number of lymph nodes needed to accurately stage neoadjuvant treated cases is unknown. However, it is not known what is the clinical significance of this in the neoadjuvant setting 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 sentinel 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.³⁷⁻³⁹ The 7th edition of the AJCC Cancer Staging⁴⁰ manual considers "tumor clusters" < 0.2 mm as isolated tumor cells (pN0) and not metastatic carcinoma. However, some investigators believe that size should not affect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, or stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.^{41,42}
- 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, isolated tumor cells were considered micrometastasis.⁴³⁻⁴⁷
- 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.^{37-39,43-47}

[See Endoscopically removed malignant polyp, rectal cancer appropriate for resection on page 1 of 6 REC-A](#)

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[See references on page 6 of 6 REC-A](#)

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PRINCIPLES OF PATHOLOGIC REVIEW (5 of 6)

KRAS Mutation Testing

- Mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to therapy with antibodies targeted to the epidermal growth factor receptor.^{48,49}
- Testing for Mutations in Codons 12 and 13 should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA – 88) as qualified to perform high complex clinical laboratory (molecular pathology) testing. No specific methodology is recommended (sequencing, hybridization, etc.).
- The testing can be performed on formalin fixed paraffin embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis as literature has shown that the KRAS mutations are similar in both specimen types.⁵⁰

BRAF Mutation Testing

- Patients with a V600E BRAF mutation appear to have a poorer prognosis. Retrospective subset analyses suggest potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after patient has progressed on first-line therapy.^{51,52}
- Testing for the BRAF V600E mutation can be performed on formalin fixed paraffin embedded tissues. This is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting BRAF V600E mutation. This testing should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) and qualified to perform highly complex clinical laboratory (molecular pathology) testing.

Evaluation of Mesorectum (TME)

- The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).⁵³⁻⁵⁵

[See Endoscopically removed malignant polyp, rectal cancer appropriate for resection on page 1 of 6 REC-A](#)

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[See references on page 6 of 6 REC-A](#)

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**PRINCIPLES OF PATHOLOGIC REVIEW (6 of 6) - References**

- ¹Volk EE, Goldblum JR, Petras RE, et al. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. *Gastroenterology* 1995;109:1801-1807.
- ²Cooper HS, Deppisch LM, Gourley WK, et al. Endoscopically removed malignant colorectal polyps: clinical pathological correlations. *Gastroenterology* 1995;108:1657-1665.
- ³Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology* 2004;127:385-394.
- ⁴Seitz U, Bohnacker S, Seewald S, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal polyps? Presentation of 114 patients and review of the literature. *Dis Colon Rectum* 2004;47:1789-1797.
- ⁵Morson BC, Whiteway JE, Jones EA, et al. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. *Gut* 1984;25:437-444.
- ⁶Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985;89:328-336.
- ⁷Netzer P, Binck J, Hammer B, et al. Significance of histological criteria for the management of patients with malignant colorectal polyps. *Scand J Gastroenterol* 1997;323:915-916.
- ⁸Hager T, Gall FP, and Hermanek P. Local excision of cancer of the rectum. *Dis Colon Rect* 1983;26:149-151.
- ⁹Willett CG, Tepper JE, Donnelly S, et al. Patterns of failure following local excision and local excision and postoperative radiation therapy for invasive rectal adenocarcinoma. *J Clin Oncol* 1989;7:1003-1008.
- ¹⁰Nascimbeni R, Burgart LJ, Nivatvongs S, and Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum* 2002;45:2001-2006.
- ¹¹Compton CC and Greene FL. The staging of colorectal cancer: 204 and beyond. *Cancer J Clin* 2004;54:295-308.
- ¹²Compton CC, Fielding LP, Burkhardt LJ, et al. Prognostic factors in colorectal cancer. College of American pathologists consensus statement. *Arch Pathol Lab Med* 2000;124:979-994.
- ¹³Nagtegaal ID, Merijnenc M, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictive local occurrence in rectal carcinoma. Not one millimeter but two millimeters is the limit. *Am J Surg* 2002;26:350-357.
- ¹⁴Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surgery* 2002;89 327-334.
- ¹⁵Washington MK, Berlin J, Branton P, et al. Protocol for examination of specimens from patients with primary carcinoma of the colon and rectum. *Arch Pathol Lab Med* 2009;133:1539.
- ¹⁶Edge SB, Byrd D, Compton C, et al (eds). *AJCC Cancer Staging Manual 7th Edition*. Springer NY, 2010.
- ¹⁷Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 2008;26:303-312.
- ¹⁸Rodel C, Martus P, Papadopoulos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005;23:8688-8696.
- ¹⁹Gavioli M, Luppi G, Losi L, et al. Incidence and clinical impact of sterilized disease and minimal residual disease after preoperative radiochemotherapy for rectal cancer. *Dis Colon Rectum* 2005;48:1851-1857.
- ²⁰Nissan A, Stojadinovic A, Shia J, et al. Predictors of recurrence in patients with T2 and early T3, N0 adenocarcinoma of the rectum treated by surgery alone. *J Clin Oncol* 2006;24:4078-4084.
- ²¹Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol* 2009;27:5131-5137.
- ²²Fujita S, Shimoda T, Yoshimura K, et al. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. *J Surg Oncol* 2003;84:127-131.
- ²³Quah HM. Identification of patients with high risk stage II colon cancer for adjuvant therapy. *Dis Colon Rect* 2008;51:53-507.
- ²⁴Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. *J Clin Pathol* 2007;117:287-294.
- ²⁵Lo DS, Pollett A, Siu LL, et al. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. *Cancer* 2008;112:50-54.
- ²⁶Sobin HL and Green EFL. TNM classification. Clarification of number of regional lymph nodes for PNO. *Cancer* 2001;92:452.
- ²⁷Sarli L, Bader G, Lusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. *European Journal of Cancer* 2005;41:272-279.
- ²⁸Chaplin S, Scerottini G-P, Bosman FT, et al. For patients with Duke's B (TNM stage II) colorectal carcinoma, examination of six or fewer lymph nodes is related to poor prognosis. *Cancer* 1998;83:666-72.
- ²⁹Maurel J, Launoy G, Grosclaude P, et al. Lymph node harvest reporting in patients with carcinoma of the large bowel. A French population-based study. *Cancer* 1998;82:1482-6.
- ³⁰Pocard M, Panis Y, Malassagane B, et al. Assessing the effectiveness of mesorectal excision in rectal cancer. *Dis Colon Rectum* 1998;41:839-845.
- ³¹Joseph NE, Sigurdson ER, Hamlin AL, et al. Accuracy of determining nodal negativity in colorectal cancer on the basis of number of nodes retrieved on resection. *Ann of Surg Oncol* 2003;10:213-218.
- ³²Goldstein NS. Lymph node recurrences from 2427 PT3 colorectal resection specimens spanning 45 years. Recommendations for a minimum number of recovered lymph nodes based on predictive probabilities. *Am J Surg Pathol* 2002;26:179-189.
- ³³Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol* 2001;19:157-162.
- ³⁴Scott KWM and Grace RH. Detection of lymph node metastasis and colorectal carcinoma before and after fat clearance. *Br J Surg* 1989;76:1165-1167.
- ³⁵Wichmann MW, Mollar C, Meyer G, et al. Effect of pre-operative radiochemotherapy on lymph node retrieval after resection of rectal cancer. *Arch Surg* 2002;137:206-210.
- ³⁶Baxter NN, Morris AM, Rothenberger DA, and Tepper JE. Impact of pre-operative radiation for rectal cancer on subsequent lymph node evaluation: population based analysis. *Int J Radiation Oncology Biol Phys* 2005;61:426-431.
- ³⁷Turner RR, Nora DT, Trochas D, and Bilchik AJ. Colorectal carcinoma in nodal staging. Frequency and nature of cytokeratin positive cells in sentinel and nonsentinel lymph nodes. *Arch Pathol Lab Med* 2003;127:673-679.
- ³⁸Wood TF, Nora DT, Morton DL, et al. One hundred consecutive cases of sentinel node mapping in early colorectal carcinoma. Detection of missed micrometastasis. *J Gastrointest Surg* 2002;6:322-330.
- ³⁹Wiese DA, Sha S, Badin J, et al. Pathological evaluation of sentinel lymph nodes in colorectal carcinoma. *Arch Pathol Lab Med* 2000;124:1759-1763.
- ⁴⁰AJCC Cancer Staging Manual, 7th ed. Edge SB, Byrd D, Compton CC, et al. (editors) Springer, New York, 2010.
- ⁴¹Jass JB, O'Brien MJ, Riddell RH, Snover DC, on behalf of the Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of surgically resected specimens of colorectal carcinoma. *Hum Pathol* 2007;38:537-545.
- ⁴²Hermanek P, Hutter RVP, Sobin LH, Wittekind CH. Classification of isolated tumor cells and micrometastasis. *Cancer* 1999;86:2668-73.
- ⁴³Noura S, Yamamoto H, Ohnishi T, et al. Comparative detection of lymph node micrometastasis of stage II colorectal cancer by reverse transcriptase polymerase chain reaction in immunohistochemistry. *J Clin Oncol* 2002;20:4232-4241.
- ⁴⁴Yasuda K, Adachi Y, Shiraishi N, et al. Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. *Ann Surg Oncol* 2001;8:300-304.
- ⁴⁵Noura S, Yamamoto H, Miyake Y, et al. Immunohistochemical assessment of localization of frequency of micrometastasis in lymph nodes of colorectal cancer. *Clin Cancer Research* 2002;8:759-767.
- ⁴⁶Oberg A, Stenling R, Tavelin B, Lindmark G. Are lymph node micrometastasis of any clinical significance in Duke stages A and B colorectal cancer? *Dis Colon Rectum* 1998;41:1244-1249.
- ⁴⁷Greenson JK, Isenhardt TCE, Rice R, et al. Identification of occult micrometastasis in pericolic lymph nodes of Duke's B colorectal cancer. Patient's using monoclonal antibodies against cytokeratin and CC49. Correlation with long term survival. *Cancer* 1994;73:563-9.
- ⁴⁸Lievre A, Bachatte J-B, Blige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with Cetuximab. *J Clin Oncol* 2008;26:374-379.
- ⁴⁹Amado IG, Wolf M, Peters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626-1634.
- ⁵⁰Etienne-Gimeldi M-C, Formenta J-L, Francoal M, et al. KRAS mutations in treatment outcome in colorectal cancer in patients receiving exclusive fluoropyrimidine. *Clin Cancer Research* 2008;14:4830-4835.
- ⁵¹Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008;26:5705-5712.
- ⁵²Bokmeyer C, Kohne C, Rougier C, et al. Cetuximab with chemotherapy as first-line treatment for metastatic colorectal cancer: Analysis of the CRYSTAL and OPUS studies according to KRAS and BRAF mutation analysis. *J Clin Oncol* 2010;28:15s(suppl;abstr 3506).
- ⁵³Parfitt JR and Driman KR. Total mesorectal excision specimen for rectal cancer: A review of its pathological assessment. *J Clin Pathol* 60:849-855, 2007.
- ⁵⁴Jass JR, O'Brien MJ, Riddell RH, Snover DC. On behalf of the association of Directors of Anatomic and Surgical Pathology recommendations for the reporting of surgically resected specimens in colorectal carcinoma. *Human Pathol* 38:537-545, 2007.
- ⁵⁵Nagtegaal ID, Vandevelde CJA, Derworx EV, et al. Macroscopic evaluation of the rectal cancer resection margin: Clinical significance of the pathologist in quality control. *J Clin Oncol* 20: 1729-1734, 2002.

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PRINCIPLES OF SURGERY (1 of 3)

Transanal excision:¹

- **Criteria**
 - ▶ < 30% circumference of bowel
 - ▶ < 3 cm in size
 - ▶ Margin clear (> 3 mm)
 - ▶ Mobile, nonfixed
 - ▶ Within 8 cm of anal verge
 - ▶ T1 only
 - ▶ Endoscopically removed polyp with cancer or indeterminate pathology
 - ▶ No lymphovascular (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 endoscopic microsurgery (TEM) may be used. TEM for more proximal lesions may be technically feasible.

Transabdominal Resection: Abdominoperineal resection or low anterior resection or coloanal anastomosis using total mesorectal excision.

- **Management Principles**
 - ▶ The treating surgeon should perform a rigid proctoscopy before initiating treatment
 - ▶ Removal of primary tumor with adequate margins
 - ▶ Laparoscopic surgery is preferred in the setting of a clinical trial.²
 - ▶ 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, < 5 cm from anal verge), negative distal bowel wall margin of 1-2 cm may be acceptable, this must be confirmed to be tumor free by frozen section.
 - ▶ Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.
- **Lymph node dissection^{3,4}**
 - ▶ Biopsy or remove clinically suspicious nodes beyond the field of resection if possible.
 - ▶ Extended resection not indicated in the absence of clinically suspected nodes.

[See Criteria for Resectability of Metastases on page 2 of 3 REC-B](#)

¹Nash GM, Weiser MR, Guillem JG, et al. Long-term survival after transanal excision of T1 rectal cancer. *Dis Colon Rectum* 2009;52:577-82.

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

³Gunderson LL, Sargent DJ, Tepper JB, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. *J Clin Oncol* 2004;22(10):1785-1796.

⁴Greene FL, Stewart AK, Norton HJ. New tumor-node-metastasis staging strategy for node-positive (stage III) rectal cancer: an analysis. *J Clin Oncol* 2004;22(10):1778-1784.

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**PRINCIPLES OF SURGERY (2 of 3)****CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY****Liver**

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.¹
- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of adequate hepatic function is required.^{2,3}
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.⁴⁻⁶ Plan for a debulking resection (less than an R0 resection) is not recommended.
- Patients with resectable metastatic disease and primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the hepatectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization or staged liver resections can be considered.
- Ablative techniques may be considered alone or in conjunction with resection.¹ All original sites of disease need to be amenable to ablation or resection.
- Some institutions use arterially-directed embolic therapy in select patients with chemotherapy resistant/refractory disease, without obvious systemic disease, with predominant hepatic metastases (category 3).
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3).
- Re-resection can be considered in selected patients.⁷

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.⁸⁻¹¹
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.¹²⁻¹⁵
- Re-resection can be considered in selected patients.¹⁶
- Ablative techniques can be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable (category 3)

Evaluation for conversion to resectable disease

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

[See footnotes on page 3 of 3 REC-B](#)**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 SURGERY (3 of 3) - REFERENCES**

- ¹ Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004;239:818-825; discussion 825-7.
- ² Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. *Registry of Hepatic Metastases. Surgery* 1988;103:278-288.
- ³ Hughes KS, Simon R, Songhorabodi S, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery* 1986;100:278-284.
- ⁴ Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997;15:938-946.
- ⁵ Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Surgical resection of liver metastases from colo-rectal cancers. *Int Surg* 1987;72:70-72.
- ⁶ Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999;230:309-318; discussion 318-321.
- ⁷ Adam R, Bismuth H, Castaing D, et al. Repeat hepatectomy for colorectal liver metastases. *Ann Surg* 1997;225:51-62.
- ⁸ McAfee MK, Allen MS, Trastek VF, Ilstrup DM, Deschamps C, Pairolero PC. Colorectal lung metastases: results of surgical excision. *Ann Thorac Surg* 1992;53:780-785; discussion 785-786.
- ⁹ Regnard JF, Grunewald D, Spaggiari L, et al. Surgical treatment of hepatic and pulmonary metastases from colorectal cancers. *Ann Thorac Surg* 1998;66:214-218; discussion 218-219.
- ¹⁰ Inoue M, Kotake Y, Nakagawa K, Fujiwara K, Fukuhara K, Yasumitsu T. Surgery for pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 2000;70:380-383.
- ¹¹ Sakamoto T, Tsubota N, Iwanaga K, Yuki T, Matsuoka H, Yoshimura M. Pulmonary resection for metastases from colorectal cancer. *Chest* 2001;119:1069-1072.
- ¹² Rena O, Casadio C, Viano F, et al. Pulmonary resection for metastases from colorectal cancer: factors influencing prognosis. Twenty-year experience. *Eur J Cardiothorac Surg* 2002;21:906-912.
- ¹³ Irshad K, Ahmad F, Morin JE, Mulder DS. Pulmonary metastases from colorectal cancer: 25 years of experience. *Can J Surg* 2001;44:217-221.
- ¹⁴ Ambiru S, Miyazaki M, Ito H, et al. Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. *Cancer* 1998;82:274-278.
- ¹⁵ Yano T, Hara N, Ichinose Y, Yokoyama H, Miura T, Ohta M. Results of pulmonary resection of metastatic colorectal cancer and its application. *J Thorac Cardiovasc Surg* 1993;106:875-879.
- ¹⁶ Hendriks JM, Romijn S, Van Putte B, et al. Long-term results of surgical resection of lung metastases. *Acta Chir Belg* 2001;101:267-272.
- ¹⁷ Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001;8:347-353.
- ¹⁸ Rivoire M, De Cian F, Meeus P, Negrier S, Sebban H, Kaemmerlen P. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. *Cancer* 2002;95:2283-2292.
- ¹⁹ Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol*. 2006 May 1;24(13):2065-72.
- ²⁰ Pawlik TM, Olin K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. *J Gastrointest Surg*. 2007 Jul;11(7):860-8.
- ²¹ Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol*. 2006 Aug 20;24(24):3939-45.
- ²² Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol*. 2006;13:1284-92.

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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. A total of approximately 6 months of perioperative treatment is preferred.

Postoperative adjuvant chemotherapy:

- **mFOLFOX 6¹**
Oxaliplatin 85 mg/m² IV over 2 hours, day 1, leucovorin* 400 mg/m² IV over 2 hours, day 1, 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)[†] continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.
- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)²**
Leucovorin 400 mg/m² IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)[†] continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.
- **Capecitabine³**
Capecitabine 1250 mg/m² twice daily days 1-14 every 3 wks to a total of 6 mo perioperative therapy.
- **CapeOx⁴**
Oxaliplatin 130 mg/m² over 2 hours, day 1. Capecitabine 1000 mg/m² twice daily days 1-14 every 3 wks. Repeat every 3 weeks to a total of 6 mo perioperative therapy.
- **FLOX⁵**
5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8 week cycle x 3 with oxaliplatin 85 mg/m² IV administered on weeks 1, 3, and 5 of each 8 week cycle. Repeat every 3 weeks to a total of 6 mo perioperative therapy.
- **5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8 week cycle. Repeat every 8 weeks to a total of 6 mo perioperative therapy.⁶**

Dosing Schedules for concurrent chemotherapy/RT:

- **XRT + continuous infusion 5-FU⁷**
5-FU 225 mg/m² over 24 h 5 or 7 d/wk during XRT
- **XRT + 5-FU/leucovorin⁸**
5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 d during wk 1 and 5 of XRT
- **XRT + Capecitabine^{9,10}**
Capecitabine 825 mg/m² twice daily 5 or 7 d/wk + XRT x 5 wks

**IMPORTANT NOTE REGARDING
LEUCOVORIN SHORTAGE, PLEASE SEE [MS-9](#)**

[See footnotes on page 2 of 2 REC-C](#)

*Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

[†]NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.

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PRINCIPLES OF ADJUVANT THERAPY (2 of 2) - REFERENCES

- ¹Cassidy J, Clarke S, Diaz Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008;26:2006-12.
- ²Andre T, Louvet C, Maindault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. *Eur J Cancer* 1999;35(9):1343-7.
- ³Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005;352(26):2696-2704.
- ⁴Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. *J Clin Oncol* 2007;25:102-109. Haller DG, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer. *J Clin Oncol* 2011;29:1465-1471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21383294>
- ⁵Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. *J Clin Oncol* 2007;25:2198-2204.
- ⁶Petrelli N, Douglass Jr HO, Herrare L, et al. The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. *J Clin Oncol* 1989;7:1419-1426.
- ⁷O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994; 331:502-507.
- ⁸Tepper JE, O'Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control--final report of Intergroup 0114. *J Clin Oncol* 2002;20:1744-1750.
- ⁹Roh MS, Yothers GA, O'Connell MJ, et al. The impact of capecitabine and oxaliplatin in the preoperative multimodality treatment in patients with carcinoma of the rectum: NSABP R-04 [abstract]. *J Clin Oncol* 2011;29 (suppl):3503. Available at: http://abstract.asco.org/AbstView_102_76910.html
- ¹⁰Hofheinz R, Wenz FK, Post S, et al. Capecitabine (Cape) versus 5-fluorouracil (5-FU)-based (neo)adjuvant chemoradiotherapy (CRT) for locally advanced rectal cancer (LARC): Long-term results of a randomized, phase III trial [abstract]. *J Clin Oncol* 2011;29 (suppl):3504. Available at: http://abstract.asco.org/AbstView_102_77485.html

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PRINCIPLES OF RADIATION THERAPY

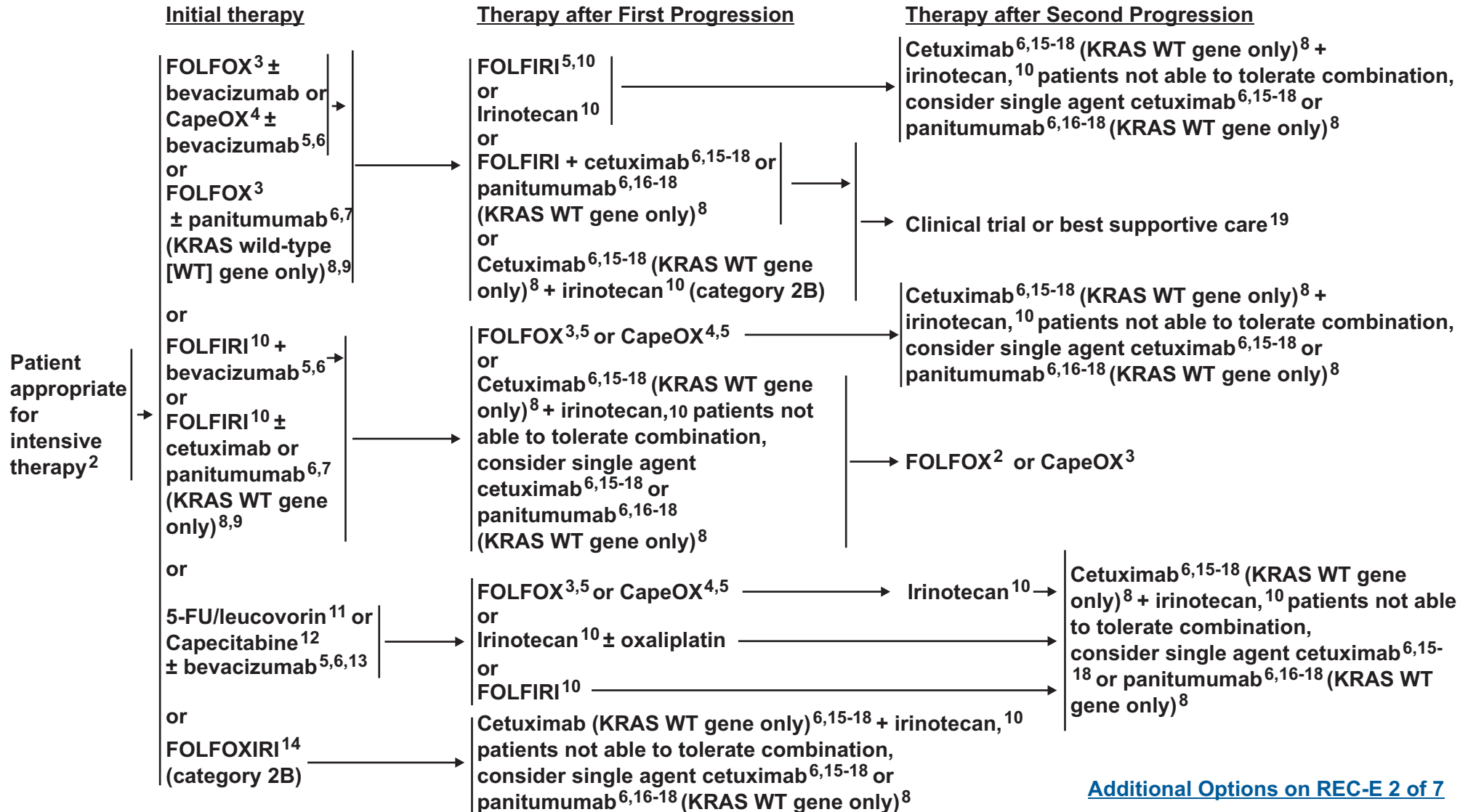
- Radiation therapy fields should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
- Multiple radiation therapy fields should be used (generally a 3 or 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) should only be used in the setting of a clinical trial or in unique clinical situations including re-irradiation of recurrent disease after previous radiotherapy.
- Radiation doses:
 - ▶ 45-50 Gy in 25-28 fractions to the pelvis.
 - ▶ For resectable cancers, after 45 Gy a tumor bed boost with a 2 cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
 - ▶ Small bowel dose should be limited to 45 Gy.
- Intraoperative 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 and/or brachytherapy 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, if technically feasible.
- 5-fluorouracil based chemotherapy should be delivered concurrently with radiation therapy.
- In patients with a limited number of liver or lung metastases, radiotherapy can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3D conformal radiotherapy, IMRT or stereotactic body radiosurgery (SBRT). (category 3)
- Side effect management:
 - Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.

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CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 1 of 7)



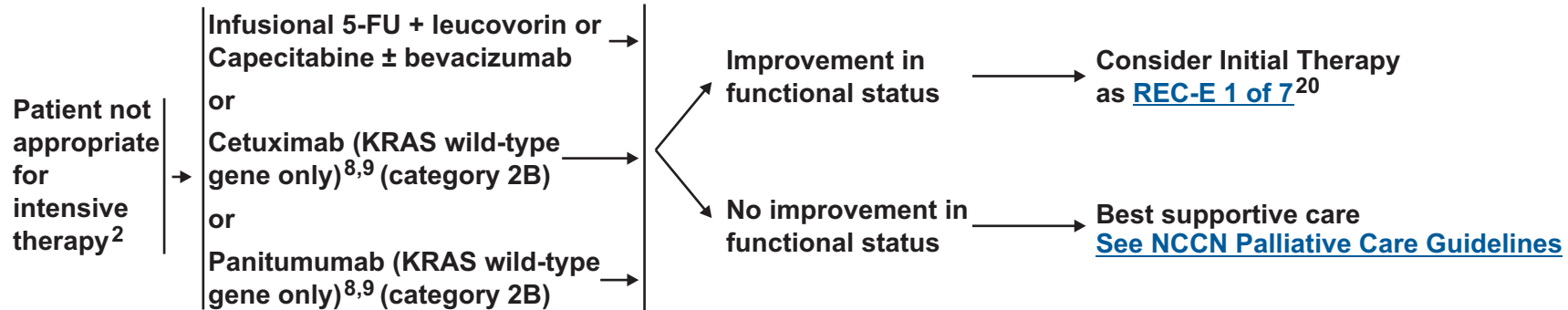
[Additional Options on REC-E 2 of 7](#)
[See footnotes on page REC-E 3 of 7](#)

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CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:¹ (PAGE 2 of 6)

Initial therapy

Therapy after First Progression



[See footnotes on page REC-E 3 of 7](#)

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**CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 7)**

- ¹For chemotherapy references, [see Chemotherapy Regimens and References \(REC-E pages 4 - 7\)](#).
- ²PET-CT should not be used to monitor progress of therapy. CT with contrast or MRI is recommended.
- ³Discontinuation of oxaliplatin should be strongly considered from FOLFOX or CapeOX after 3-4 months of therapy (or sooner if significant neurotoxicity develops \geq grade 2) 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. There are insufficient data to support the routine use of Ca/Mg infusion to prevent oxaliplatin-related neurotoxicity.
- ⁴The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1250 mg/m² 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/m² twice daily dose is the recommended starting dose, with close monitoring in the first cycle for toxicity, and dose adjustments as indicated.
- ⁵There are insufficient data to support continuation of bevacizumab with a second-line regimen after progression on a bevacizumab-containing first line regimen, and such continuation of bevacizumab beyond progression is not recommended. If bevacizumab is 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.
- ⁶Combination therapy involving cytotoxics, anti-EGFRs and anti-VEGFs is not recommended. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 2009;27:672-80. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 2009;360(6):563-572.
- ⁷If cetuximab or panitumumab are used as initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy.
- ⁸[See Principles of Pathologic Review \(REC-A 5 of 6\)](#) - KRAS and BRAF Mutation Testing.
- ⁹Patients with a V600E BRAF mutation appear to have a poorer prognosis. Retrospective subset analyses suggest potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status.
- ¹⁰Irinotecan 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.
- ¹¹Infusional 5-FU is preferred.
- ¹²Patients with diminished creatinine clearance may require dose modification of capecitabine.
- ¹³A treatment option for patients not able to tolerate oxaliplatin or irinotecan.
- ¹⁴Data are not mature for the addition of biologic agents to FOLFOXIRI.
- ¹⁵Cetuximab is indicated in combination with irinotecan-based therapy or as single agent therapy for patients who cannot tolerate irinotecan.
- ¹⁶EGFR 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.
- ¹⁷There 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.
- ¹⁸Patients with a V600E BRAF mutation appear to have a poorer prognosis. Limited available data suggest lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after patient has progressed on first-line therapy.
- ¹⁹Single agent or combination therapy with capecitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.
- ²⁰The 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 - CHEMOTHERAPY REGIMENS (PAGE 4 of 7)

FOLFOX

mFOLFOX 6

Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days
(total 2400 mg/m² over 46-48 hours)[†] IV continuous infusion
Repeat every 2 weeks^{1,2}

mFOLFOX6 + Bevacizumab^{2,3,¶}

Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days
(total 2400 mg/m² over 46-48 hours)[†] IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

mFOLFOX6 + Panitumumab^{2,4}

Oxaliplatin 85 mg/m² IV over 2 hours, day 1
Leucovorin* 400 mg/m² IV over 2 hours, day 1
5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/day x 2 days
(total 2400 mg/m² over 46-48 hours)[†] IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

CapeOX^{1,5}

Oxaliplatin 130 mg/m² IV over 2 hours, day 1
Capecitabine 850-1000[‡] mg/m² twice daily PO for 14 days
Repeat every 3 weeks

CapeOX + Bevacizumab^{1,5,¶}

Oxaliplatin 130 mg/m² IV over 2 hours, day 1
Capecitabine 850-1000[‡] mg/m² PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

**IMPORTANT NOTE REGARDING LEUCOVORIN
SHORTAGE, PLEASE SEE [MS-9](#)**

[See References on page REC-E 7 of 7](#)

*Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

[†]NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 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/m² 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.

[¶]Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 5 of 7)

FOLFIRI⁶

Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)[†] continuous infusion
Repeat every 2 weeks

FOLFIRI⁶ + Bevacizumab^{7,††}

Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)[†] IV continuous infusion
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI⁶ + Cetuximab

Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)[†] IV continuous infusion
Repeat every 2 weeks
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly⁸
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks⁹

FOLFIRI⁶ + Panitumumab¹⁰

Irinotecan 180 mg/m² IV over 30-90 minutes, day 1
Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46-48 hours)[†] IV continuous infusion
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

IMPORTANT NOTE REGARDING LEUCOVORIN SHORTAGE, PLEASE SEE [MS-9](#)

[See References on page REC-E 7 of 7](#)

*Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

[†]NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 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/m² 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.

^{†††}Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 6 of 7)

Capecitabine¹¹

850-1250 mg/m² PO twice daily, days 1-14
Repeat every 3 weeks

Capecitabine¹¹ + Bevacizumab[†]

850-1250 mg/m² PO twice daily, days 1-14
Repeat every 3 weeks
Bevacizumab 5 mg/kg IV, day 1 weekly

Bolus or infusional 5-FU/leucovorin

Roswell-Park regimen¹²

Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin,
days 1, 8, 15, 22, 29, 36
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)⁶

Leucovorin 400 mg/m² IV over 2 hours on day 1,
followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/day x 2
days (total 2400 mg/m² over 46-48 hours)[†] continuous infusion
Repeat every 2 weeks

Weekly

Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV
bolus injection 1h after the start of leucovorin. Repeat weekly.¹³
5-FU 2600 mg/m² by 24 h infusion plus leucovorin 500 mg/m²
Repeat every week¹⁴

IROX¹⁵

Oxaliplatin 85 mg/m² IV over 2 hours, followed by irinotecan 200
mg/m² over 30 or 90 minutes every 3 weeks

FOLFOXIRI¹⁶

Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² day 1, leucovorin
400* mg/m² day 1, fluorouracil 3,200 mg/m² over 48 h continuous
infusion starting on day 1
Repeat every 2 weeks

Irinotecan

Irinotecan 125 mg/m² IV over 30-90 minutes, days 1, 8
Repeat every 3 weeks^{17,18}
Irinotecan 300-350 mg/m² IV over 30-90 minutes, day 1
Repeat every 3 weeks

Cetuximab (KRAS wild-type gene only) ± irinotecan^{9,19}

Cetuximab 400 mg/m² 1st infusion, then 250 mg/m² IV weekly
or Cetuximab 500 mg/m² IV every 2 weeks⁹
±

Irinotecan 300-350 mg/m² IV every 3 weeks
or Irinotecan 180 mg/m² IV every 2 weeks
or Irinotecan 125 mg/m² on days 1, 8 and repeat every 3 weeks

Cetuximab (KRAS wild-type gene only)

Cetuximab 400 mg/m² 1st infusion, then 250 mg/m² IV weekly¹⁹
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks⁹

Panitumumab²⁰ (KRAS wild-type gene only)

Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

**IMPORTANT NOTE REGARDING LEUCOVORIN
SHORTAGE, PLEASE SEE [MS-9](#)**

[See References on page REC-E 7 of 7](#)

*Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

[†]NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m²/day NOT 2400 mg/m² over 48 hours) to minimize medication errors.

^{††}Bevacizumab may be safely given at a rate of 0.5 mg/kg/minute (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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**CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES (PAGE 7 of 7)**

- ¹Cassidy J, Clarke S, Diaz Rubio E, et al. Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *J Clin Oncol* 2008;26:2006-12.
- ²Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br J Cancer* 2002;87:393-399. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12177775>.
- ³Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. *BMC Cancer* 2007;7:91.
- ⁴Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697-4705.
- ⁵European studies showing equivalent efficacy for CapeOX used at a higher dose; however, European patients consistently tolerate capecitabine with less toxicity than American patients.
- ⁶Andre T, Louvet C, Maindault-Goebel F, et al. CPT-11 (irinotecan) addition to bimonthly, high-dose leucovorin and bolus and continuous-infusion 5-fluorouracil (FOLFIRI) for pretreated metastatic colorectal cancer. *Eur J Cancer* 1999;35(9):1343-7.
- ⁷Fuchs CS, Marshall J, Mitchell E, et al. Randomized, controlled trial of irinotecan plus infusional, bolus, or oral fluoropyrimidines in first-line treatment of metastatic colorectal cancer: results from the BICC-C Study. *J Clin Oncol* 2007;25:4779-4786. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17947725>
- ⁸Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-345.
- ⁹Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *Br J Cancer* 2008;99:455-458.
- ¹⁰Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;28:4706-4713. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20921462>.
- ¹¹VanCutsem E, Twelves C, Cassidy J, et al. Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. *J Clin Oncol* 2001;19:4097-4106.
- ¹²Wolmark N, Rockette H, Fisher B, et al. The benefit of leucovorin-modulated fluorouracil as postoperative adjuvant therapy for primary colon cancer: results from National Surgical Adjuvant Breast and Bowel Protocol C-03. *J Clin Oncol* 1993;11:1879-1887.
- ¹³Jäger E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. *J Clin Oncol* 1996;14:2274-2279.
- ¹⁴Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *The Lancet* 2000;355:1041-47.
- ¹⁵Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single agent fluoropyrimidine therapy for metastatic colorectal carcinoma. *J Clin Oncol* 2008;26:4544-4550.
- ¹⁶Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007;25(13):1670-1676.
- ¹⁷Cunningham D, Pyrhonen S, James R, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *The Lancet* 1998;352:1413-1418.
- ¹⁸Fuchs CS, Moore MR, Harker G, et al. Phase III comparison of two irinotecan dosing regimens in second-line therapy of metastatic colorectal cancer. *J Clin Oncol* 2003;21:807-814.
- ¹⁹Van Cutsem E, Humblet H, Gelderblom J, et al. Cetuximab dose-escalation in patients with metastatic colorectal cancer with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): Pharmacokinetic and efficacy data of a randomized study. 2007 Gastrointestinal Cancers Symposium. Abstract 237.

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**PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care****Colorectal Cancer Surveillance:**

- See [REC-7](#)
- Long term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years.

Management of Late Sequelae of Disease or Treatment:¹⁻⁵

- Chronic Diarrhea or Incontinence
 - Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.
- Urogenital Dysfunction after Resection and/or Pelvic Radiation^{6,7}
 - Screen for sexual dysfunction, erectile dysfunction, dyspareunia, and vaginal dryness
 - Screen for urinary incontinence, frequency, and urgency
 - Consider referral to urologist or gynecologist for persistent symptoms.

Prescription for Survivorship and Transfer of Care to Primary Care Physician:⁸ (If primary physician will be assuming cancer surveillance responsibilities)

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

¹Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer. *Cancer* 2007;110: 2075-2082.

²Sprangers MAG, Taal BG, Aaronson NK, et al. Quality of life in colorectal cancer: stoma vs. nonstoma patients. *Dis Colon Rectum* 1995;38:361-369.

³Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. *Alimentary Pharmacology and Therapeutics* 2003;18:987-994.

⁴DeSnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. *European Journal of Cancer Care* 2006;15:244-251.

⁵McGough C, Baldwin C, Frost C, Andreyev HJN. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. *British Journal of Cancer* 2004;90:2278-2287.

Cancer Screening Recommendations:

These recommendations are for average risk patients.

Recommendations for high risk individuals should be made on an individual basis.

- Breast Cancer: See the [NCCN Breast Cancer Screening Guidelines](#)
 - Cervical Cancer: See the [NCCN Cervical Cancer Screening Guidelines](#)
 - Prostate Cancer: See the [NCCN Prostate Early Detection Guidelines](#)
- Counseling Regarding Healthy Lifestyle and Wellness:⁹**
- Maintain a healthy body weight throughout life.
 - Adopt a physically active lifestyle (At least 30 minutes of moderate intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (i.e. ostomy, neuropathy).
 - Consume a healthy diet with emphasis on plant sources.
 - Limit alcohol consumption.
 - Smoking cessation counseling as appropriate.

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

⁶Lange MM, Mass CP, Marijnen CAM, et al. Risk factors for sexual dysfunction after rectal cancer treatment. *Eur J Cancer* 2009;45:1578-88.

⁷Lange MM, Mass CP, Marijnen CAM, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. *Brit J Cancer* 2008;95:1020-28.

⁸Hewitt M, Greenfield S, Stovall E. From Cancer Patient to Cancer Survivor: Lost in Transition. Washington, D.C.:The National Academies Press;2006.

⁹Kushi LH, Byers T, Doyle C, et al and The American Cancer Society 2006 Nutrition and Physical Activity Guidelines Advisory Committee. American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention: Reducing the Risk of Cancer With Healthy Food Choices and Physical Activity *CA Cancer J Clin* 2006;56:254-281.

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.



NCCN Guidelines™ Version 1.2012 Staging Rectal Cancer

Table 1. Definitions for T, N, M

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^a
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into the pericorectal tissues
- T4a Tumor penetrates to the surface of the visceral peritoneum^b
- T4b Tumor directly invades or is adherent to other organs or structures^{b,c}

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1-3 regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in 2-3 regional lymph nodes
- N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 Metastasis in four or more regional lymph nodes
- N2a Metastasis in 4-6 regional lymph nodes
- N2b Metastasis in seven or more regional lymph nodes

Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
- M1b Metastases in more than one organ/site or the peritoneum

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

^bDirect invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

^cTumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN site-specific factor should be used for perineural invasion.

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Table 2. Anatomic Stage/Prognostic Groups

| 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 | T4a | N0 | M0 | B | B2 |
| IIC | T4b | N0 | M0 | B | B3 |
| IIIA | T1-T2 | N1/N1c | M0 | C | C1 |
| | T1 | N2a | M0 | C | C1 |
| IIIB | T3-T4a | N1/N1c | M0 | C | C2 |
| | T2-T3 | N2a | M0 | C | C1/C2 |
| IIIC | T1-T2 | N2b | M0 | C | C1 |
| | T4a | N2a | M0 | C | C2 |
| | T3-T4a | N2b | M0 | C | C2 |
| IVB | T4b | N1-N2 | M0 | C | C3 |
| | Any T | Any N | M1a | - | - |
| IVA | Any T | Any N | M1b | - | - |

Note : cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (e.g., ypTNM). Patients who have a complete pathologic response are ypT0N0cM0 that may be similar to Stage Group 0 or I. The r prefix is to be used for those cancers that have recurred after a disease-free interval (rTNM).

*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.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 02/25/11

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

In 2010, an estimated 39,670 new cases of rectal cancer will have occurred in the United States (22,620 cases in men; 17,050 cases in women). During the same year, it is estimated that 51,370 people will have died from rectal and colon cancer.¹ Although colorectal cancer is ranked as the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the U.S., mortality from colorectal cancer has decreased by more than 33% from 1990 to 2006.¹ This decrease may be due to both earlier diagnoses 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 or invasive carcinoma are at increased risk for colorectal cancer.^{2,3} Therefore, all rectal cancer patients 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 7th edition of the American Joint Committee on Cancer's (AJCC) Cancer Staging Manual (Table 1 of the guidelines).⁴ Several changes to the staging of colorectal cancer were made in the 7th edition. For instance, based on new data showing differential prognosis,⁵ T4 lesions have now been subdivided into T4a (tumor penetrates to the surface of the visceral peritoneum) and T4b (tumor directly invades or is adherent to other organs or structures). Another change of note is the subdivision of N1 into N1a (metastasis in 1 node), N1b (metastasis in 2-3 nodes), and N1c (without regional nodal metastases, but with tumor deposits in the subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues); and of N2 into N2a (metastasis in 4-6 nodes) and N2b (metastasis in 7 or more nodes). These subsets reflect new data showing that the number of involved nodes influences prognosis⁶ and new data on the prognostic value of tumor deposits within the lymph drainage area of the primary tumor.⁷⁻⁹ Stage I rectal cancer is defined as T1-T2, N0, M0. Stage II disease is subdivided into IIA (if the primary tumor is T3, N0, M0), IIB (for T4a, N0, M0 lesions), and IIIC (for T4b, N0, M0). Stage III



disease is subdivided into IIIA (T1-2, N1/N1c, M0 or T1, N2a, M0), IIIB (T3-4a, N1/N1c, M0 or T2-T3, N2a, M0 or T1-T2, N2b, M0), and IIIC (T4a, N2a, M0 or T3-4a, N2b, M0 or T4b, N1-2, M0). Stage IVA disease is defined as any T, any N, and the presence of distant metastasis confined to 1 organ or site (M1a). Stage IVB disease is defined as any T, any N, with metastases in more than 1 organ or site or in the peritoneum (M1b).⁴ In addition, the 7th edition of the AJCC staging manual includes the suggestion that the surgeon mark the area of the specimen with the deepest tumor penetration so that the pathologist can directly evaluate the status of the resection margins.⁴ The completeness of the resection is scored as R0 for complete tumor resection with all margins negative; R1 for incomplete tumor resection with microscopic involvement of a margin; and R2 for incomplete tumor resection with gross residual tumor that was not resected.⁴

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 cancer¹⁰ includes: (1) gross description of the tumor and specimen; (2) grade of the cancer; (3) depth of penetration and extension to adjacent structures (T); (4) number of regional lymph nodes evaluated; (5) number of positive regional lymph nodes (N); (6) the presence of distant metastases to other organs, the peritoneum of an abdominal structure, or non-regional lymph nodes (M); (7) the status of proximal, distal, and circumferential (radial) margins^{4, 10-15}; (8) neoadjuvant treatment effect^{4, 10, 16, 17}; (9) lymphovascular invasion^{4, 10, 18}; (10) perineural invasion¹⁹⁻²¹; and (11) the number of tumor deposits.^{9, 22} The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.⁴

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer.²³ 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.²³ The CRM is the closest radial margin between the deepest penetration of the tumor and the edge of resected soft tissue around the rectum (ie, the retroperitoneal or subperitoneal aspect of the tumor) or from the edge of a lymph node and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen that often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.²⁴ A positive CRM has been defined as tumor within 1 mm from the transected margin.^{13, 15, 25, 26}

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,^{23, 25, 27, 28} including in patients undergoing neoadjuvant therapy,¹⁴ and is an important consideration when post-operative treatment decisions are made. Furthermore, in a retrospective study of over 17,000 patients with rectal cancer, CRM was found to be a better predictor of local recurrence for patients undergoing surgery as initial therapy than for those who had received preoperative therapy.¹⁴ CRM positivity based solely on intranodal tumor should be noted as such; some studies have shown that positive intranodal CRM is associated with lower recurrence rates than a positive CRM by direct tumor extension. Additional components of the pathological evaluation of the surgical specimen following a total mesorectal excision (TME) are described under Surgical Approaches.

The AJCC and the College of American Pathologists (CAP) recommend evaluation of 10-14 and 12-18 lymph nodes to accurately identify stage II colorectal cancers, respectively.^{4, 10, 23} The number of lymph nodes that can be retrieved varies with age and gender of the patient and on tumor grade or site.²⁹ The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify stage II rectal cancer.³⁰ 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.^{31, 32} Furthermore, 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, $P \leq 0.0001$).^{33, 34} The panel recommends a minimum of 12 lymph nodes be examined.

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 and the identification of particular tumor antigens through immunohistochemical (IHC) analysis have been reported.^{35, 36} 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 or by H&E, so-called isolated tumor cells (ITC), to be micrometastasis.^{36, 37} In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.³⁸ Furthermore, in a recent study involving 156 patients with colon cancer and 44 patients with rectal cancer, this “ultra-staging” of lymph nodes only changed the staging for 1% of patients.³⁹ Others have noted that micrometastasis found in node-negative patients did not predict

outcome.⁴⁰ Presently, the use of sentinel lymph nodes and detection of cancer cells by IHC should be considered investigational, and the results should be used with caution in clinical management decisions.

The 7th edition of the AJCC Staging Manual and the most recent College of American Pathologists Guidelines require that the pathology report comment on treatment effects of neoadjuvant therapy.^{4, 10} The minimum requirement is a yes/no whether a definitive treatment effect is identified. However, it is the opinion of the panel, as well as of the College of American Pathologists, that the tumor response should be graded on a scale of 0 (complete response – no viable cancer cells observed) to 3 (poor response – minimal or no tumor kill; extensive residual cancer).^{4, 10, 16, 17}

Several studies have demonstrated that the presence of perineural invasion (PNI) is associated with a significantly worse prognosis.¹⁹⁻²¹ For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at 1 institution found a 4-fold greater 5-year survival in patients without perineural invasion versus patient whose tumors invaded nearby neural structures.²⁰ Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year disease-free survival compared to those without PNI (29% vs. 82%; $P = 0.0005$).²¹ Similar results were seen for patients with stage III disease.¹⁹

Extra-nodal tumor deposits, or satellite nodules, are irregular discrete tumor deposits in the pericolic or perirectal fat that show no evidence of residual lymph node tissue, but that are within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to be due to lymphovascular invasion or occasionally perineural invasion. The number of extra-nodal tumor deposits should be recorded in the

pathology report, since they have been shown to be associated with reductions in disease-free and overall survival.^{9, 22, 41} Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5% 5-year survival rate compared to 37.0% for patients with pN0 tumors and the presence of satellite nodules ($P < 0.0001$)⁹ Extra-nodal tumor deposits are classified as pN1c.⁴

The receptor for epidermal growth factor (EGFR) has been shown to be overexpressed in 19% of colorectal tumors.⁴² Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways, but EGFR status is not predictive of treatment efficacy.^{43, 44} Furthermore, cetuximab and panitumumab are only effective in approximately 10-20% of patients with colorectal cancer.⁴³⁻⁴⁵ The RAS/RAF/MAPK pathway is downstream of EGFR; mutations in components of this pathway have been studied in hopes to find predictive markers for response to these therapies, as discussed below.

A sizable body of literature has demonstrated that mutations in codons 12 and 13 in exon 2 of the coding region of the KRAS gene predict lack of response to cetuximab or panitumumab therapy.⁴⁶⁻⁵⁴ Therefore, the panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer *at the time of diagnosis of stage IV disease*. The recommendation for KRAS testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting, but rather, this early establishment of KRAS status is appropriate in order to plan for the treatment continuum, so that the information may be obtained in a non-time-sensitive manner, and the patient and provider can discuss the implications of a KRAS mutation, if present, while other treatment options still exist. KRAS mutations are early events in colorectal cancer

formation, and there is a tight correlation between mutation status in the primary tumor and in the metastases.^{55, 56} For this reason, KRAS genotyping can be done on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of KRAS genotyping if an archived specimen from either the primary tumor or a metastasis is available. The panel recommends that KRAS gene testing be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.

Patients with a V600E BRAF mutation appear to have a poorer prognosis.^{57, 58} In one study, patients with BRAF V600E mutations in primary colorectal tumors showed significantly decreased progression-free survival (2.7 vs 9.8 months; $P < 0.001$) and median overall survival (14 vs 30 months; $P < 0.001$) than patients whose tumors contained wild-type BRAF.⁵⁷ Retrospective subset analyses suggest potential benefit from anti-EGFR monoclonal antibodies in the first-line setting with active chemotherapy regardless of V600E mutation status.⁵⁹ Limited available data suggest a lack of antitumor activity from anti-EGFR monoclonal antibodies in the presence of a V600E mutation when used after a patient has progressed on first-line therapy.⁶⁰ Testing for the BRAF V600E mutation can be performed on formalin-fixed paraffin-embedded tissues. This is usually performed by PCR amplification and direct DNA sequence analysis. As with KRAS testing (see above), BRAF testing should be performed only in CLIA-88 molecular pathology laboratories.



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 pathology⁶¹ and consult with the patient. A malignant rectal polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1).⁶² Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis.²³ 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.⁶¹ Favorable histological features include lesions of grade 1 or 2, without angiolymphatic invasion, and with a negative resection margin.⁶¹

In addition to the option of observation, the panel includes the option of rectal surgery in patients with a completely removed, single-specimen, sessile polyp (pT1) 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.⁶³ For pedunculated and sessile polyps, unfavorable histopathological features are: grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. In such cases, risk of nodal involvement is higher. 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 or by the presence of tumor cells within the diathermy of the transected margin.^{61, 64-66} For a pedunculated or sessile polyp with fragmented specimen or margins that cannot be assessed, either a transanal excision or a

transabdominal resection is recommended. In patients with unfavorable pathologic features, transabdominal resection should be considered in order to include lymphadenectomy. Results from a preoperative endoscopic ultrasound evaluation may provide additional information to guide choice of surgical approach, although the accuracy of this method to detect residual cancer is limited (see section on Clinical Evaluation/Staging, below).⁶⁷ All patients who have resected polyps should undergo surveillance as described in the guidelines.⁶⁸

Management of Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge by rigid proctoscopy.⁶⁹ Some support for this definition comes from the study of Kapiteijn et al,⁷⁰ 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.⁷⁰ A recent retrospective review of patients with rectal or rectosigmoid cancer demonstrated that treatment options were impacted by whether the location of the rectal lesion was characterized by rigid proctoscopy or colonoscopy.⁷¹

The 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 of minimal impact on quality of life can be challenging.⁷² 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.⁷³⁻⁷⁵ Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy for selected patients that combines chemoradiation (chemoRT) with operative treatment as part of the treatment regimen is recommended.

Clinical Evaluation/Staging

The initial clinical workup of patients with rectal cancer provides important preoperative information on the clinical stage of disease. 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 to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum, rigid proctoscopy to provide a determination of the location of the cancer (ie, measurement of the distance of the tumor from the anal verge should be performed by the responsible surgeon using rigid proctoscopy), and a complete physical examination, including assessment of performance status, to determine operative risk, carcinoembryonic antigen (CEA) 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 endorectal ultrasound and magnetic resonance imaging (MRI) makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.⁷⁶ Additional information regarding the extent of disease and the occurrence of distant metastases can be determined preoperatively through CT scans. Thus, endorectal ultrasound or endorectal or pelvic MRI, and CT scans of the chest, abdomen and pelvis are recommended for the preoperative staging of rectal cancer.

Results from a meta-analysis of 90 studies involving the accuracy of endoscopic ultrasound, MRI, and CT in preoperatively staging rectal cancer demonstrated that endoscopic ultrasound and MRI have similarly high sensitivities for evaluating the depth of tumor penetration into the muscularis propria (94%), although endoscopic ultrasound was found to be more specific than MRI in the evaluation of local tumor invasion (86% vs. 69%).⁷⁷ 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.^{77, 78} 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,⁷⁷ the sensitivities and specificities of the 3 imaging modalities for accurately evaluating lymph node involvement were comparable: CT (55% and 74%); endoscopic ultrasound (67% and 78%); and MRI (66% and 76%). However, only CT and MRI can evaluate iliac and mesenteric or retroperitoneal nodes.⁷⁷ 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.⁷⁹ A disadvantage of endoscopic ultrasound is a high degree of operator dependence.⁷⁷ An advantage of MRI is its ability to

provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia.⁷⁷ 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.⁷⁸⁻⁸⁰

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.^{81, 82} These methods include local procedures, such as polypectomy, transanal excision, and transanal endoscopic microsurgery (TEM), and more invasive procedures involving a transabdominal resection (eg, low anterior resection [LAR], proctectomy with total mesorectal excision [TME] and coloanal anastomosis, or abdominoperineal resection [APR]).^{81, 82}

Transanal excision may be appropriate for selected cT1, N0 early-stage cancers. Small (<3 cm), well to moderately differentiated tumors that are within 8 cm of the anal verge and limited to less than 30% of the rectal circumference and for which there is no evidence of nodal involvement can be approached with transanal excision with negative margins. Transanal endoscopic microsurgery (TEM) can facilitate excision of small tumors through the anus when lesions can be adequately identified in the rectum. TEM may be technically feasible for

more proximal lesions. Both transanal excision and TEM involve a full thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (>3 mm) deep and mucosal margins are required, and tumor fragmentation should be avoided. The excised specimen should be oriented and pinned before fixation and brought to the pathologist by the surgeon (ie, to facilitate an oriented histopathologic evaluation of the specimen). Advantages of a local procedure include minimal morbidity (eg, a sphincter-sparing procedure) and mortality and rapid postoperative recovery.^{72, 83} If pathologic examination reveals adverse features such as high grade, positive margins, lymphovascular invasion (LVI) or perineural invasion, a more radical resection is recommended. Data are limited on long-term patient outcomes, including risk of local recurrence, for patients undergoing local excision for T2 tumors.⁸³

Limitations of a transanal excision include the absence of pathologic staging of nodal involvement. Further, there is evidence to indicate that lymph node micrometastases are both more common in early rectal lesions and unlikely to be identified by endorectal ultrasound.⁸⁴ These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.^{83, 85} A recent retrospective study of 282 patients undergoing either transanal excision or radical resection for T1 rectal cancer from 1985 to 2004 showed respective local recurrence rates of 13.2% and 2.7% for these 2 groups (P=0.001).⁸⁵ A similar retrospective study of 2,124 patients showed local recurrence rates of 12.5% and 6.9% for patients undergoing local excision versus standard resection, respectively (P=0.003).⁸³

Patients with rectal cancer who do not meet requirements for local surgery should be treated with a transabdominal resection. Organ-preserving procedures that maintain sphincter function are preferable,

but not possible in all cases. For lesions in the mid to upper rectum, a low anterior resection (LAR) extended 4-5 cm below the distal edge of the tumor, followed by creation of a colorectal anastomosis, is the treatment of choice. Where creation of an anastomosis is not possible, colostomy is required. Wide mesorectal excision is recommended in order to facilitate adequate lymphadenectomy and improve the probability of achieving negative circumferential margins.

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer are limited.^{86, 87} In the CLASICC trial comparing laparoscopically-assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.⁸⁶ No significant differences in local recurrence, DFS, or overall survival were observed between the 2 groups of patients with rectal cancer based on surgical approach. However, factors that may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically-assisted surgery for colorectal cancer have been described,⁸⁸ and laparoscopic surgery for rectal cancer is not recommended by the panel outside of a clinical trial.

For low rectal lesions, abdominoperineal resection (APR) or LAR with coloanal anastomosis is required. In such procedures, total mesorectal excision (TME) is recommended. A TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a “tumor package” through sharp dissection and is designed to spare the autonomic nerves.^{72, 82, 89} In cases where anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis. Pathologists play a key role in evaluating the surgical specimen following TME which includes a macroscopic assessment of both its external appearance/completeness and the CRM^{90, 91} Detailed descriptions of how the quality of the mesorectal

specimens should be scored were provided in the Dutch Rectal Cancer Trial, and these guidelines are endorsed by the NCCN panel.¹³

An APR involves en bloc resection of the rectosigmoid, the rectum, and the anus, as well as the surrounding mesentery, mesorectum (TME), and perianal soft tissue, and it necessitates creation of a colostomy.⁹²

An APR is necessary in cases where a margin-negative resection of the tumor would result in loss of anal sphincter function and 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. Sphincter preservation may become possible in cases where initial tumor bulk prevented consideration of such surgery and exposure to the tumor is improved by chemoRT. An APR should be performed when tumor directly involves the anal sphincter or the levator muscles. Recent retrospective comparisons of the outcomes of patients undergoing an APR versus a LAR in the treatment of rectal cancer have shown those treated with an APR to have worse local control and overall survival.^{93, 94} Whether these differences can be attributed to the surgical procedure alone, to patient- and tumor-related characteristics, or some combination of these factors is presently unclear. However, results from a recent retrospective study of 3,633 patients with T3-4 rectal cancer tumors included in 5 large European trials suggest that there is an association between the APR procedure itself and the increased risks of recurrence and death.⁹³

The lymphatic drainage regions of rectal tumors are influenced by their position in the rectum. More distal tumors are more likely to be characterized by both upward and lateral lymphatic drainage whereas the likelihood of only upward mesorectal drainage is much higher for more proximal tumors.⁹⁵ The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of



the levator muscles.⁹⁶ The panel does not recommend extension of nodal dissection beyond the field of resection (eg, into the distribution of iliac lymph nodes) unless these nodes are clinically suspicious.

Leucovorin Shortage

There is currently a shortage of leucovorin in the United States. There are no specific data to guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m² of levo-leucovorin is equivalent to 400 mg/m² of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.⁹⁷ Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high dose (500 mg/m²) or low dose (20 mg/m²) leucovorin.⁹⁸ Also, the Mayo Clinic and North Central Cancer Treatment (NCTTG) group determined that there was no therapeutic difference between the use of high (200 mg/m²) or low (20 mg/m²) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.⁹⁹ Finally, if none of the above options are available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

Neoadjuvant/Adjuvant Therapy

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

Combined-modality therapy consisting of surgery, radiation therapy (RT), and chemotherapy is recommended for the majority of patients with stage II (T3-4, node-negative disease with tumor penetration through the muscle wall) or stage III rectal cancer (T3-4, 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 preservation of normal tissue.¹⁰⁰⁻¹⁰² First of all, reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Second, irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Finally, preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected).



One disadvantage of using preoperative RT is the possibility of over-treating early-stage tumors that do not require adjuvant radiation.^{101, 103} Improvements in preoperative staging techniques, such as MRI or CT scans, allow for more accurate staging, although the risk of over-staging disease has not been eliminated.¹⁰⁴

Several European studies have looked at the efficacy of a shorter course of radiation (25 Gy over 5 days) for the treatment of rectal cancer. The results of the Swedish Rectal Cancer Trial evaluating the use of short-course RT administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence with this approach compared with surgery alone.¹⁰⁵ However, a follow-up study published in 2005 showed that the patients with short-course preoperative RT had increased relative risk for postoperative hospitalization due to bowel obstructions and other gastrointestinal complications.¹⁰⁶ A number of other studies also investigating the effectiveness of preoperative short-course RT in patients with rectal cancer staged as T1-3 have demonstrated that overall survival was not significantly affected despite improvements in local control of disease.^{70, 107-109} A recent multicenter, randomized study of 1,350 patients with rectal cancer compared (a) short-course preoperative RT and no postoperative treatment with (b) no preoperative RT and a postoperative approach that 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.¹¹⁰ Results indicated that patients in the preoperative RT arm (a) had significantly lower local recurrence rates and a 6% absolute improvement in 3-year disease-free survival (DFS) (P=0.03), although no difference in overall survival was observed between the 2 arms of the study.^{110, 111} Overall, it appears that short-course RT gives effective local control and the same overall survival as more conventional RT

schedules, and therefore may be an appropriate choice in some situations.

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 pT3 and/or N1-2.^{112, 113} 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). 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).¹¹³ These conclusions have been supported in a recent systematic review which included 4 randomized controlled trials.¹¹²

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.¹⁰¹ 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 (27% vs 40%; P=0.001), 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 tumoricidal effect of RT when the 2 approaches were used concurrently.¹¹⁴ 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.¹¹⁴ 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.¹¹⁵ 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. In subsequent exploratory analyses of data from the group of patients in this trial who underwent complete tumor resection without evidence of distant disease before or at surgery, those patients with disease characterized as ypT0-2 showed significant benefit from adjuvant chemotherapy with respect to DFS and overall survival.¹¹⁶ These findings may indicate that patients are more likely to benefit from adjuvant therapy if their disease can be down-staged by chemoRT.

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,¹⁰¹ this conclusion has not been supported by 2 recent meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.^{117, 118}

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.^{24, 119} It has been suggested that some patients with disease at lower risk of local recurrence (eg, proximal rectal cancer staged as T3, N0, M0, characterized by clear margins and favorable prognostic features) may be adequately treated with surgery and adjuvant chemotherapy.^{24, 120, 121} In addition, 22% of 188 patients clinically staged with T3, N0 rectal cancer by either EUS or MRI who subsequently received preoperative chemoRT had positive lymph nodes following pathologic review of the surgical specimens according to results of a recent retrospective multicenter study,¹⁰⁴ suggesting that many patients are under-staged and would benefit from chemoRT. Therefore, the guidelines recommend preoperative chemoRT for patients with T3, N0 disease.

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 non-inferior to bolus 5-FU plus LV.¹²¹ 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.¹²² 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.¹²³ Most of the patients in this study had node-positive disease.

Postoperative chemoRT regimens commonly employ a “sandwich” approach – whereby chemotherapy (typically 5-FU based) is administered before and after the chemoRT regimen.¹²¹⁻¹²³ The use of FOLFOX or capecitabine chemotherapy before and after postoperative chemoRT is an extrapolation of the available data in colon cancer.^{124, 125}

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, as well as consideration of inclusion of the inguinal nodes for tumors invading into the distal anal canal. Recommended doses of radiation are typically 45-50 Gy in 25-28 fractions to the pelvis using 3 or 4 fields. Positioning and other techniques to minimize radiation to the small bowel are encouraged. For unresectable cancers, doses higher than 54 Gy may be required, and the dose of radiation to the small bowel should be limited to 45 Gy. As an additional boost, intraoperative radiotherapy (IORT),¹²⁶⁻¹²⁸ which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment, should be considered for patients with T4 tumors or recurrent cancers to facilitate resection. If IORT is not available, 10-20 Gy to a limited volume can be considered soon after surgery, prior to adjuvant chemotherapy.

Radiotherapy can be considered in highly selected cases in which the patient has a limited number of liver or lung metastases (category 3 recommendation) or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include 3D conformal radiotherapy, stereotactic body radiosurgery, and intensity modulated

radiotherapy (IMRT), which uses computer-imaging to focus RT to the tumor site and potentially decrease toxicity to normal tissue.¹²⁹⁻¹³¹

Coordination of preoperative therapy, surgery and adjuvant chemotherapy is important. For patients treated with preoperative chemoRT, the panel recommends an interval of 5 to 10 weeks following completion of full-dose 5-½ week chemoRT prior to performance of surgical resection in order to allow patient recuperation from chemoRT-associated toxicities. Although longer intervals from completion of chemoRT to surgery have been shown to be associated with an increase in pathologic complete response rates,¹³²⁻¹³⁴ 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.¹³⁵

A total of 6 months perioperative chemotherapy with or without RT is preferred. Adjuvant chemotherapy 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.¹³⁶ The addition of 5-FU-based adjuvant chemotherapy to preoperative chemoRT provided no benefit to the rate of local recurrence in the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group Trial 22921.¹¹⁵ However, this study did show an improvement in disease-free survival (hazard ratio=0.87; 95% CI, 0.72-1.04; P=0.13) of patients receiving adjuvant chemotherapy (+/- RT) following preoperative RT (+/- 5-FU-based chemotherapy).¹¹⁵

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.^{124, 125} The phase III ECOG E3201 trial was

designed to investigate 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. This study was replaced with an alternative trial with bevacizumab, but results from an initial 165 patients indicate that adjuvant FOLFOX can be safely used in this patient population.¹³⁷ Nevertheless, the optimal duration of treatment with adjuvant FOLFOX in rectal cancer is still unclear.^{138, 139} In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.¹⁴⁰ The use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) is justified when preoperative chemoRT is administered. In addition, the NSABP-07 trial demonstrated similar disease-free survival benefits to those reported in the MOSAIC trial with only 9 cycles of an oxaliplatin-containing adjuvant regimen.¹⁴¹ A summary of ongoing clinical trials in early-stage rectal cancer has been presented.¹⁴²

Treatment of Nonmetastatic Rectal Cancer

Recommendations for patients with T1 and T2 lesions

Node-negative T1 lesions are treated with transabdominal resection or transanal excision, as appropriate. Node-negative T2 lesions are treated with transabdominal resection, since local recurrence rates of 11% to 45% have been observed for T2 lesions following local excision alone.^{72, 143, 144} 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.¹⁴⁵ 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 or if

the tumor is restaged to T2, then a transabdominal re-resection should be performed. Following transabdominal resection, patients with tumors staged as pT1-2, N0, M0 require no further treatment. If pathology review reveals pT3, N0, M0 or node-positive disease, either a “sandwich regimen” consisting of an optional first round of adjuvant chemotherapy with 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin,¹⁴⁶ followed by concurrent 5-FU/RT (continuous infusion or bolus infusion along with LV) or capecitabine/RT, followed by 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin is recommended. Systemic chemotherapy should be considered as an adjuvant treatment for those 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” as described in the preceding paragraph. The panel recommends postoperative therapy for a total duration of perioperative therapy of approximately 6 months. For patients with pathologic evidence of proximal T3, N0, M0 disease with clear margins and favorable prognostic features following an upfront resection, the incremental benefit of RT is likely to be small and chemotherapy alone can be considered, although most patients are not likely to be part of this subset.

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. Upfront surgery should be reserved for patients with medical contraindications to chemoRT. Preoperative continuous infusional 5-FU/RT is the preferred treatment option (category 1 for node-positive disease). Alternative regimens include bolus 5-FU/LV/RT or capecitabine/RT. Patients who receive preoperative radiotherapy should undergo transabdominal resection 5 to 10 weeks following completion of neoadjuvant therapy. The panel recommends postoperative adjuvant therapy for a duration giving approximately 6 months total of pre- and postoperative chemotherapy (regardless of surgical pathology results) with 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin.

Patients with disease characterized as T3, 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. For patients with disease staged as pT3, N0, M0 or pT1-3, N1-2, M0 following initial treatment by transabdominal resection, approximately 6 months of postoperative chemotherapy “sandwich regimen” with an optional first round of 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin, followed by concurrent 5-FU/RT (5-FU as continuous infusion or bolus infusion with LV) or capecitabine/RT, followed by 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin should be reconsidered. 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 of RT is likely to be 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 or bolus 5-FU with LV/RT or capecitabine/RT. If possible, resection should be considered following preoperative chemoRT. Adjuvant therapy to complete 6 months with either 5-FU with or without LV, or FOLFOX or capecitabine with or without oxaliplatin is recommended regardless of the surgical pathology results.

Treatment of Metastatic Disease

Approximately 50%-60% of patients diagnosed with colorectal cancer will develop colorectal metastases.^{147, 148} 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; 80%-90% of these patients are initially evaluated to have unresectable metastatic liver disease.^{147, 149-151} Metastatic disease more frequently develops metachronously following treatment for colorectal cancer, with the liver as a common site of involvement.¹⁵² 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 a 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.¹⁵³ For patients presenting with synchronous metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver.¹⁵⁴

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.¹⁵⁵ 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.¹⁵⁰ Furthermore, rates of 5-year survival for patients with metastatic liver disease not undergoing surgery have been shown to be quite low in a number of studies.^{147, 156} 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.^{147, 157} Recent reports have shown 5-year survival rates following resection of hepatic colorectal metastases exceeding 50%.^{158, 159} 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.¹⁶⁰

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 complete resection of all evident disease, with negative surgical margins, while maintaining adequate liver reserve.¹⁶¹⁻¹⁶³ Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to prolong survival or cure the disease,¹⁶⁴ since incomplete resection or debulking has not been shown to be beneficial.^{148, 161} When patients present with colorectal cancer and synchronous liver metastases, resection of the primary tumor and liver can be done in a simultaneous or staged approach.¹⁶⁵ When the remnant liver is insufficient in size based on cross-sectional imaging volumetrics, preoperative portal vein

embolization of the involved liver can be done to expand the future liver remnant.¹⁶⁶ In other cases, complete resection can be safely achieved using 2-stage liver resection.¹⁶⁷

Resection is the standard of care for the local treatment of metastatic disease that is initially resectable. In other cases, patients with significant response to preoperative chemotherapy can be converted from unresectable to resectable status.¹⁶⁸ However, some patients in this group who cannot undergo resection due to comorbidity, location of the metastatic lesion(s), or an estimate of inadequate liver volume following resection may be candidates for tumor ablation therapy.¹⁶⁹ A number of retrospective studies have compared radiofrequency ablation (RFA) and liver resection in the treatment of liver metastases,¹⁷⁰⁻¹⁷² although RFA has not been well studied in this setting.¹⁷³ Most of these studies have shown RFA to be inferior to resection with respect to rates of local recurrence and 5-year overall survival.¹⁶⁸ It is presently unclear whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are due to patient selection bias, technological limitations of RFA or a combination of these 2 factors.¹⁷⁰ Nevertheless, the panel does not consider ablation to be a substitute for resection in patients with completely resectable disease. In addition, resection or ablation (either alone or in combination with resection) should be reserved for patients with disease that is completely amenable to local therapy. Use of surgery, ablation, or the combination of the two with the goal of less than complete resection/ablation of all known sites of disease is not recommended.

The consensus of the panel is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation

(ie, with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status.

The majority of patients diagnosed with metastatic colorectal disease are initially classified as having unresectable disease. For those with liver-limited unresectable disease, however, preoperative chemotherapy is being increasingly employed to downsize colorectal metastases in some cases in order to convert these lesions to a resectable status (ie, conversion chemotherapy). Preoperative chemotherapy has also been administered to patients with metastatic disease determined to be initially resectable (ie, neoadjuvant therapy). Potential advantages of this approach include: earlier treatment of micrometastatic disease; determination of responsiveness to chemotherapy, which can be prognostic and help plan postoperative therapy; and avoidance of local therapy in those who progress early. Potential disadvantages include: chemotherapy-induced liver injury; missing the “window of opportunity” for resection through the possibility of disease progression; and achievement of a complete response, thereby making it difficult to identify areas for resection.^{150, 174, 175} Furthermore, results from a study of colorectal cancer patients receiving preoperative chemotherapy indicated that viable cancer was 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.^{175, 176} It is therefore essential that during treatment with preoperative 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 preoperative regimen and facilitates an appropriately-timed surgical intervention.¹⁷⁷ When preoperative chemotherapy is planned for patients with initially unresectable disease, the panel recommends that

a surgical re-evaluation should be planned 2 months after initiation of preoperative chemotherapy, and that those patients who continue to receive preoperative chemotherapy undergo surgical re-evaluation every 2 months thereafter.¹⁷⁸⁻¹⁸¹

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,¹⁸² although the ability of these factors to predict outcome following resection may be limited.^{158, 159, 184, 185} However, decision-making relating to whether to offer preoperative chemotherapy begins with an initial evaluation of the degree of resectability of metastatic disease. Chemotherapy is recommended in conjunction with liver resection, particularly in those patients who are chemotherapy naïve. However, the optimal sequencing of chemotherapy remains unclear. Patients with initially resectable disease may undergo liver resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) chemotherapy can be used. This question is the subject of an ongoing NCI-sponsored cooperative trial (NSABP C-11).

In selected patients with initially unresectable disease, preoperative chemotherapy can potentially convert patients to a resectable state. In the study of Pozzo et al, it was reported that preoperative 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.¹⁸⁶ 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)¹⁴⁹, 42 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, 1,104 initially unresectable patients with colorectal liver disease were treated with chemotherapy that included oxaliplatin in the majority of cases. Of these patients, 138 (12.5%) classified as “good responders” underwent secondary hepatic resection following preoperative chemotherapy.¹⁸³ The 5-year survival rate for these 138 patients overall was 33%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%) were able to undergo curative resection (16 were hepatic) following treatment.¹⁸⁷ The median overall survival time in this group was 42.4 months.

The choice of chemotherapy regimen in the preoperative setting is dependent on a number of factors including whether the patient has resectable or potentially convertible metastatic disease, and the response rates and safety/toxicity issues associated with the regimens. Although the benefits of preoperative or postoperative chemotherapy for patients with liver metastases have not yet been fully validated in randomized clinical trials, a recent European Organization for Research and Treatment of Cancer (EORTC) phase III study evaluating use of perioperative FOLFOX4 (6 cycles before and 6 cycles after surgery) for patients with initially resectable liver metastases demonstrated absolute improvements in 3-year progression-free survival of 8.1% ($P=0.041$) and 9.2% ($P=0.025$) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.¹⁸⁸ The partial response rate after preoperative FOLFOX was 40%, and operative mortality was <1% in both treatment groups.

There have been recent favorable reports of randomized clinical trials evaluating preoperative FOLFIRI or FOLFOX as conversion therapies in combination with anti-EGFR inhibitors.^{189, 190} For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.¹⁸⁹ Retrospective analysis showed that, in both treatment arms combined, resectability increased from 32% to 60% following chemotherapy in patients with wild-type KRAS ($P < 0.0001$). In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI in 2 randomized clinical trials.^{191, 192} Significantly improved rates of response and overall survival were reported for patients in the FOLFOXIRI arm in one of the studies,¹⁹¹ but not in the other.¹⁹²

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 in NCCN Colon Cancer Guidelines) has led to its use in combination with these regimens in the preoperative setting, although the safety of administering bevacizumab pre- or postoperatively, in combination with 5-FU-based regimens has not been adequately evaluated. A retrospective evaluation of data from 2 randomized trials of 1,132 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; $P=0.28$).¹⁹³ 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 drug¹⁹⁴) between the last dose of bevacizumab and elective surgery. Further support for this recommendation comes from results of a single center, nonrandomized phase II trial of patients with potentially resectable liver metastases.¹⁹⁵ This study showed no increase in bleeding or wound complications when the bevacizumab component of CapeOX plus bevacizumab therapy was stopped 5 weeks prior to surgery (ie, bevacizumab excluded from the sixth cycle of therapy). In addition, no significant differences in bleeding, wound, or hepatic complications were observed in a retrospective trial evaluating effects of preoperative bevacizumab stopped ≤ 8 weeks vs. > 8 weeks prior to resection of liver colorectal metastases for patients receiving oxaliplatin- or irinotecan-containing regimens.¹⁹⁶

Other reported risks associated with the preoperative chemotherapy approach include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.¹⁷⁷ To limit the development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable.

As mentioned above, colorectal metastatic disease can also occur in the lung.¹⁹⁷ Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases. Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in selected cases.¹⁹⁸

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 similarly staged colon cancer. In particular, initial treatment options for potentially resectable rectal cancer include: preoperative chemoRT directed toward treatment of the primary cancer; preoperative combination chemotherapy regimen plus a biologic agent to target metastatic disease; and a surgical approach (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 preoperative pelvic RT may decrease tolerance to systemic bevacizumab-containing adjuvant regimens, thereby limiting subsequent treatment of systemic disease. However, data to guide decisions regarding optimal treatment approaches in this population of patients are very limited. Of note, patients with stage II/III rectal cancer enrolled in a large randomized trial evaluating the effect of adding chemotherapy to preoperative RT were found to be 2.6-times more likely to develop distant metastases than local recurrence of disease after a median follow-up of over 5 years.¹¹⁵

Based largely on extrapolation from Stage III disease and limited randomized data for Stage IV disease, the panel recommends the use of postoperative adjuvant chemotherapy in patients who have undergone liver or lung resection and are chemo-naïve and who have received preoperative chemoRT. The total chemotherapy duration should be approximately 6 months. Postoperative chemoRT is recommended for patients with synchronous metastases who have not received prior chemoRT and who are at higher risk for pelvic recurrence 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 (ie, HAI) is listed in the guidelines as an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone by HAI and intravenous 5-FU with or without LV was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.^{150, 199} The study was not powered for long-term survival, but there was a trend (not significant) towards better long term outcome in the group receiving HAI at later follow-up periods.^{150, 200} A number of other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy was compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy.¹⁵⁰ Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.¹⁵⁷ However, limitations on the use of HAI therapy include the potential for biliary toxicity,¹⁵⁰ and the requirement for specific technical expertise. The consensus of the panel is that HAI therapy should be considered selectively and only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

Finally, a number of non-extirpative liver-directed therapies are available for the treatment of unresectable metastatic disease in highly selected patients, although their role of such therapies of colorectal metastases is controversial. These therapies include arterial radioembolization with yttrium-90 microspheres,^{201, 202} arterial chemoembolization,²⁰¹ and conformal (stereotactic) radiation therapy.²⁰³ Use of arterial-directed embolic therapy is a category 3 recommendation for select patients with predominant hepatic metastases, and conformal external beam radiation therapy is not recommended for patients with liver or lung metastases unless the

patient is symptomatic or it is used in the setting of a clinical trial, and it should not be used indiscriminately in patients who are potentially resectable. See sections on Recommendations for the Treatment of Synchronous Metastases/Unresectable Disease and Recommendations for the Treatment of Metachronous Metastases.

Recommendations for Treatment of Synchronous Metastases/Resectable Disease

As part of the pre-treatment work-up, the panel recommends tumor KRAS gene status testing for all patients with metastatic colorectal cancer at the time of diagnosis of metastatic disease. If KRAS is found to be wild-type, BRAF testing can be considered (see discussion of KRAS and BRAF testing above).

All patients with stage IV disease (any T, any N, M1) with resectable liver or lung metastases should undergo staged or synchronous resection of metastases and rectal lesion. Surgery can be the initial treatment, or it can be preceded by combination chemotherapy for 2 to 3 months (eg, FOLFOX, CapeOX, or FOLFIRI regimens with or without bevacizumab or FOLFOX, CapeOX, or FOLFIRI with or without cetuximab or panitumumab (for KRAS wild-type tumors only)) with or without subsequent chemoRT. Alternatively, surgery can be preceded by treatment with continuous infusional 5-FU/pelvic RT or bolus 5-FU with LV/pelvic RT or capecitabine/RT. For patients receiving neoadjuvant therapy, surgery should be performed 5 to 10 weeks following completion of such treatment. Upfront systemic treatment has the goal of early eradication of micrometastases, while the goal of consolidating chemoRT is local control of disease prior to surgery.

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 6 months total duration, as described above).^{122, 123} The panel acknowledges 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 recommends that these patients receive an active adjuvant chemotherapy regimen (for 6 months) for advanced disease, with the exception of FOLFOXIRI, which is not recommended in this setting. The adjuvant therapy recommendation for patients who have received neoadjuvant chemoRT is an active chemotherapy regimen for advanced disease (see below; total duration of pre- plus postoperative chemotherapy should be 6 months). In contrast, postoperative chemoRT should be considered for patients who have undergone preoperative combination therapy with pT3-4, Any N, or Any T, N1-2 disease (total duration of preoperative and postoperative chemotherapy should be 6 months). Those patients undergoing preoperative combination therapy followed by preoperative chemoRT should not receive postoperative chemotherapy.

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, combined modality therapy with 5-FU/RT or capecitabine/RT (category 2B), resection of the involved rectal segment, laser canalization, diverting colostomy, or stenting. Primary treatment should be followed by an active chemotherapy regimen for metastatic disease.

For patients with asymptomatic liver or lung disease that is deemed to be unresectable, the panel recommends chemotherapy corresponding to initial therapy for metastatic disease to attempt to render these patients candidates for resection. Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease,²⁰⁴ and these patients should be re-evaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing such therapy.

Primary treatment of unresectable synchronous liver or lung metastases by palliative surgery to remove the primary tumor should be considered only if the patient has an unequivocal imminent risk of obstruction or acute significant bleeding. It should be noted that symptomatic improvement in the primary is often seen with first-line systemic chemotherapy, even within the first 1 to 2 weeks, and routine palliative resection of a synchronous primary lesion should not be done in the absence of overt, serious symptoms.¹⁵⁴ Complications from the primary lesion are uncommon in these circumstances, and its removal delays initiation of systemic chemotherapy. An intact primary is not a contraindication to bevacizumab use. The risk of gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, as large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare (see section on Chemotherapy for Advanced or Metastatic Disease in the NCCN Colon Cancer Guidelines).

Ablative therapy of metastatic disease, either alone or in combination with resection, can also be considered when all measurable metastatic disease can be treated (see Principles of Surgery).¹⁶⁹ Post-treatment follow-up for patients classified as stage IV and no evidence of disease (NED) is described in the section on Post-Treatment Surveillance.



Patients with unresectable metastatic disease not converting to resectability after therapy should receive chemotherapy for advanced or metastatic disease with treatment selection based, in part, on whether the patient is or is not an appropriate candidate for intensive therapy.

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

Recommendations for Treatment of Metachronous Metastases

Routine use of PET to monitor for disease recurrence is not recommended. It should be noted that the CT that accompanies a “PET/CT” is usually a non-contrast CT, and thus not of ideal quality for routine surveillance. Upon documentation of metachronous potentially resectable metastatic disease by dedicated contrast-enhanced CT or MRI, characterization of the extent of disease by PET scan should be considered. 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.^{205, 206} Specifically, Joyce et al reported that preoperative PET changed or precluded curative-intent liver resection in 25% of patients.²⁰⁵

As with other conditions in which Stage IV disease is diagnosed, a tumor analysis (metastases or original primary) for KRAS genotyping in order to define whether anti-EGFR agents can be considered in the list of potential options for this patient (see discussion of KRAS testing,

above). Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases.

The management of metachronous metastatic disease is further distinguished from that of synchronous disease by also including an evaluation of the chemotherapy history of the patient, and by the absence of transabdominal resection as a treatment option. 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 initial resection followed by chemotherapy with an active chemotherapy regimen for 6 months or neoadjuvant chemotherapy for 2 to 3 months followed by resection. These latter patients are given FOLFOX or they repeat their neoadjuvant therapy if a response to the neoadjuvant regimen is observed; observation or an active chemotherapy regimen is recommended for patients without a response to neoadjuvant therapy. For patients with a history of previous chemotherapy, the treatment options are the same, with the exception that observation can replace the postoperative active chemotherapy regimen.

Patients determined by cross-sectional imaging or PET scan to have unresectable (including those considered potentially convertible or unconvertible) disease should receive an active 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 or cetuximab/panitumumab (KRAS wild type only). Patients progressing on FOLFOX administered more than 12

months previously or on 5-FU/LV or capecitabine or with no previous chemotherapy should undergo an active chemotherapy regimen. There are insufficient data to support continuation of bevacizumab with a second-line regimen after progression on a bevacizumab-containing first-line regimen, and such continuation beyond progression is not recommended. Patients potentially convertible to resectability should be re-evaluated for disease conversion to a resectable status every 2 months; those with chemotherapy-responsive disease who are converted to a resectable state should undergo resection followed by observation or postoperative therapy for a total of 6 months of perioperative therapy. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) remains at option at centers with experience with the surgical and medical oncologic aspects of this procedure.

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

Potentially resectable isolated pelvic/anastomotic recurrence is optimally managed by preoperative RT and concurrent infusional 5-FU, if full course RT was not given previously. Resection followed by the option of IORT should be considered if it can be safely delivered.²⁰⁷ However, debulking that results in gross residual cancer is not recommended. Patients who were previously treated with chemoRT can undergo resection followed by additional chemoRT. Patients with unresectable lesions are treated with chemotherapy with or without

radiation according to their ability to tolerate therapy. The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative. The panel currently considers the treatment of disseminated carcinomatosis with cytoreductive surgery (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy^{208, 209} to be investigational and does not endorse such therapy outside of a clinical trial. However, the panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

Patients presenting with serial elevation in CEA levels should have a complete physical exam, colonoscopy, chest/abdominal/pelvic CT scan, and possibly a PET-CT scan. In the case of negative findings, the patient should be re-evaluated in 3 months and every 3 months thereafter by CT and possibly PET-CT. Patients with positive findings should be treated as described above for pelvic/anastomotic recurrence or metachronous metastases as appropriate.

Treatment of Locally Recurrent Disease

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease. In a single-center study, Yu et al reported low rates of 5-year local recurrence (ie, 5-year locoregional control rate of 91%) for patients with rectal cancer treated with surgery and either RT or chemoRT, and 49% of recurrences occurred in the low pelvic and presacral regions with an additional 14% occurring in the mid and high pelvis.²¹⁰ Patients with disease recurrence at the anastomotic site are more likely than those with an isolated pelvic recurrence to be cured following re-resection.^{211, 212} 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.²¹²

**Chemotherapy for Advanced or Metastatic Disease**

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

Post-Treatment Surveillance

The approach to monitoring and surveillance of patients with rectal cancer is similar to that described for colon cancer with the addition of proctoscopy to evaluate the rectal anastomosis for local recurrence for patients who have undergone an LAR. Anastomotic recurrence of rectal cancer has a much more favorable prognosis than local recurrence at other locations in the pelvis,^{211, 212} although the optimal timing for surveillance of the rectal anastomosis is not known. Furthermore, no specific data clearly support the use of rigid versus flexible proctoscopy, and the utility of endoscopic ultrasound for early surveillance is not defined. 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, and to identify new metachronous neoplasms at a preinvasive stage. Advantages of more intensive follow-up of stage II and/or stage III patients have been demonstrated prospectively in several studies²¹³⁻²¹⁵ and in 3 recent meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.²¹⁶⁻²¹⁸ 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.²¹⁹ The meta-analysis demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor. Further, 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.²²⁰ Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.^{221, 222}

The following panel recommendations for post-treatment surveillance pertain to patients with stage I-stage III disease who have undergone successful treatment (ie, no known residual disease): history and physical examination every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years; and a CEA test at baseline and every 3 to 6 months for 2 years, then every 6 months for the next 5 years if the patient is a potential candidate for resection of isolated metastases.^{216, 223, 224} Colonoscopy is recommended at approximately 1 year following resection (or at approximately 3 to 6 months post-resection if not performed preoperatively due to an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia), in which case colonoscopy should be repeated in 1 year.²²⁵ More frequent colonoscopies may be indicated in patients who present with colorectal cancer before age 50.²²⁵ Proctoscopy should be considered every 6 months for 5 years to evaluate for local recurrence at the rectal anastomosis for patients who have undergone an LAR, as discussed above. Chest, abdominal and pelvic CT scans are recommended annually for the first 3 years in stage II and III patients (ie, patients considered at high risk of recurrence, for example those with lymphatic or venous invasion by the tumor or with poorly differentiated tumors).^{216, 222} PET-CT scanning is not routinely recommended and should

generally not be obtained either as a routine pre-operative baseline study or for routine surveillance.

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 (ie, can be seen once every 6 months). This principle also applies to CEA testing,²²⁶ 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.²²³ 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,²²⁷ 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.²²⁵ 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. Post-treatment PET-CT scan is not routinely recommended for surveillance of patients with resected early-stage colorectal cancer to detect recurrence of the original cancer.^{216, 222} Furthermore, PET-CT scan is not routinely recommended to detect metastatic disease in the absence of other evidence of such disease.²²²

Post-treatment surveillance also includes a survivorship care plan involving disease preventive measures such as immunizations against influenza and pneumococcal infections at prescribed intervals and regular dental care, and early disease detection through periodic

screening for second primary cancers (eg, breast, cervical, or prostate cancers) and routine health monitoring to screen for comorbid conditions including psychosocial distress associated with rectal cancer and its treatment.

Other recommendations include monitoring for late sequelae of rectal cancer or of the treatment of rectal cancer,²²⁸ such as: chronic diarrhea or incontinence (eg, patients with stoma)²²⁹⁻²³²; persistent neuropathy - a well known side effect of oxaliplatin treatment¹²⁴; pelvic pain/pelvic fractures; and urogenital dysfunction following resection or pelvic irradiation.^{229, 233-235} Specific management interventions to address these side effects are described in a recent review.²³⁶

There is also evidence to indicate that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy body mass index (BMI), engaging in regular exercise, and making certain dietary choices are associated with improved outcomes following treatment for colon cancer. For example, a retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI ≥ 35 kg/m² had an increased risk of disease recurrence and death.²³⁷ In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, disease-free survival was found to be directly dependent on how much exercise these patients received.²³⁸ Furthermore, a diet consisting of more fruits, vegetables, poultry and fish, and less red meat, as well as diets higher in whole grains and lower in refined grains and concentrated sweets was found to be associated with an improved outcome in terms of cancer recurrence or death.²³⁹ A discussion of lifestyle characteristics that may be associated with a decreased risk of colorectal cancer recurrence also provides “a teachable moment” for the promotion of overall health, and an



opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle.

Managing an Increasing Carcinoembryonic Antigen Level

Management of 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, a PET scan should be performed with repeat CT scans recommended every 3 months or until either disease is identified or CEA stabilizes or declines. The opinion of the panel on the usefulness of PET scan in the scenario of an elevated CEA with negative, good-quality CT scans was divided (ie, some panel members favored use of PET in this scenario while others noted that the likelihood of PET identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). Use of PET scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called "blind" or "CEA-directed" laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,²⁴⁰ nor is the use of anti-CEA-radiolabeled scintigraphy.

Summary

The NCCN Rectal Cancer Guidelines panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology is necessary for treating patients with rectal cancer. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes when possible. Patients with very early stage tumors that are node-negative by endorectal ultrasound or endorectal or pelvic MRI and who meet carefully defined criteria can be managed with a transanal excision. A transabdominal resection is appropriate for all other rectal lesions.

Preoperative chemoRT is preferred for the majority of patients with suspected or proven T3/T4 disease and/or regional node involvement and adjuvant chemotherapy is recommended. Patients with recurrent localized disease should be considered for resection with or without radiotherapy.

A patient with metastatic disease in the liver or lung should be considered for surgical resection if he or she is a candidate for surgery and if complete resection (R0) or ablation can be achieved. Preoperative chemotherapy can be considered as initial therapy in patients with synchronous or metachronous resectable metastatic disease (ie, neoadjuvant therapy) or when a response to chemotherapy may convert a patient from an unresectable to a resectable state (ie, conversion therapy). Other options for patients with resectable synchronous metastases are initial treatment with chemoRT or chemotherapy with or without bevacizumab or cetuximab/panitumumab (KRAS wild type tumor only) followed by consolidating chemoRT. Resection should be followed by adjuvant therapy based on prior therapy received.

The recommended post-treatment surveillance program for rectal cancer patients includes serial CEA determinations, as well as periodic chest, abdominal, and pelvic CT scans, and periodic evaluations by colonoscopy and proctoscopy. Recommendations for patients with previously untreated disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression and plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or metastatic disease depend on whether or not the patient is appropriate for intensive therapy. The more intensive



initial therapy options include FOLFOX, FOLFIRI, CapeOX, and FOLFOXIRI (category 2B). Addition of a biologic agent (eg, bevacizumab, cetuximab, or panitumumab) is either recommended or listed as an option in combination with some of these regimens, depending on available data. Chemotherapy options for patients with progressive disease are dependent on the choice of initial therapy. The panel endorses the concept that treating patients in a clinical trial has priority over standard treatment regimens.

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Discussion
update in
progress

References

- Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277-300. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20610543>.
- Ahsan H, Neugut AI, Garbowski GC, et al. Family history of colorectal adenomatous polyps and increased risk for colorectal cancer. *Ann Intern Med* 1998;128:900-905. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9634428>.
- Bonelli L, Martines H, Conio M, et al. Family history of colorectal cancer as a risk factor for benign and malignant tumours of the large bowel. A case-control study. *Int J Cancer* 1988;41:513-517. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3356486>.
- Edge SBB, D.R.; Compton, C.C.; Fritz, A.G.; Greene, F.L.; Trotti, A., ed *AJCC Cancer Staging Manual* (ed 7th Edition). New York: Springer; 2010.
- Altekruse SF, Kosary CL, Krapcho M, et al. *SEER Cancer Statistics Review, 1975-2007*. National Cancer Institute, Bethesda, MD 2010. Available at: http://seer.cancer.gov/csr/1975_2007/.
- Gunderson LL, Jessup JM, Sargent DJ, et al. Revised tumor and node categorization for rectal cancer based on surveillance, epidemiology, and end results and rectal pooled analysis outcomes. *J Clin Oncol* 2010;28:256-263. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19949015>.
- Nagtegaal ID, Quirke P. Colorectal tumour deposits in the mesorectum and pericolon; a critical review. *Histopathology* 2007;51:141-149. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17532768>.
- Puppa G, Maisonneuve P, Sonzogni A, et al. Pathological assessment of pericolonic tumor deposits in advanced colonic carcinoma: relevance to prognosis and tumor staging. *Mod Pathol* 2007;20:843-855. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17491597>.
- Ueno H, Mochizuki H, Hashiguchi Y, et al. Extramural cancer deposits without nodal structure in colorectal cancer: optimal categorization for prognostic staging. *Am J Clin Pathol* 2007;127:287-294. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17210518>.
- Washington MK, Berlin J, Branton P, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. *Arch Pathol Lab Med* 2009;133:1539-1551. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19792043>.
- Compton CC, Fielding LP, Burgart LJ, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 2000;124:979-994. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10888773>.
- Compton CC, Greene FL. The staging of colorectal cancer: 2004 and beyond. *CA Cancer J Clin* 2004;54:295-308. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15537574>.
- Nagtegaal ID, Marijnen CA, Kranenbarg EK, et al. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol* 2002;26:350-357. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11859207>.
- Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 2008;26:303-312. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18182672>.
- Wibe A, Rendedal PR, Svensson E, et al. Prognostic significance of the circumferential resection margin following total mesorectal excision for rectal cancer. *Br J Surg* 2002;89:327-334. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11872058>.



16. Gavioli M, Luppi G, Losi L, et al. Incidence and clinical impact of sterilized disease and minimal residual disease after preoperative radiochemotherapy for rectal cancer. *Dis Colon Rectum* 2005;48:1851-1857. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16132481>.

17. Rodel C, Martus P, Papadopoulos T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. *J Clin Oncol* 2005;23:8688-8696. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16246976>.

18. Nissan A, Stojadinovic A, Shia J, et al. Predictors of recurrence in patients with T2 and early T3, N0 adenocarcinoma of the rectum treated by surgery alone. *J Clin Oncol* 2006;24:4078-4084. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16943525>.

19. Fujita S, Shimoda T, Yoshimura K, et al. Prospective evaluation of prognostic factors in patients with colorectal cancer undergoing curative resection. *J Surg Oncol* 2003;84:127-131. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14598355>.

20. Liebig C, Ayala G, Wilks J, et al. Perineural invasion is an independent predictor of outcome in colorectal cancer. *J Clin Oncol* 2009;27:5131-5137. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19738119>.

21. Quah HM, Chou JF, Gonen M, et al. Identification of patients with high-risk stage II colon cancer for adjuvant therapy. *Dis Colon Rectum* 2008;51:503-507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18322753>.

22. Lo DS, Pollett A, Siu LL, et al. Prognostic significance of mesenteric tumor nodules in patients with stage III colorectal cancer. *Cancer* 2008;112:50-54. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18008365>.

23. Compton CC. Key issues in reporting common cancer specimens: problems in pathologic staging of colon cancer. *Arch Pathol Lab Med*

2006;130:318-324. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16519558>.

24. Lai LL, Fuller CD, Kachnic LA, Thomas CR, Jr. Can pelvic radiotherapy be omitted in select patients with rectal cancer? *Semin Oncol* 2006;33:S70-74. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17178292>.

25. Glynne-Jones R, Mawdsley S, Novell JR. The clinical significance of the circumferential resection margin following preoperative pelvic chemo-radiotherapy in rectal cancer: why we need a common language. *Colorectal Dis* 2006;8:800-807. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17032329>.

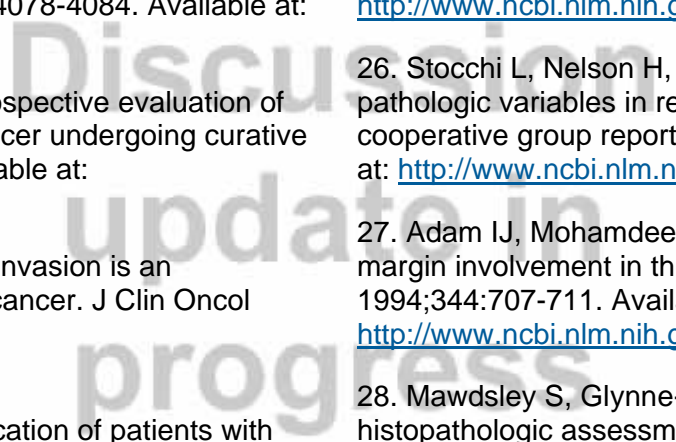
26. Stocchi L, Nelson H, Sargent DJ, et al. Impact of surgical and pathologic variables in rectal cancer: a United States community and cooperative group report. *J Clin Oncol* 2001;19:3895-3902. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11559727>.

27. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet* 1994;344:707-711. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7915774>.

28. Mawdsley S, Glynne-Jones R, Grainger J, et al. Can histopathologic assessment of circumferential margin after preoperative pelvic chemoradiotherapy for T3-T4 rectal cancer predict for 3-year disease-free survival? *Int J Radiat Oncol Biol Phys* 2005;63:745-752. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16199310>.

29. Sarli L, Bader G, Iusco D, et al. Number of lymph nodes examined and prognosis of TNM stage II colorectal cancer. *Eur J Cancer* 2005;41:272-279. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15661553>.

30. Wong SL, Ji H, Hollenbeck BK, et al. Hospital lymph node examination rates and survival after resection for colon cancer. *JAMA*





2007;298:2149-2154. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18000198>.

31. Pocard M, Panis Y, Malassagne B, et al. Assessing the effectiveness of mesorectal excision in rectal cancer: prognostic value of the number of lymph nodes found in resected specimens. *Dis Colon Rectum* 1998;41:839-845. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9678368>.

32. Tepper JE, O'Connell MJ, Niedzwiecki D, et al. Impact of number of nodes retrieved on outcome in patients with rectal cancer. *J Clin Oncol* 2001;19:157-163. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11134208>.

33. Baxter NN, Morris AM, Rothenberger DA, Tepper JE. Impact of preoperative radiation for rectal cancer on subsequent lymph node evaluation: a population-based analysis. *Int J Radiat Oncol Biol Phys* 2005;61:426-431. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15667963>.

34. Wichmann MW, Muller C, Meyer G, et al. Effect of preoperative radiochemotherapy on lymph node retrieval after resection of rectal cancer. *Arch Surg* 2002;137:206-210. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11822961>.

35. Turner RR, Nora DT, Trocha SD, Bilchik AJ. Colorectal carcinoma nodal staging. Frequency and nature of cytokeratin-positive cells in sentinel and nonsentinel lymph nodes. *Arch Pathol Lab Med* 2003;127:673-679. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12741889>.

36. Wood TF, Nora DT, Morton DL, et al. One hundred consecutive cases of sentinel lymph node mapping in early colorectal carcinoma: detection of missed micrometastases. *J Gastrointest Surg* 2002;6:322-329; discussion 229-330. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12022982>.

37. Yasuda K, Adachi Y, Shiraishi N, et al. Pattern of lymph node micrometastasis and prognosis of patients with colorectal cancer. *Ann Surg Oncol* 2001;8:300-304. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11352302>.

38. Braat AE, Oosterhuis JW, Moll FC, et al. Sentinel node detection after preoperative short-course radiotherapy in rectal carcinoma is not reliable. *Br J Surg* 2005;92:1533-1538. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16231281>.

39. Wiese D, Sirop S, Yestrepsky B, et al. Ultrastaging of sentinel lymph nodes (SLNs) vs. non-SLNs in colorectal cancer--do we need both? *Am J Surg* 2010;199:354-358; discussion 358. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20226909>.

40. Noura S, Yamamoto H, Miyake Y, et al. Immunohistochemical assessment of localization and frequency of micrometastases in lymph nodes of colorectal cancer. *Clin Cancer Res* 2002;8:759-767. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11895906>.

41. Ueno H, Mochizuki H. Clinical significance of extrabowel skipped cancer infiltration in rectal cancer. *Surg Today* 1997;27:617-622. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9306563>.

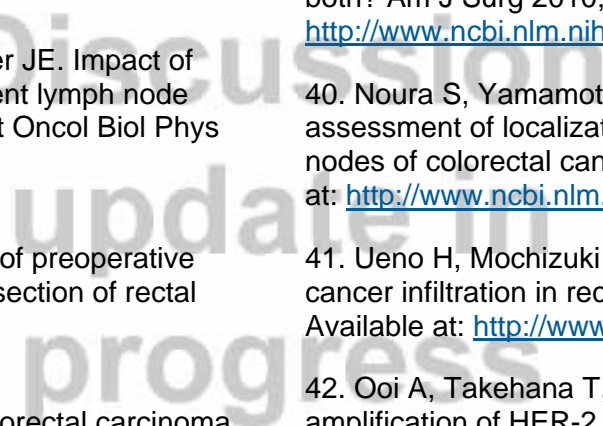
42. Ooi A, Takehana T, Li X, et al. Protein overexpression and gene amplification of HER-2 and EGFR in colorectal cancers: an immunohistochemical and fluorescent in situ hybridization study. *Mod Pathol* 2004;17:895-904. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15143334>.

43. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337-345. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15269313>.

44. Saltz LB, Meropol NJ, Loehrer PJ, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the



epidermal growth factor receptor. *J Clin Oncol* 2004;22:1201-1208. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14993230>.

45. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007;25:1658-1664. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17470858>.

46. Amado RG, Wolf M, Peeters M, et al. Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626-1634. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18316791>.

47. Baselga J, Rosen N. Determinants of RASistance to anti-epidermal growth factor receptor agents. *J Clin Oncol* 2008;26:1582-1584. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18316790>.

48. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. *J Clin Oncol* 2009;27:663-671. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19114683>.

49. De Roock W, Piessevaux H, De Schutter J, et al. KRAS wild-type state predicts survival and is associated to early radiological response in metastatic colorectal cancer treated with cetuximab. *Ann Oncol* 2008;19:508-515. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17998284>.

50. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 2008;359:1757-1765. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18946061>.

51. Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab.

J Clin Oncol 2007;25:3230-3237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17664471>.

52. Lievre A, Bachet J-B, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol* 2008;26:374-379. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18202412>.

53. Tejpar S, Peeters M, Humblet Y, et al. Relationship of efficacy with KRAS status (wild type versus mutant) in patients with irinotecan-refractory metastatic colorectal cancer (mCRC), treated with irinotecan (q2w) and escalating doses of cetuximab (q1w): The EVEREST experience (preliminary data) [abstract]. *J Clin Oncol* 2008;26 (May 20 suppl):4001. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/4001.

54. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;360:1408-1417. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19339720>.

55. Artale S, Sartore-Bianchi A, Veronese SM, et al. Mutations of KRAS and BRAF in primary and matched metastatic sites of colorectal cancer. *J Clin Oncol* 2008;26:4217-4219. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18757341>.

56. Etienne-Grimaldi M-C, Formento J-L, Francoual M, et al. K-Ras mutations and treatment outcome in colorectal cancer patients receiving exclusive fluoropyrimidine therapy. *Clin Cancer Res* 2008;14:4830-4835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18676755>.

57. Saridaki Z, Papadatos-Pastos D, Tzardi M, et al. BRAF mutations, microsatellite instability status and cyclin D1 expression predict metastatic colorectal patients' outcome. *Br J Cancer* 2010;102:1762-1768. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20485284>.

58. Samowitz WS, Sweeney C, Herrick J, et al. Poor survival associated with the BRAF V600E mutation in microsatellite-stable colon cancers. *Cancer Res* 2005;65:6063-6069. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16024606>.
59. Bokemeyer C, Kohne C, Rougier P, et al. Cetuximab with chemotherapy (CT) as first-line treatment for metastatic colorectal cancer (mCRC): Analysis of the CRYSTAL and OPUS studies according to KRAS and BRAF mutation status [abstract]. *J Clin Oncol* 2010;28 (May 20 suppl):3506. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/3506.
60. Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 2008;26:5705-5712. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19001320>.
61. Cooper HS, Deppisch LM, Gourley WK, et al. Endoscopically removed malignant colorectal polyps: clinicopathologic correlations. *Gastroenterology* 1995;108:1657-1665. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7768369>.
62. Hamilton SR, Bosman FT, Boffetta P, et al. Carcinoma of the colon and rectum. In: Bosman FT, Carneiro F, Hruban RH, Theise ND, eds. *WHO Classification of Tumours of the Digestive System*. Lyon: IARC; 2010.
63. Nivatvongs S, Rojanasakul A, Reiman HM, et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. *Dis Colon Rectum* 1991;34:323-328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1848810>.
64. Seitz U, Bohnacker S, Seewald S, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal adenomas? Presentation of 114 patients and review of the literature. *Dis Colon Rectum* 2004;47:1789-1796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15622570>.
65. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterology* 2004;127:385-394. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15300569>.
66. Volk EE, Goldblum JR, Petras RE, et al. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. *Gastroenterology* 1995;109:1801-1807. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7498644>.
67. Garcia-Aguilar J, Hernandez de Anda E, Rothenberger DA, et al. Endorectal ultrasound in the management of patients with malignant rectal polyps. *Dis Colon Rectum* 2005;48:910-916; discussion 916-917. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15868240>.
68. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *CA Cancer J Clin* 2006;56:143-159; quiz 184-145. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16737947>.
69. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst* 2001;93:583-596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11309435>.
70. Kapiteijn E, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001;345:638-646. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11547717>.
71. Schoellhammer HF, Gregorian AC, Sarkisyan GG, Petrie BA. How important is rigid proctosigmoidoscopy in localizing rectal cancer? *Am J Surg* 2008;196:904-908; discussion 908. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19095107>.
72. Baxter NN, Garcia-Aguilar J. Organ preservation for rectal cancer. *J Clin Oncol* 2007;25:1014-1020. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17350952>.



73. Rajput A, Bullard Dunn K. Surgical management of rectal cancer. *Semin Oncol* 2007;34:241-249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17560986>.

74. Weiser MR, Landmann RG, Wong WD, et al. Surgical salvage of recurrent rectal cancer after transanal excision. *Dis Colon Rectum* 2005;48:1169-1175. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15793645>.

75. Wiig JN, Larsen SG, Giercksky KE. Operative treatment of locally recurrent rectal cancer. *Recent Results Cancer Res* 2005;165:136-147. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15865028>.

76. Bartram C, Brown G. Endorectal ultrasound and magnetic resonance imaging in rectal cancer staging. *Gastroenterol Clin North Am* 2002;31:827-839. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12481733>.

77. Bipat S, Glas AS, Slors FJM, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. *Radiology* 2004;232:773-783. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15273331>.

78. Klessen C, Rogalla P, Taupitz M. Local staging of rectal cancer: the current role of MRI. *Eur Radiol* 2007;17:379-389. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17008990>.

79. Lahaye MJ, Engelen SM, Nelemans PJ, et al. Imaging for predicting the risk factors--the circumferential resection margin and nodal disease--of local recurrence in rectal cancer: a meta-analysis. *Semin Ultrasound CT MR* 2005;26:259-268. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16152740>.

80. Beets-Tan RG, Beets GL. Rectal cancer: review with emphasis on MR imaging. *Radiology* 2004;232:335-346. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15286305>.

81. Guillem JG, Cohen AM. Current issues in colorectal cancer surgery. *Semin Oncol* 1999;26:505-513. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10528898>.

82. Lindsetmo RO, Joh YG, Delaney CP. Surgical treatment for rectal cancer: an international perspective on what the medical gastroenterologist needs to know. *World J Gastroenterol* 2008;14:3281-3289. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18528924>.

83. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. *Ann Surg* 2007;245:726-733. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17457165>.

84. Landmann RG, Wong WD, Hoepfl J, et al. Limitations of early rectal cancer nodal staging may explain failure after local excision. *Dis Colon Rectum* 2007;50:1520-1525. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17674104>.

85. Nash GM, Weiser MR, Guillem JG, et al. Long-term survival after transanal excision of T1 rectal cancer. *Dis Colon Rectum* 2009;52:577-582. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19404055>.

86. Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. *J Clin Oncol* 2007;25:3061-3068. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17634484>.

87. Ng SSM, Leung KL, Lee JFY, et al. Laparoscopic-assisted versus open abdominoperineal resection for low rectal cancer: a prospective randomized trial. *Ann Surg Oncol* 2008;15:2418-2425. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18392659>.

88. Wagman LD. Laparoscopic and open surgery for colorectal cancer: reaching equipoise? *J Clin Oncol* 2007;25:2996-2998. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17634477>.



89. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery--the clue to pelvic recurrence? *Br J Surg* 1982;69:613-616. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/6751457>.
90. Nagtegaal ID, van de Velde CJ, van der Worp E, et al. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. *J Clin Oncol* 2002;20:1729-1734. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11919228>.
91. Parfitt JR, Driman DK. The total mesorectal excision specimen for rectal cancer: a review of its pathological assessment. *J Clin Pathol* 2007;60:849-855. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17046842>.
92. Marr R, Birbeck K, Garvican J, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. *Ann Surg* 2005;242:74-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15973104>.
93. den Dulk M, Putter H, Collette L, et al. The abdominoperineal resection itself is associated with an adverse outcome: the European experience based on a pooled analysis of five European randomised clinical trials on rectal cancer. *Eur J Cancer* 2009;45:1175-1183. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19128956>.
94. Pahlman L, Bohe M, Cedermark B, et al. The Swedish rectal cancer registry. *Br J Surg* 2007;94:1285-1292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17661309>.
95. Steup WH, Moriya Y, van de Velde CJH. Patterns of lymphatic spread in rectal cancer. A topographical analysis on lymph node metastases. *Eur J Cancer* 2002;38:911-918. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11978516>.
96. Schlag PM. Surgical Sphincter Preservation in Rectal Cancer. *Oncologist* 1996;1:288-292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10388006>.
97. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. QUASAR Collaborative Group. *Lancet* 2000;355:1588-1596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10821362>.
98. Jager E, Heike M, Bernhard H, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. Study Group for Palliative Treatment of Metastatic Colorectal Cancer Study Protocol 1. *J Clin Oncol* 1996;14:2274-2279. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8708717>.
99. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group study. *Cancer* 1989;63:1026-1030. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2465076>.
100. Kachnic LA. Should preoperative or postoperative therapy be administered in the management of rectal cancer? *Semin Oncol* 2006;33:S64-69. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17178291>.
101. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;351:1731-1740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15496622>.
102. Wagman R, Minsky BD, Cohen AM, et al. Sphincter preservation in rectal cancer with preoperative radiation therapy and coloanal anastomosis: long term follow-up. *Int J Radiat Oncol Biol Phys* 1998;42:51-57. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9747819>.
103. Madoff RD. Chemoradiotherapy for rectal cancer--when, why, and how? *N Engl J Med* 2004;351:1790-1792. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15496630>.



104. Guillem JG, Diaz-Gonzalez JA, Minsky BD, et al. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. *J Clin Oncol* 2008;26:368-373. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18202411>.

105. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997;336:980-987. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9091798>.

106. Birgisson H, Pahlman L, Gunnarsson U, Glimelius B. Adverse effects of preoperative radiation therapy for rectal cancer: long-term follow-up of the Swedish Rectal Cancer Trial. *J Clin Oncol* 2005;23:8697-8705. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16314629>.

107. Peeters KCMJ, Marijnen CAM, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007;246:693-701. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17968156>.

108. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;93:1215-1223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16983741>.

109. Siegel R, Burock S, Wernecke KD, et al. Preoperative short-course radiotherapy versus combined radiochemotherapy in locally advanced rectal cancer: a multi-centre prospectively randomised study of the Berlin Cancer Society. *BMC Cancer* 2009;9:50. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19200365>.

110. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a

multicentre, randomised trial. *Lancet* 2009;373:811-820. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19269519>.

111. Stephens RJ, Thompson LC, Quirke P, et al. Impact of short-course preoperative radiotherapy for rectal cancer on patients' quality of life: data from the Medical Research Council CR07/National Cancer Institute of Canada Clinical Trials Group C016 randomized clinical trial. *J Clin Oncol* 2010;28:4233-4239. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20585099>.

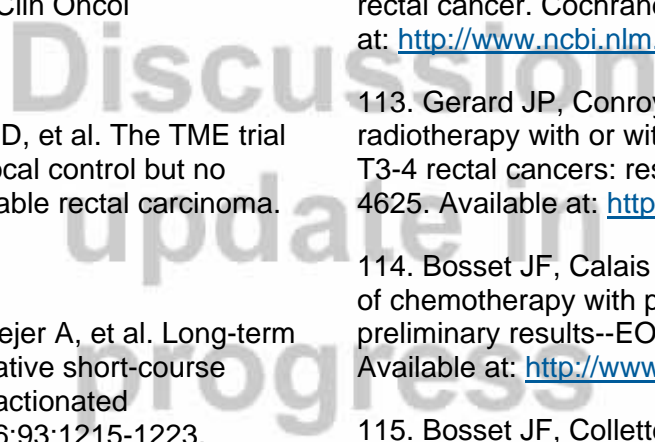
112. Ceelen WP, Van Nieuwenhove Y, Fierens K. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. *Cochrane Database Syst Rev* 2009;CD006041. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19160264>.

113. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. *J Clin Oncol* 2006;24:4620-4625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17008704>.

114. Bosset JF, Calais G, Mineur L, et al. Enhanced tumoricidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results--EORTC 22921. *J Clin Oncol* 2005;23:5620-5627. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16009958>.

115. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006;355:1114-1123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16971718>.

116. Collette L, Bosset J-F, den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Radiation Oncology Group. *J Clin Oncol* 2007;25:4379-4386. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17906203>.





117. Bujko K, Kepka L, Michalski W, Nowacki MP. Does rectal cancer shrinkage induced by preoperative radio(chemo)therapy increase the likelihood of anterior resection? A systematic review of randomised trials. *Radiother Oncol* 2006;80:4-12. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16730086>.

118. Wong RK, Tandan V, De Silva S, Figueredo A. Pre-operative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane Database Syst Rev* 2007:CD002102. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17443515>.

119. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. *J Clin Oncol* 2005;23:6199-6206. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16135487>.

120. Gunderson LL, Sargent DJ, Tepper JE, et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. *J Clin Oncol* 2004;22:1785-1796. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15067027>.

121. Tepper JE, O'Connell M, Niedzwiecki D, et al. Adjuvant therapy in rectal cancer: analysis of stage, sex, and local control--final report of intergroup 0114. *J Clin Oncol* 2002;20:1744-1750. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11919230>.

122. Smalley SR, Benedetti JK, Williamson SK, et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. *J Clin Oncol* 2006;24:3542-3547. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16877719>.

123. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med*

1994;331:502-507. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8041415>.

124. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;27:3109-3116. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19451431>.

125. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. *N Engl J Med* 2005;352:2696-2704. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15987918>.

126. Hahnloser D, Haddock MG, Nelson H. Intraoperative radiotherapy in the multimodality approach to colorectal cancer. *Surg Oncol Clin N Am* 2003;12:993-1013, ix. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14989129>.

127. Valentini V, Balducci M, Tortoreto F, et al. Intraoperative radiotherapy: current thinking. *Eur J Surg Oncol* 2002;28:180-185. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11884054>.

128. Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. *J Clin Oncol* 2007;25:971-977. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17350946>.

129. ACR-ASTRO Practice Guideline for Intensity-Modulated Radiation Therapy (IMRT). The American College of Radiology; 2007. Available at: http://www.acr.org/SecondaryMainMenuCategories/quality_safety/guidelines/ro/imrt.aspx. Accessed 2010.

130. Hong TS, Ritter MA, Tome WA, Harari PM. Intensity-modulated radiation therapy: emerging cancer treatment technology. *Br J Cancer* 2005;92:1819-1824. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15856036>.

131. Meyer J, Czito B, Yin F-F, Willett C. Advanced radiation therapy technologies in the treatment of rectal and anal cancer: intensity-

modulated photon therapy and proton therapy. Clin Colorectal Cancer 2007;6:348-356. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17311699>.

132. Habr-Gama A, Perez RO, Proscurshim I, et al. Interval between surgery and neoadjuvant chemoradiation therapy for distal rectal cancer: does delayed surgery have an impact on outcome? Int J Radiat Oncol Biol Phys 2008;71:1181-1188. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18234443>.

133. Moore HG, Gittleman AE, Minsky BD, et al. Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. Dis Colon Rectum 2004;47:279-286. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14991488>.

134. Tulchinsky H, Shmueli E, Figer A, et al. An interval >7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. Ann Surg Oncol 2008;15:2661-2667. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18389322>.

135. Tran C-L, Udani S, Holt A, et al. Evaluation of safety of increased time interval between chemoradiation and resection for rectal cancer. Am J Surg 2006;192:873-877. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17161111>.

136. Wolmark N, Wieand HS, Hyams DM, et al. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. J Natl Cancer Inst 2000;92:388-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10699069>.

137. Benson AB, Catalan P, Meropol NJ, et al. ECOG E3201: Intergroup randomized phase III study of postoperative irinotecan, 5-fluorouracil (FU), leucovorin (LV) (FOLFIRI) vs oxaliplatin, FU/LV (FOLFOX) vs FU/LV for patients (pts) with stage II/ III rectal cancer receiving either pre or postoperative radiation (RT)/ FU [abstract]. J Clin

Oncol 2006;24 (June 20 suppl):3526. Available at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/3526.

138. Fakhri M. Treating rectal cancer: key issues reconsidered. Oncology (Williston Park) 2008;22:1444-1446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19322952>.

139. Minsky BD, Guillem JG. Multidisciplinary management of resectable rectal cancer. New developments and controversies. Oncology (Williston Park) 2008;22:1430-1437. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19086601>.

140. Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350:2343-2351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15175436>.

141. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol 2007;25:2198-2204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17470851>.

142. Benson AB, 3rd. New approaches to assessing and treating early-stage colon and rectal cancers: cooperative group strategies for assessing optimal approaches in early-stage disease. Clin Cancer Res 2007;13:6913s-6920s. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18006800>.

143. Garcia-Aguilar J, Mellgren A, Sirivongs P, et al. Local excision of rectal cancer without adjuvant therapy: a word of caution. Ann Surg 2000;231:345-351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10714627>.

144. Sengupta S, Tjandra JJ. Local excision of rectal cancer: what is the evidence? Dis Colon Rectum 2001;44:1345-1361. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11584215>.

145. Willett CG, Compton CC, Shellito PC, Efird JT. Selection factors for local excision or abdominoperineal resection of early stage rectal cancer. *Cancer* 1994;73:2716-2720. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8194011>.

146. Schmoll HJ, Cartwright T, Tabernero J, et al. Phase III trial of capecitabine plus oxaliplatin as adjuvant therapy for stage III colon cancer: a planned safety analysis in 1,864 patients. *J Clin Oncol* 2007;25:102-109. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17194911>.

147. Van Cutsem E, Nordlinger B, Adam R, et al. Towards a pan-European consensus on the treatment of patients with colorectal liver metastases. *Eur J Cancer* 2006;42:2212-2221. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16904315>.

148. Yoo PS, Lopez-Soler RI, Longo WE, Cha CH. Liver resection for metastatic colorectal cancer in the age of neoadjuvant chemotherapy and bevacizumab. *Clin Colorectal Cancer* 2006;6:202-207. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17026789>.

149. Alberts SR, Horvath WL, Sternfeld WC, et al. Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group phase II study. *J Clin Oncol* 2005;23:9243-9249. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16230673>.

150. Kemeny N. Management of liver metastases from colorectal cancer. *Oncology (Williston Park)* 2006;20:1161-1176, 1179; discussion 1179-1180, 1185-1166. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17024869>.

151. Muratore A, Zorzi D, Bouzari H, et al. Asymptomatic colorectal cancer with un-resectable liver metastases: immediate colorectal resection or up-front systemic chemotherapy? *Ann Surg Oncol* 2007;14:766-770. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17103261>.

152. Fong Y, Cohen AM, Fortner JG, et al. Liver resection for colorectal metastases. *J Clin Oncol* 1997;15:938-946. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9060531>.

153. Tsai M-S, Su Y-H, Ho M-C, et al. Clinicopathological features and prognosis in resectable synchronous and metachronous colorectal liver metastasis. *Ann Surg Oncol* 2007;14:786-794. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17103254>.

154. Poultides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. *J Clin Oncol* 2009;27:3379-3384. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19487380>.

155. Foster JH. Treatment of metastatic disease of the liver: a skeptic's view. *Semin Liver Dis* 1984;4:170-179. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/6205450>.

156. Stangl R, Altendorf-Hofmann A, Charnley RM, Scheele J. Factors influencing the natural history of colorectal liver metastases. *Lancet* 1994;343:1405-1410. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/7515134>.

157. Venook AP. The Kemeny Article Reviewed Management of Liver Metastases From Colorectal Cancer: Review 2. *Oncology* 2006;20.

Available at:

<http://www.cancernetwork.com/display/article/10165/108033>.

158. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. *Ann Surg* 2002;235:759-766. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12035031>.

159. Pawlik TM, Scoggins CR, Zorzi D, et al. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. *Ann Surg* 2005;241:715-722, discussion 722-714. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15849507>.



160. Charnsangavej C, Clary B, Fong Y, et al. Selection of patients for resection of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;13:1261-1268. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16947009>.

161. Altendorf-Hofmann A, Scheele J. A critical review of the major indicators of prognosis after resection of hepatic metastases from colorectal carcinoma. *Surg Oncol Clin N Am* 2003;12:165-192. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12735137>.

162. Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. *Oncologist* 2008;13:51-64. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18245012>.

163. Vauthey J-N, Zorzi D, Pawlik TM. Making unresectable hepatic colorectal metastases resectable--does it work? *Semin Oncol* 2005;32:118-122. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16399448>.

164. Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005;16:1311-1319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15870084>.

165. Reddy SK, Pawlik TM, Zorzi D, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. *Ann Surg Oncol* 2007;14:3481-3491. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17805933>.

166. Covey AM, Brown KT, Jarnagin WR, et al. Combined portal vein embolization and neoadjuvant chemotherapy as a treatment strategy for resectable hepatic colorectal metastases. *Ann Surg* 2008;247:451-455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18376189>.

167. Adam R, Miller R, Pitombo M, et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. *Surg Oncol Clin N Am* 2007;16:525-536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17606192>.

168. Abdalla EK. Commentary: Radiofrequency ablation for colorectal liver metastases: do not blame the biology when it is the technology. *Am J Surg* 2009;197:737-739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18789420>.

169. Abdalla EK, Vauthey J-N, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. *Ann Surg* 2004;239:818-825. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15166961>.

170. Gleisner AL, Choti MA, Assumpcao L, et al. Colorectal liver metastases: recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. *Arch Surg* 2008;143:1204-1212. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19075173>.

171. Hur H, Ko YT, Min BS, et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. *Am J Surg* 2009;197:728-736. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18789428>.

172. Reuter NP, Woodall CE, Scoggins CR, et al. Radiofrequency ablation vs. resection for hepatic colorectal metastasis: therapeutically equivalent? *J Gastrointest Surg* 2009;13:486-491. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18972167>.

173. Wong SL, Mangu PB, Choti MA, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. *J Clin Oncol* 2010;28:493-508. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19841322>.

174. Leonard GD, Brenner B, Kemeny NE. Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *J Clin Oncol* 2005;23:2038-2048. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15774795>.



175. van Vledder MG, de Jong MC, Pawlik TM, et al. Disappearing colorectal liver metastases after chemotherapy: should we be concerned? *J Gastrointest Surg* 2010;14:1691-1700. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20839072>.

176. Benoist S, Brouquet A, Penna C, et al. Complete response of colorectal liver metastases after chemotherapy: does it mean cure? *J Clin Oncol* 2006;24:3939-3945. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16921046>.

177. Bilchik AJ, Poston G, Curley SA, et al. Neoadjuvant chemotherapy for metastatic colon cancer: a cautionary note. *J Clin Oncol* 2005;23:9073-9078. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16361615>.

178. Adam R, Avisar E, Ariche A, et al. Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. *Ann Surg Oncol* 2001;8:347-353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11352309>.

179. Pawlik TM, Olino K, Gleisner AL, et al. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. *J Gastrointest Surg* 2007;11:860-868. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17492335>.

180. Rivoire M, De Cian F, Meeus P, et al. Combination of neoadjuvant chemotherapy with cryotherapy and surgical resection for the treatment of unresectable liver metastases from colorectal carcinoma. *Cancer* 2002;95:2283-2292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12436433>.

181. Vauthey J-N, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *J Clin Oncol* 2006;24:2065-2072. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16648507>.

182. Hayashi M, Inoue Y, Komeda K, et al. Clinicopathological analysis of recurrence patterns and prognostic factors for survival after

hepatectomy for colorectal liver metastasis. *BMC Surg* 2010;10:27. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20875094>.

183. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. *Ann Surg* 2004;240:644-657; discussion 657-648. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15383792>.

184. Elias D, Liberale G, Vernerey D, et al. Hepatic and extrahepatic colorectal metastases: when resectable, their localization does not matter, but their total number has a prognostic effect. *Ann Surg Oncol* 2005;12:900-909. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16184442>.

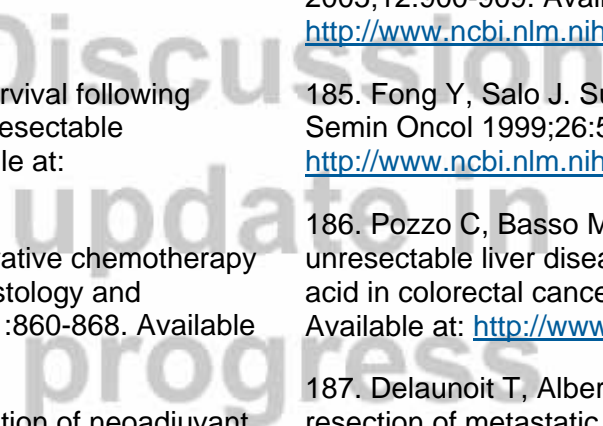
185. Fong Y, Salo J. Surgical therapy of hepatic colorectal metastasis. *Semin Oncol* 1999;26:514-523. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10528899>.

186. Pozzo C, Basso M, Cassano A, et al. Neoadjuvant treatment of unresectable liver disease with irinotecan and 5-fluorouracil plus folinic acid in colorectal cancer patients. *Ann Oncol* 2004;15:933-939. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15151951>.

187. Delaunoy T, Alberts SR, Sargent DJ, et al. Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. *Ann Oncol* 2005;16:425-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15677624>.

188. Nordlinger B, Sorbye H, Glimelius B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *Lancet* 2008;371:1007-1016. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18358928>.

189. Folprecht G, Gruenberger T, Bechstein WO, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM



randomised phase 2 trial. *Lancet Oncol* 2010;11:38-47. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19942479>.

190. Tan BR, Zubal B, Hawkins W, et al. Preoperative FOLFOX plus cetuximab or panitumumab therapy for patients with potentially resectable hepatic colorectal metastases. 2009 Gastrointestinal Cancers Symposium 497. Available at: http://www.asco.org/ASCOv2/Meetings/Abstracts?vmview=abst_detail_view&confID=63&abstractID=10593.

191. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. *J Clin Oncol* 2007;25:1670-1676. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17470860>.

192. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG). *Br J Cancer* 2006;94:798-805. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16508637>.

193. Scappaticci FA, Fehrenbacher L, Cartwright T, et al. Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab. *J Surg Oncol* 2005;91:173-180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16118771>.

194. Package Insert. AVASTIN® (bevacizumab). South San Francisco, CA: Genentech, Inc.; 2009. Available at: <http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=14571&CFID=54483017&CFTOKEN=2b448b8f5210987e0-3B42D442-0B95-3FCF-32E159177FB92553&jsessionid=ca30e3863753695d5d38>. Accessed 2010.

195. Gruenberger B, Tamandl D, Schueller J, et al. Bevacizumab, capecitabine, and oxaliplatin as neoadjuvant therapy for patients with potentially curable metastatic colorectal cancer. *J Clin Oncol* 2008;26:1830-1835. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18398148>.

196. Reddy SK, Morse MA, Hurwitz HI, et al. Addition of bevacizumab to irinotecan- and oxaliplatin-based preoperative chemotherapy regimens does not increase morbidity after resection of colorectal liver metastases. *J Am Coll Surg* 2008;206:96-9106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18155574>.

197. Lee WS, Yun SH, Chun HK, et al. Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. *Int J Colorectal Dis* 2007;22:699-704. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17109105>.

198. Headrick JR, Miller DL, Nagorney DM, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. *Ann Thorac Surg* 2001;71:975-979; discussion 979-980. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11269484>.

199. Kemeny N, Huang Y, Cohen AM, et al. Hepatic arterial infusion of chemotherapy after resection of hepatic metastases from colorectal cancer. *N Engl J Med* 1999;341:2039-2048. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10615075>.

200. Kemeny NE, Gonen M. Hepatic arterial infusion after liver resection. *N Engl J Med* 2005;352:734-735. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15716576>.

201. Hong K, McBride JD, Georgiades CS, et al. Salvage therapy for liver-dominant colorectal metastatic adenocarcinoma: comparison between transcatheter arterial chemoembolization versus yttrium-90 radioembolization. *J Vasc Interv Radiol* 2009;20:360-367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19167245>.

202. Mulcahy MF, Lewandowski RJ, Ibrahim SM, et al. Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. *Cancer* 2009;115:1849-1858. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19267416>.
203. Katz AW, Carey-Sampson M, Muhs AG, et al. Hypofractionated stereotactic body radiation therapy (SBRT) for limited hepatic metastases. *Int J Radiat Oncol Biol Phys* 2007;67:793-798. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17197128>.
204. Bartlett DL, Berlin J, Lauwers GY, et al. Chemotherapy and regional therapy of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 2006;13:1284-1292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16955384>.
205. Joyce DL, Wahl RL, Patel PV, et al. Preoperative positron emission tomography to evaluate potentially resectable hepatic colorectal metastases. *Arch Surg* 2006;141:1220-1226; discussion 1227. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17178965>.
206. Pelosi E, Deandreis D. The role of 18F-fluoro-deoxy-glucose positron emission tomography (FDG-PET) in the management of patients with colorectal cancer. *Eur J Surg Oncol* 2007;33:1-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17126522>.
207. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol* 2008;15:1937-1947. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18389321>.
208. Esquivel J, Sticca R, Sugarbaker P, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in the management of peritoneal surface malignancies of colonic origin: a consensus statement. Society of Surgical Oncology. *Ann Surg Oncol* 2007;14:128-133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17072675>.
209. Yan TD, Black D, Savady R, Sugarbaker PH. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. *J Clin Oncol* 2006;24:4011-4019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16921055>.
210. Yu TK, Bhosale PR, Crane CH, et al. Patterns of locoregional recurrence after surgery and radiotherapy or chemoradiation for rectal cancer. *Int J Radiat Oncol Biol Phys* 2008;71:1175-1180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18207667>.
211. Hoffman JP, Riley L, Carp NZ, Litwin S. Isolated locally recurrent rectal cancer: a review of incidence, presentation, and management. *Semin Oncol* 1993;20:506-519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8211198>.
212. Lowy AM, Rich TA, Skibber JM, et al. Preoperative infusional chemoradiation, selective intraoperative radiation, and resection for locally advanced pelvic recurrence of colorectal adenocarcinoma. *Ann Surg* 1996;223:177-185. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8597512>.
213. Pietra N, Sarli L, Costi R, et al. Role of follow-up in management of local recurrences of colorectal cancer: a prospective, randomized study. *Dis Colon Rectum* 1998;41:1127-1133. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9749496>.
214. Rodriguez-Moranta F, Salo J, Arcusa A, et al. Postoperative surveillance in patients with colorectal cancer who have undergone curative resection: a prospective, multicenter, randomized, controlled trial. *J Clin Oncol* 2006;24:386-393. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16365182>.
215. Secco GB, Fardelli R, Gianquinto D, et al. Efficacy and cost of risk-adapted follow-up in patients after colorectal cancer surgery: a prospective, randomized and controlled trial. *Eur J Surg Oncol* 2002;28:418-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12099653>.



216. Desch CE, Benson AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of an American Society of Clinical Oncology practice guideline. *J Clin Oncol* 2005;23:8512-8519. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16260687>.

217. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Rev* 2007. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17253476>.

218. Renehan AG, Egger M, Saunders MP, O'Dwyer ST. Impact on survival of intensive follow up after curative resection for colorectal cancer: systematic review and meta-analysis of randomised trials. *BMJ* 2002;324:813-813. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11934773>.

219. Sargent DJ, Wieand HS, Haller DG, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. *J Clin Oncol* 2005;23:8664-8670. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16260700>.

220. Guyot F, Faivre J, Manfredi S, et al. Time trends in the treatment and survival of recurrences from colorectal cancer. *Ann Oncol* 2005;16:756-761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15790673>.

221. Li Destri G, Di Cataldo A, Puleo S. Colorectal cancer follow-up: useful or useless? *Surg Oncol* 2006;15:1-12. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16891116>.

222. Pfister DG, Benson AB, 3rd, Somerfield MR. Clinical practice. Surveillance strategies after curative treatment of colorectal cancer. *N Engl J Med* 2004;350:2375-2382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15175439>.

223. Locker GY, Hamilton S, Harris J, et al. ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal

cancer. *J Clin Oncol* 2006;24:5313-5327. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17060676>.

224. Macdonald JS. Carcinoembryonic antigen screening: pros and cons. *Semin Oncol* 1999;26:556-560. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10528904>.

225. Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and US Multi-Society Task Force on Colorectal Cancer. *CA Cancer J Clin* 2006;56:160-167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16737948>.

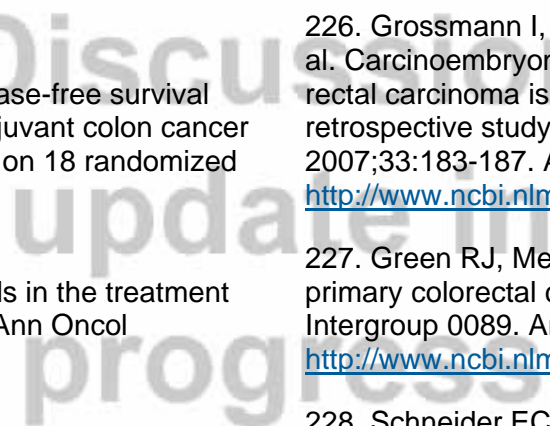
226. Grossmann I, de Bock GH, Meershoek-Klein Kranenbarg WM, et al. Carcinoembryonic antigen (CEA) measurement during follow-up for rectal carcinoma is useful even if normal levels exist before surgery. A retrospective study of CEA values in the TME trial. *Eur J Surg Oncol* 2007;33:183-187. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17174516>.

227. Green RJ, Metlay JP, Propert K, et al. Surveillance for second primary colorectal cancer after adjuvant chemotherapy: an analysis of Intergroup 0089. *Ann Intern Med* 2002;136:261-269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11848723>.

228. Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer : patient-reported symptoms 4 years after diagnosis. *Cancer* 2007;110:2075-2082. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17849466>.

229. Desnoo L, Faithfull S. A qualitative study of anterior resection syndrome: the experiences of cancer survivors who have undergone resection surgery. *Eur J Cancer Care (Engl)* 2006;15:244-251. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16882120>.

230. Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. *Aliment Pharmacol*





Ther 2003;18:987-994. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14616164>.

231. McGough C, Baldwin C, Frost G, Andreyev HJ. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. Br J Cancer 2004;90:2278-2287. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15162154>.

232. Sprangers MA, Taal BG, Aaronson NK, te Velde A. Quality of life in colorectal cancer. Stoma vs. nonstoma patients. Dis Colon Rectum 1995;38:361-369. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/7720441>.

233. Baxter NN, Habermann EB, Tepper JE, et al. Risk of pelvic fractures in older women following pelvic irradiation. JAMA 2005;294:2587-2593. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16304072>.

234. Lange MM, Maas CP, Marijnen CA, et al. Urinary dysfunction after rectal cancer treatment is mainly caused by surgery. Br J Surg 2008;95:1020-1028. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18563786>.

235. Lange MM, Marijnen CA, Maas CP, et al. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer 2009;45:1578-1588. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19147343>.

236. Denlinger CS, Barsevick AM. The challenges of colorectal cancer survivorship. J Natl Compr Canc Netw 2009;7:883-893. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19755048>.

237. Dignam JJ, Polite BN, Yothers G, et al. Body mass index and outcomes in patients who receive adjuvant chemotherapy for colon cancer. J Natl Cancer Inst 2006;98:1647-1654. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17105987>.

238. Meyerhardt JA, Heseltine D, Niedzwiecki D, et al. Impact of physical activity on cancer recurrence and survival in patients with

stage III colon cancer: findings from CALGB 89803. J Clin Oncol

2006;24:3535-3541. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16822843>.

239. Meyerhardt JA, Niedzwiecki D, Hollis D, et al. Association of dietary patterns with cancer recurrence and survival in patients with stage III colon cancer. JAMA 2007;298:754-764. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17699009>.

240. Martin EW, Minton JP, Carey LC. CEA-directed second-look surgery in the asymptomatic patient after primary resection of colorectal carcinoma. Ann Surg 1985;202:310-317. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/4037904>.

