



**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)**

# **Rectal Cancer**

Version 2.2011

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# NCCN Guidelines™ Version 2.2011 Panel Members

## Rectal Cancer

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### [NCCN Rectal Cancer Panel Members](#)

### [Summary of the Guidelines Updates](#)

#### Clinical Presentations and Primary Treatment:

- [Pedunculated polyp with invasive cancer \(REC-1\)](#)
- [Sessile polyp with invasive cancer \(REC-1\)](#)
- [Rectal cancer appropriate for resection \(REC-2\)](#)
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  - ▶ [T3, N0 or T any, N1-2: Primary and Adjuvant Treatment \(REC-4\)](#)
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To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical\\_trials/physician.html](#)

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

See [NCCN Categories of Evidence and Consensus](#)



Summary changes in the 2.2011 version of the Rectal Cancer Guidelines from the 1.2011 version include:

The previous footnote related to BRAF was removed and the following footnotes were added to the metastatic section of the Guidelines based on recent presentations:

- Footnote in the first-line setting: 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. Applies to pages [REC-5](#), [REC-E 1 of 6](#) through [REC-E 3 of 6](#).
- Footnote after progression on first-line therapy: 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. Applies to pages [REC-10](#), [REC-E 1 of 6](#), [REC-E 3 of 6](#).
- Information updated in the Principles of Pathologic Review with references on page [REC-A 5 of 6](#).



Summary changes in the 1.2011 version of the Rectal Cancer Guidelines from the 3.2010 version include:

#### [REC-3](#) and [REC-4](#)

- For patients with pT3,N0,M0 or pT1-3,N1-2 after resection, “Continuous 5-FU/RT or bolus 5-FU + leucovorin/RT or capecitabine/RT followed by 5-FU ± leucovorin or FOLFOX or capecitabine ± oxaliplatin” was added as a treatment option in the adjuvant setting.
- The combination of capecitabine and oxaliplatin was added as a treatment option in the adjuvant setting
- Capecitabine/RT was changed from a category 2B designation to a category 2A designation.

#### [REC-4](#)

- The recommendation of 5-FU ± leucovorin was changed from a category 1 designation to a category 2A designation in the adjuvant setting.

#### [REC-5](#)

- Capecitabine/RT was changed from a category 2B designation to a category 2A designation.
- The combination of capecitabine and oxaliplatin was added as a treatment option in the adjuvant setting

#### [REC-8](#)

- Isolated pelvic/anastomotic recurrence - categories added for “potentially resectable” or “unresectable”. For potentially resectable, surgical resection added as a treatment option. For unresectable, chemotherapy ± RT included as a treatment option.

#### [REC-9](#)

- Patients with resectable metachronous metastases that have a response after neoadjuvant chemotherapy and resection, the recommendation changed from “Repeat initial chemotherapy” to “Repeat neoadjuvant therapy or FOLFOX.”

#### [REC-A 2 of 6](#)

- The following parameters were added for reporting of pathologic stage: circumferential resection margin, neoadjuvant treatment effect, lymphovascular invasion, perineural invasion, extra nodal tumor deposits.
- Descriptions were added to the following new sections: Circumferential resection margin, Neoadjuvant treatment effect.

#### [REC-A 3 of 6](#)

- Descriptions were added to the following new sections: Perineural invasion, Extra nodal tumor deposits.

#### [REC-B 1 of 3](#)

- Transanal excision - bullet 2: the following changes made, “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.

#### [REC-B 2 of 3](#)

##### Liver

- Bullet noting that hepatic resection is the treatment of choice moved to the first bullet.
- Bullet 7 - “intra-arterial embolization” changed to “arterially-directed embolic therapy.”

##### Lung

- Bullet 7 - “Conformal external beam RT 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).” added to principles.

#### [REC-C 1 of 2](#)

- CapeOX dosing regimen included with reference.

#### [REC-D](#)

- Bullet 9 - “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)” added to principles.
- Bullet 10 added to the page: “Side effect management: Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis. All male patients should be evaluated for erectile dysfunction and considered for early treatment intervention if necessary.”

#### [REC-E 2 of 6](#)

- Capecitabine added as an option with bevacizumab for patients appropriate for intensive therapy. This combination was previously included only for patient not appropriate for intensive therapy.
- The combination of irinotecan + oxaliplatin (IROX) added as a treatment option for patients appropriate for intensive therapy.

#### [REC-E 3 of 6](#)

- Footnote 3 - The following sentence was added: “There are insufficient data to support the routine use of Ca/Mg infusion to prevent oxaliplatin-related neurotoxicity.”

#### [REC-E 5 of 6](#)

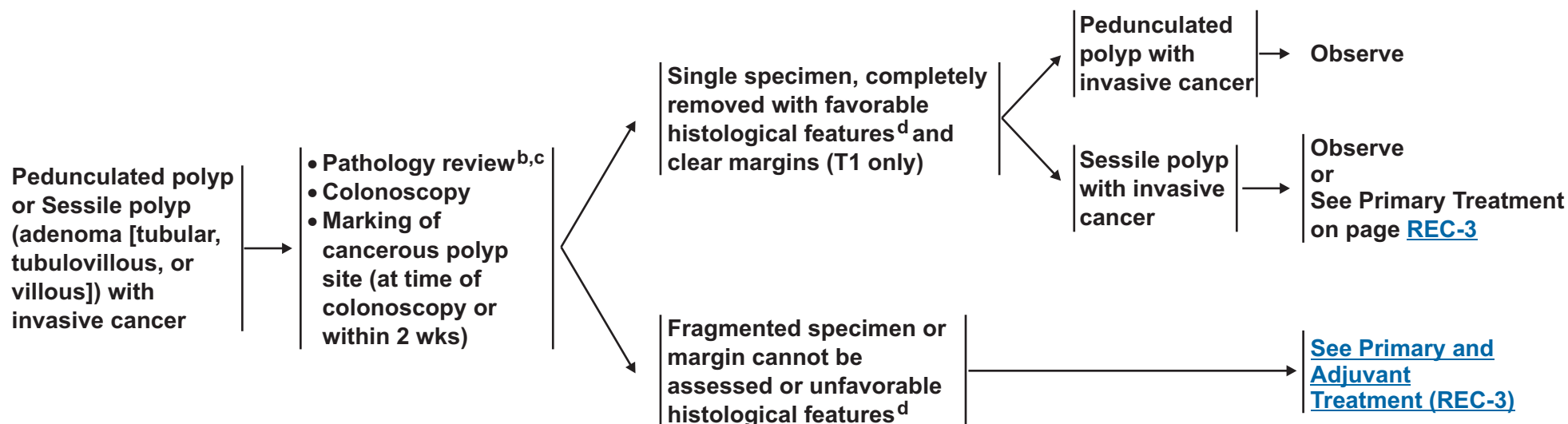
- IROX dosing regimen included with reference.



**CLINICAL  
PRESENTATION<sup>a</sup>**

**WORKUP**

**FINDINGS**



<sup>a</sup>All 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](#).

<sup>b</sup>Confirm the presence of invasive cancer (pT1). pT1s has no biological potential to metastasize.

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

<sup>d</sup>[See Principles of Pathologic Review \(REC-A\)](#) - Endoscopically removed malignant polyp.

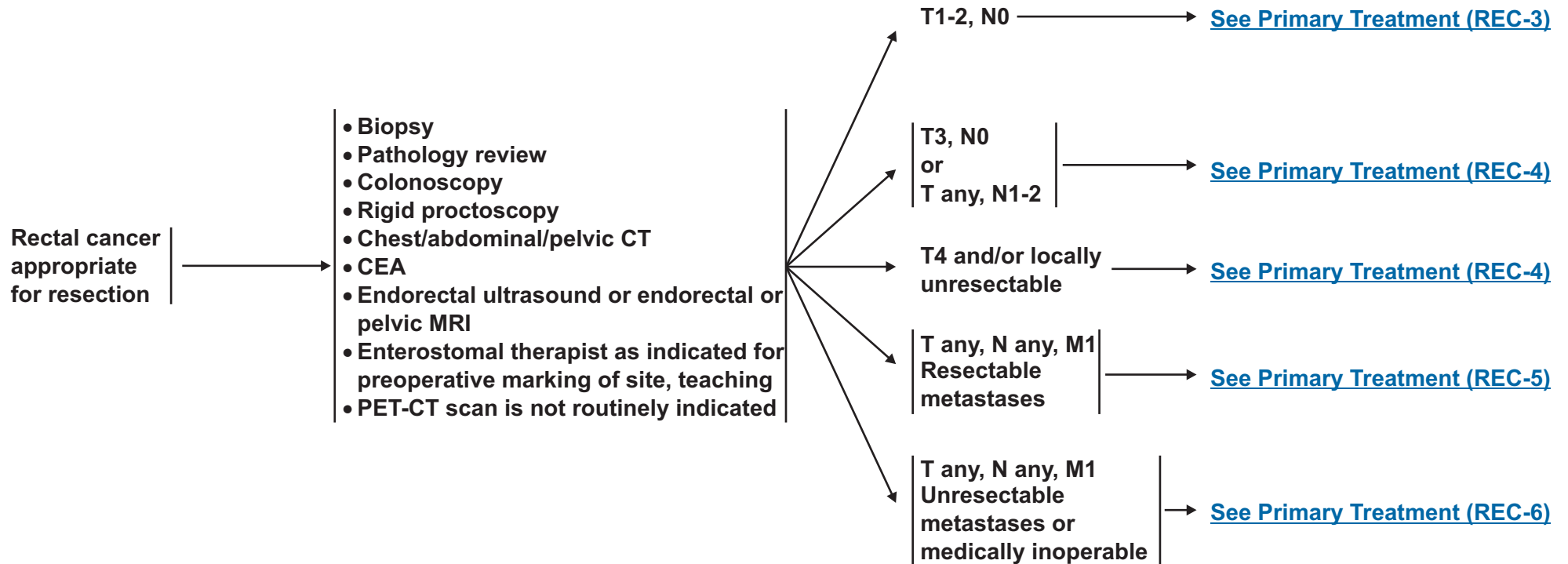
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**CLINICAL  
PRESENTATION<sup>a</sup>**

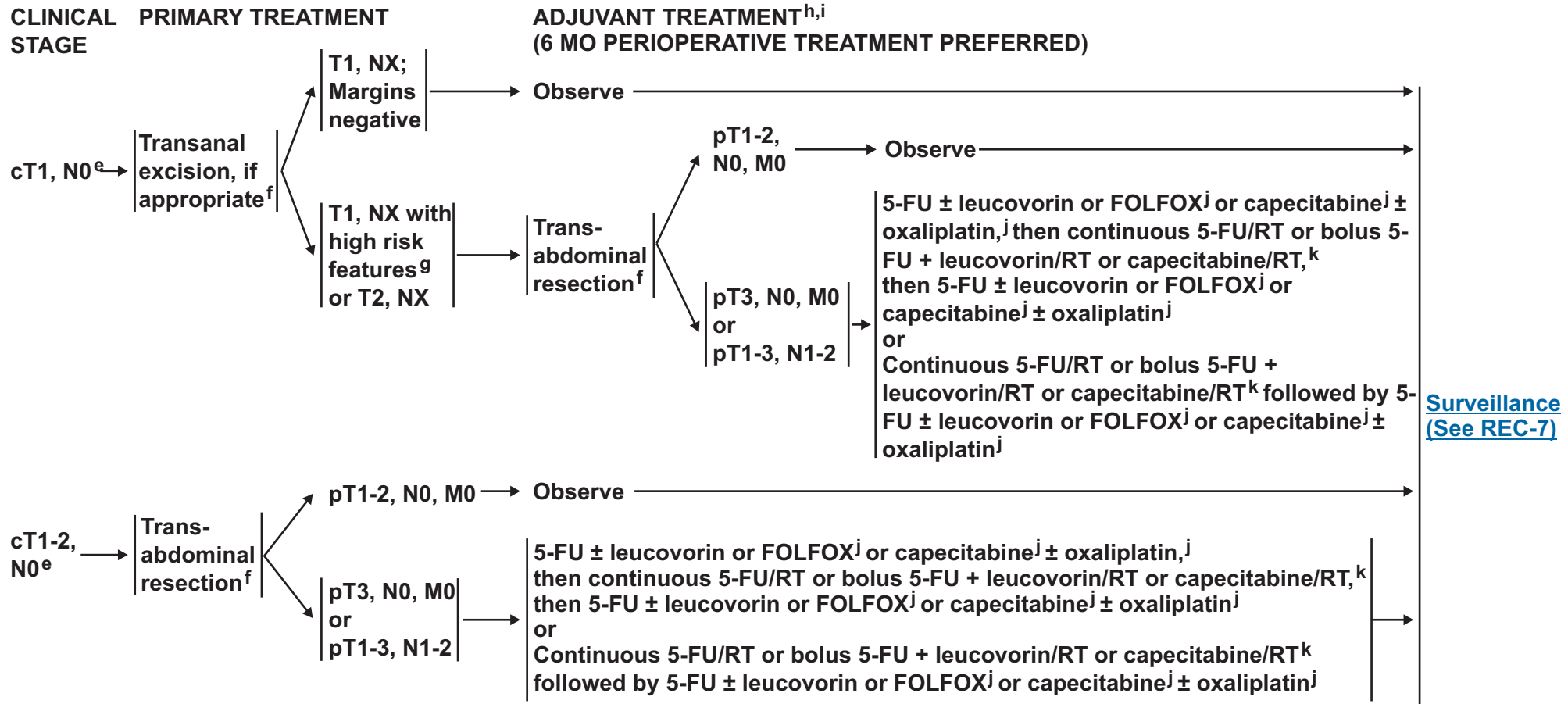
**WORKUP**

**CLINICAL STAGE**



<sup>a</sup>All 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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<sup>e</sup>T1-2, N0 should be based on assessment of endorectal ultrasound or MRI.

<sup>f</sup>See Principles of Surgery (REC-B).

<sup>g</sup>High risk features include positive margins, lymphovascular invasion and poorly differentiated tumors.

<sup>h</sup>See Principles of Adjuvant Therapy (REC-C).

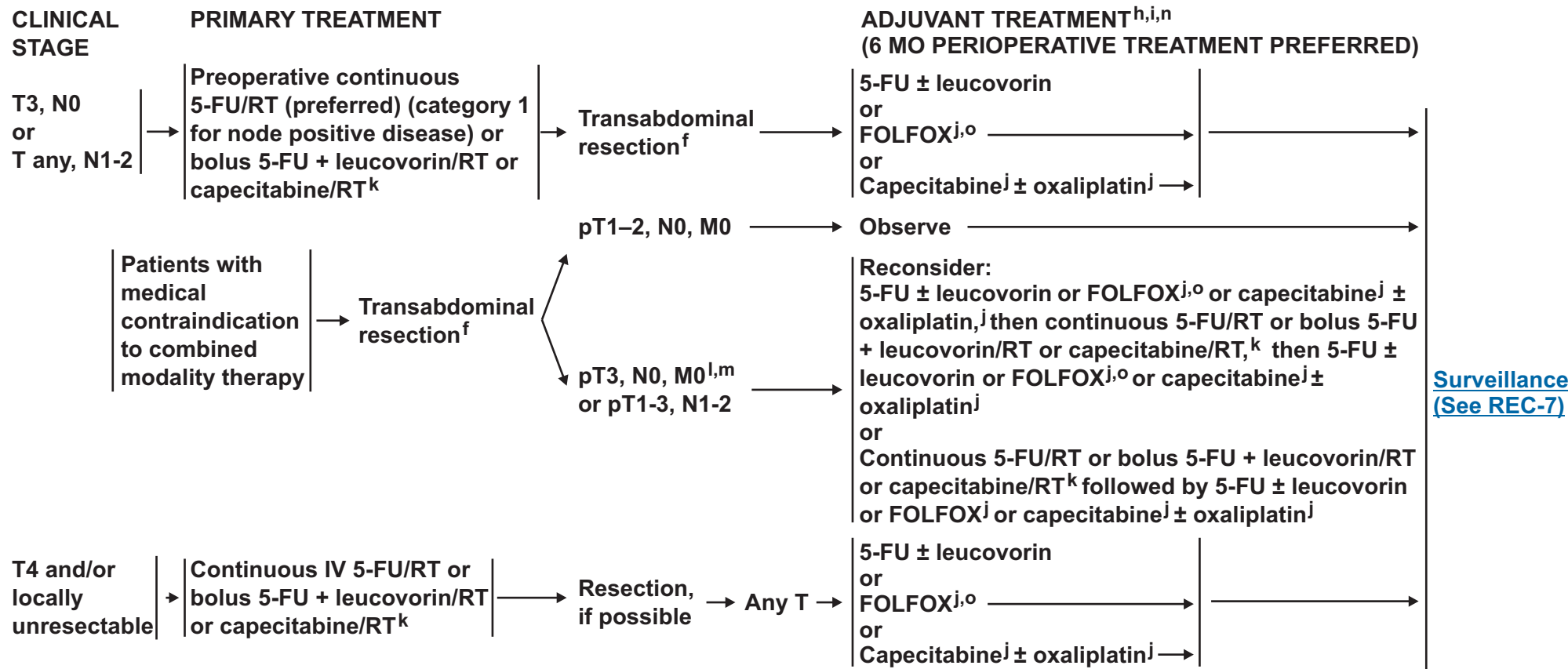
<sup>i</sup>See Principles of Radiation Therapy (REC-D).

<sup>j</sup>The use of FOLFOX or capecitabine ± oxaliplatin are extrapolations from the available data in colon cancer. Trials are still pending in rectal cancer.

<sup>k</sup>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.

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<sup>f</sup> See Principles of Surgery (REC-B).

<sup>h</sup> See Principles of Adjuvant Therapy (REC-C).

<sup>i</sup> See Principles of Radiation Therapy (REC-D).

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<sup>l</sup> The use of agents other than fluoropyrimidines are not recommended concurrently with RT.

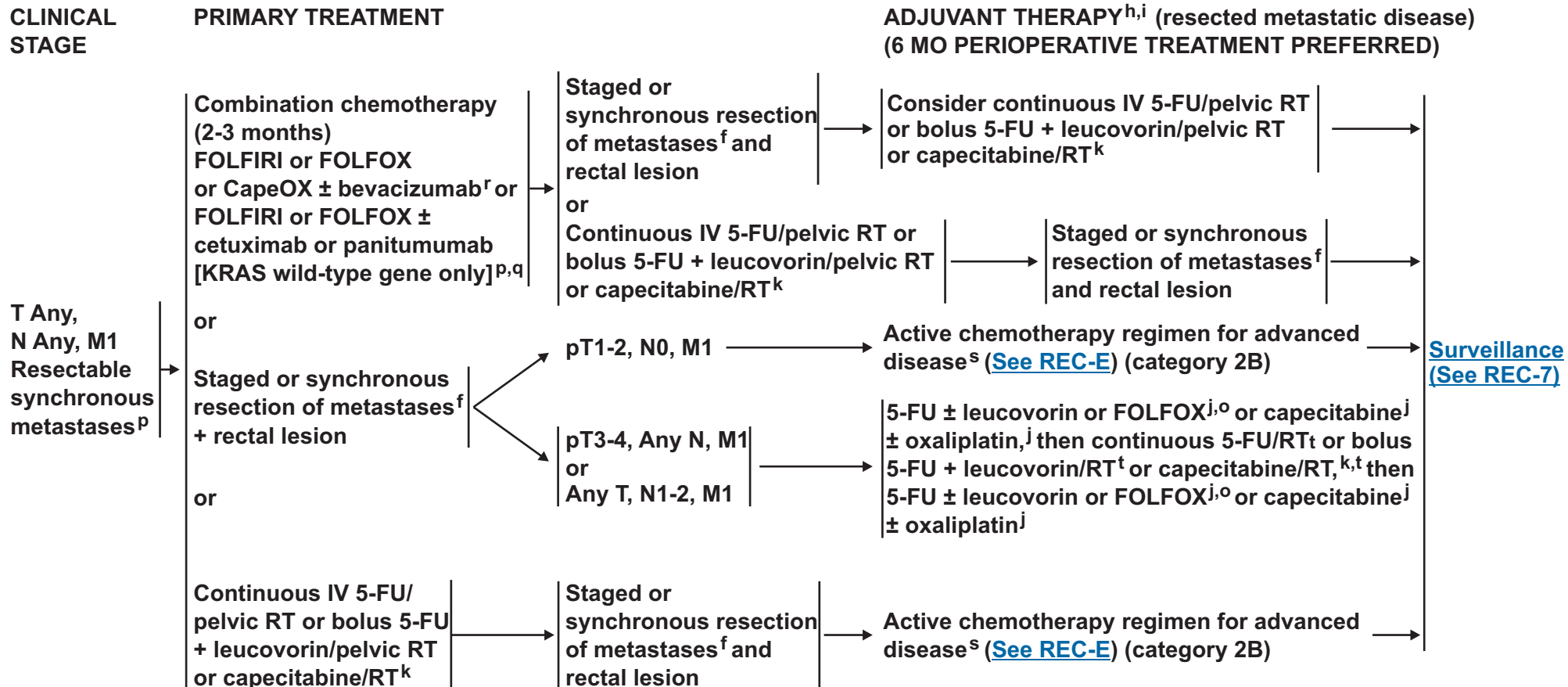
<sup>m</sup> For patients with proximal T3, N0 disease with clear margins and favorable prognostic features, the incremental benefit of RT is likely to be small. Consider chemotherapy alone.

<sup>n</sup> Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results.

<sup>o</sup> An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

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<sup>f</sup> See Principles of Surgery (REC-B).

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<sup>o</sup> An ongoing Intergroup trial compares 5-FU/leucovorin, FOLFOX, and FOLFIRI after surgery.

<sup>p</sup> Determination 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.

<sup>q</sup> 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.

<sup>r</sup> The safety of administering bevacizumab pre or postoperatively, in combination with 5-FU-based regimens, has not been adequately evaluated. There should be at least a 6 wk interval between the last dose of bevacizumab and elective surgery. There is an increased risk of stroke and other arterial events especially in age ≥ 65. The use of bevacizumab may interfere with wound healing.

<sup>s</sup> FOLFOXIRI is not recommended in this setting.

<sup>t</sup> RT only recommended for patients at increased risk for pelvic recurrence.

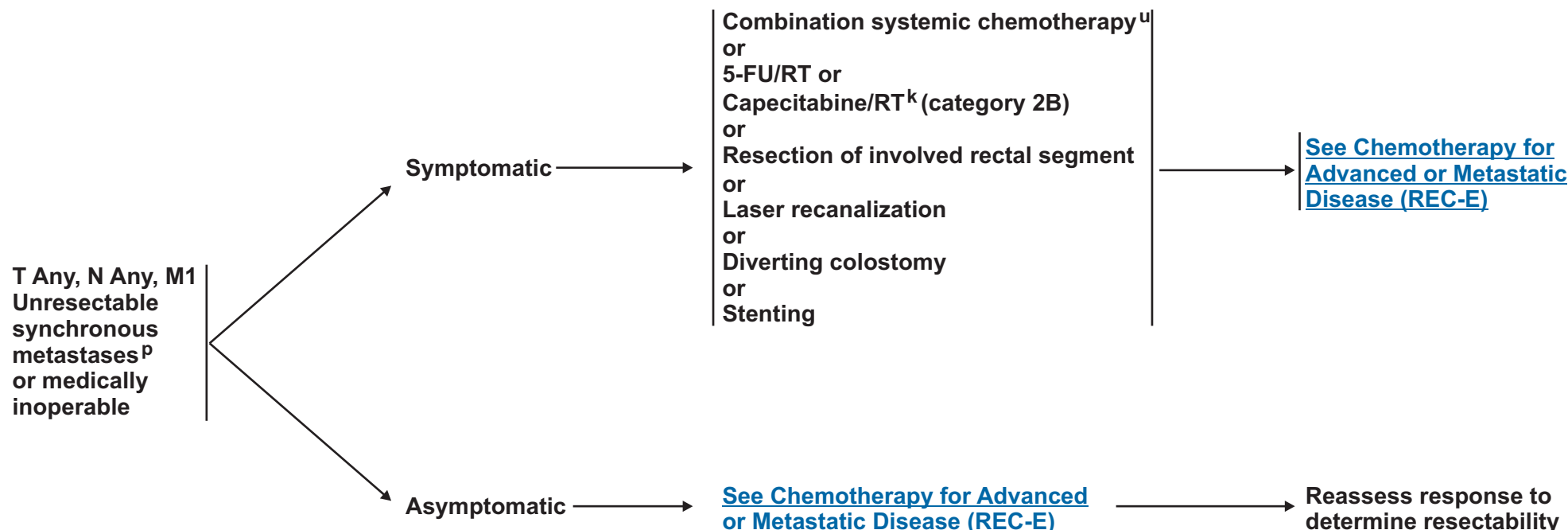
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**CLINICAL STAGE**

**PRIMARY TREATMENT**



<sup>K</sup>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.

<sup>P</sup>Determination 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.

<sup>U</sup>[See Chemotherapy for Advanced or Metastatic Disease \(REC-E\)](#).

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## SURVEILLANCE

- History and physical every 3-6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA<sup>v</sup> every 3-6 mo for 2 y, then every 6 mo for a total of 5 y for T2 or greater lesions
- Chest/abdominal/pelvic CT annually x 3 y for patients at high risk for recurrence<sup>w,x</sup>
- 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,<sup>y</sup> repeat in 3 y, then every 5 y<sup>z</sup>
- Consider proctoscopy every 6 mo x 5 y for patients status post LAR<sup>aa</sup>
- PET-CT scan is not routinely recommended
- See [Principles of Survivorship \(REC-F\)](#)

Serial CEA elevation or documented recurrence

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

<sup>v</sup>If patient is a potential candidate for resection of isolated metastasis.

<sup>w</sup>Desch CE, Benson III AB, Somerfield MR, et al. Colorectal cancer surveillance: 2005 update of the American Society of Clinical Oncology Practice Guideline. J Clin Oncol 2005;23(33):8512-8519.

<sup>x</sup>CT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor, or poorly differentiated tumors).

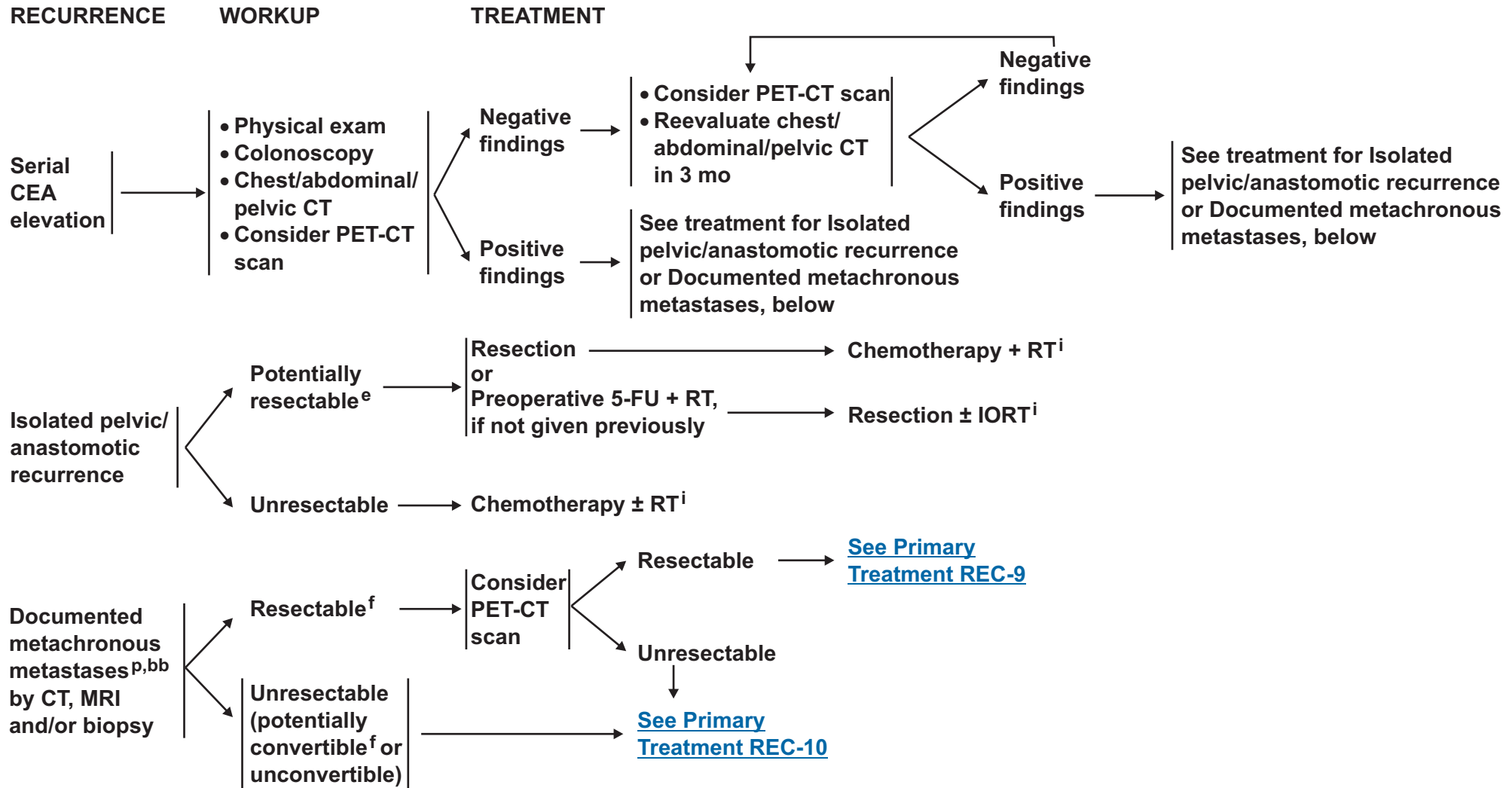
<sup>y</sup>Villous polyp, polyp > 1 cm, or high grade dysplasia.

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

<sup>aa</sup>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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<sup>f</sup> See Principles of Surgery (REC-B).

<sup>i</sup> See Principles of Radiation Therapy (REC-D).

<sup>p</sup> Determination 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.

<sup>bb</sup> Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

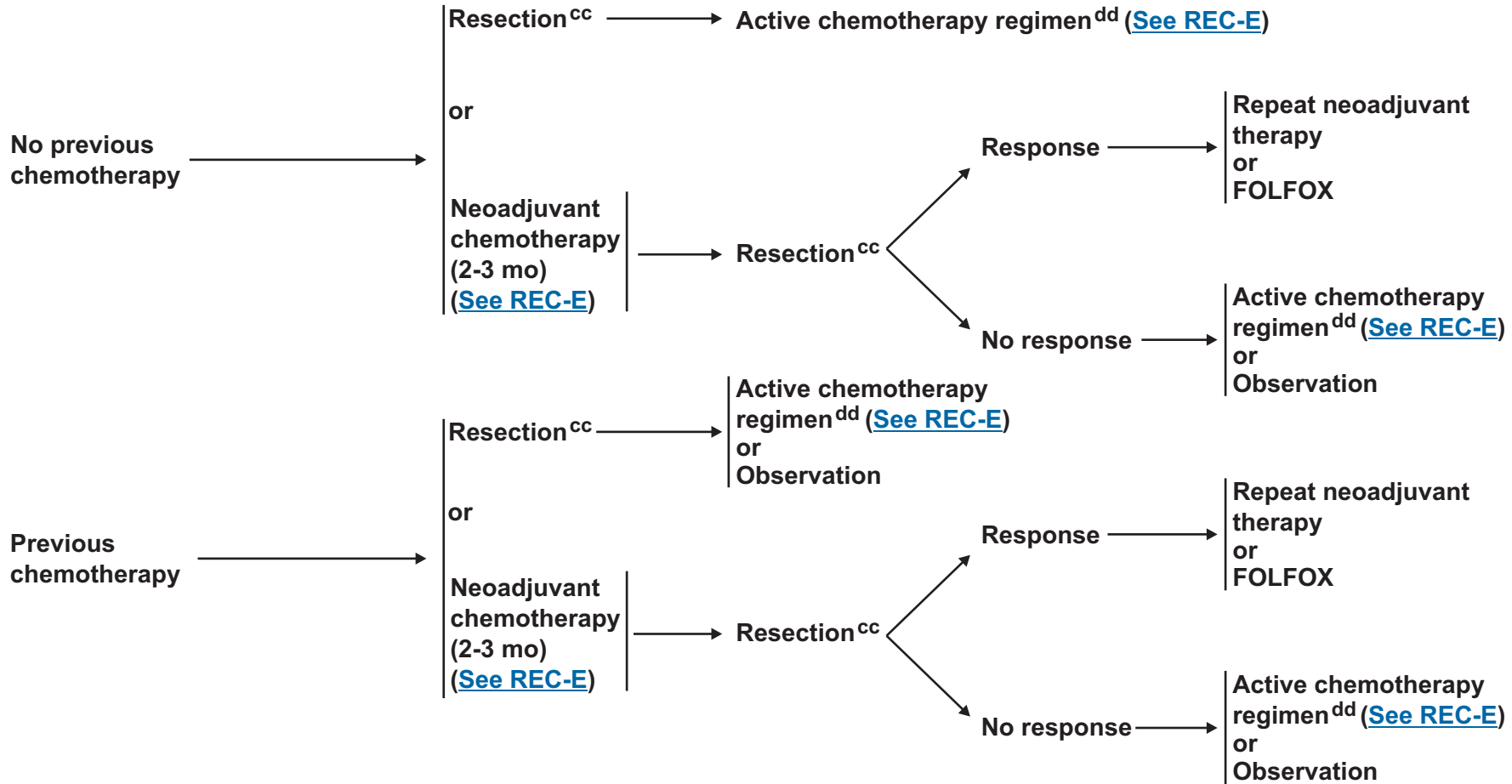
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**RESECTABLE  
METACHRONOUS METASTASES**

**PRIMARY TREATMENT**



<sup>cc</sup>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.

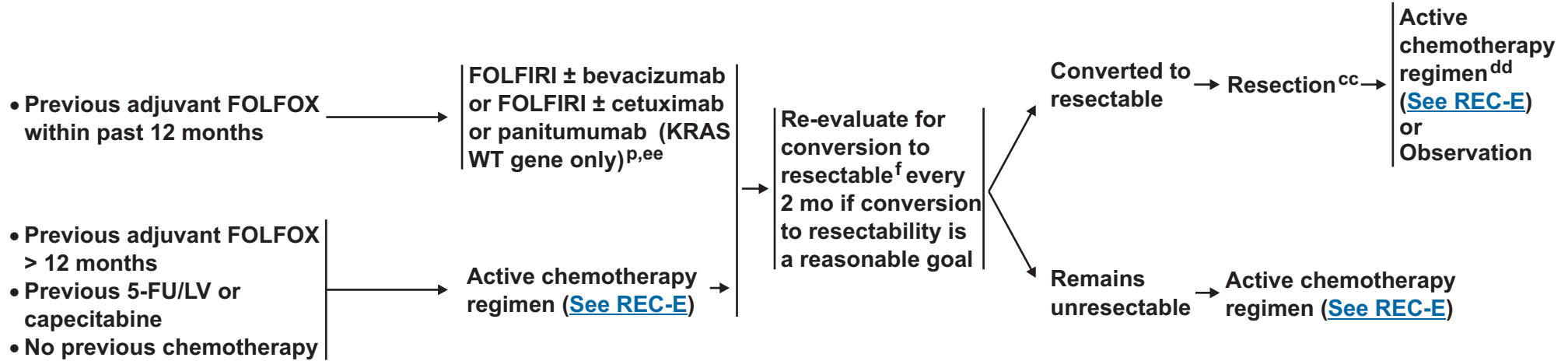
<sup>dd</sup>Perioperative therapy should be considered for up to a total of 6 months.

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**UNRESECTABLE  
METACHRONOUS METASTASES**

**PRIMARY TREATMENT**



<sup>f</sup>See Principles of Surgery (REC-B).

<sup>p</sup>Determination 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.

<sup>cc</sup>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.

<sup>dd</sup>Perioperative therapy should be considered for up to a total of 6 months.

<sup>ee</sup>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.<sup>1-4</sup>
- 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.<sup>3-7</sup>

### Transanal excision

- Favorable histopathological features: < 3 cm size, T1, grade I or II, no lymphatic or venous invasion, negative margins.<sup>8,9</sup>
- Unfavorable histopathological features: > 3 cm in size, T1, with grade III, or lymphovascular invasion, or positive margin.<sup>8-10</sup>

### 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.<sup>11-12</sup>
- ▶ A positive circumferential resection margin (CRM) has been defined as  $\leq 1$  mm<sup>13-14</sup> [See Staging \(ST-1\)](#)
- ▶ Circumferential resection margin<sup>13-17</sup>
- ▶ Neoadjuvant treatment effect<sup>15,16,18,19</sup>
- ▶ Lymphovascular invasion<sup>15,16,20</sup>
- ▶ Perineural invasion<sup>21-23</sup>
- ▶ Extra nodal tumor deposits<sup>24-25</sup>

- Circumferential resection margin - A positive CRM is defined as tumor  $\leq 1$  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.<sup>13-17</sup>

- 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.<sup>15,16,18,19</sup>

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

[See Malignant polyp, rectal cancer appropriate for resection, and pathological stage 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.<sup>21-23</sup>
- **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 colon 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).<sup>24-25</sup>

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[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 (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 stage II colorectal cancers.<sup>11,12,26</sup> 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.<sup>26-34</sup> 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.<sup>30,33</sup> The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade and tumor site.<sup>27</sup> 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,  $p < 0.001$ ).<sup>35,36</sup> 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.<sup>36</sup> 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.<sup>37-39</sup> The 7th edition of the AJCC Cancer Staging<sup>40</sup> 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.<sup>41,42</sup>
- 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.<sup>43-47</sup>
- 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.<sup>37-39,43-47</sup>

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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.<sup>48,49</sup>
- 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.<sup>50</sup>

### 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.<sup>51,52</sup>
- 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. 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).<sup>53-55</sup>

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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**

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## PRINCIPLES OF SURGERY (1 of 3)

### Transanal excision:<sup>1</sup>

- **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 not recommended outside the setting of a clinical trial
  - ▶ Treatment of draining lymphatics by total mesorectal excision
  - ▶ Restoration of organ integrity, if possible
  - ▶ Surgery should be 5-10 weeks following full dose 5 1/2 wk neoadjuvant chemoradiation

- **Total mesorectal excision**
  - ▶ Reduces positive radial margin rate.
  - ▶ Extend 4-5 cm below distal edge of tumors for an adequate mesorectal excision. In distal rectal cancers (ie, < 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<sup>2,3</sup>**
  - ▶ Biopsy or remove clinically suspicious nodes beyond the field of resection if possible.
  - ▶ Extended resection not indicated in the absence of clinically suspected nodes.

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

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

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.<sup>1</sup>
- Complete resection must be feasible based on anatomic grounds and the extent of disease, maintenance of adequate hepatic function is required.<sup>2,3</sup>
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.<sup>4-6</sup> 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.<sup>1</sup> 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.<sup>7</sup>

**Lung**

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.<sup>8-11</sup>
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.<sup>12-15</sup>
- Re-resection can be considered in selected patients.<sup>16</sup>
- 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.<sup>17-20</sup>
- 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.<sup>21</sup> Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.<sup>22</sup>

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

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## PRINCIPLES OF ADJUVANT THERAPY (1 of 2)

Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy. The chemotherapy/RT may be administered either pre or postoperatively. A total of 6 months of perioperative treatment is preferred.

### Postoperative adjuvant chemotherapy for patients receiving preoperative chemotherapy/RT:

- **Simplified biweekly infusional 5-FU/LV (sLV5FU2)<sup>1</sup>**  
Leucovorin 400 mg/m<sup>2</sup> IV over 2 hours on day 1, followed by 5-FU bolus 400 mg/m<sup>2</sup> and then 1200 mg/m<sup>2</sup>/day x 2 days (total 2400 mg/m<sup>2</sup> over 46-48 hours)<sup>†</sup> continuous infusion. Repeat every 2 weeks.
- **Leucovorin 20 mg/m<sup>2</sup> IV over 2 hours on day 1, 5-FU 500 mg/m<sup>2</sup> IV bolus injection 1h after the start of leucovorin. Repeat weekly.<sup>2</sup>**

### Postoperative adjuvant regimens for patients not receiving preoperative therapy:

- **5-FU + leucovorin x 1 cycle, then concurrent chemotherapy/XRT (see below for regimens), then 5-FU/leucovorin x 2 cycles<sup>3</sup>**
  - 5-FU 500 mg/m<sup>2</sup> IV bolus injection one h after the start of the leucovorin infusion, once a wk for 6 wks + leucovorin 500 mg/m<sup>2</sup> IV over 2 h once a wk for 6 wks. A cycle is comprised of 6 wks followed by 2 wks of rest.
- **mFOLFOX 6**  
Oxaliplatin 85 mg/m<sup>2</sup> IV over 2 hours, day 1, leucovorin\* 400 mg/m<sup>2</sup> IV over 2 hours, day 1, 5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, then 1200 mg/m<sup>2</sup>/day x 2 days (total 2400 mg/m<sup>2</sup> over 46-48 hours)<sup>†</sup> continuous infusion.<sup>4</sup> Repeat every 2 weeks to a total of 6 mo perioperative therapy.
- **Capecitabine<sup>5</sup>**  
Capecitabine 1250 mg/m<sup>2</sup> twice daily days 1-14 every 3 wks to a total of 6 mo perioperative therapy.
- **CapeOx<sup>6</sup>**  
Oxaliplatin 130 mg/m<sup>2</sup> over 2 hours, day 1. Capecitabine 1000 mg/m<sup>2</sup> twice daily days 1-14 every 3 wks x 24 wks.

### Dosing Schedules for concurrent chemotherapy/RT:

- **XRT + continuous infusion 5-FU<sup>7</sup>**  
5-FU 225 mg/m<sup>2</sup> over 24 h 5 or 7 d/wk during XRT
- **XRT + 5-FU/leucovorin<sup>8</sup>**  
5-FU 400 mg/m<sup>2</sup> IV bolus + leucovorin 20 mg/m<sup>2</sup> IV bolus for 4 d during wk 1 and 5 of XRT
- **XRT + Capecitabine<sup>9,10</sup> (category 2B)**  
Capecitabine 825 mg/m<sup>2</sup> twice daily 5 or 7 d/wk + XRT x 5 wks

\*While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>.

<sup>†</sup>NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m<sup>2</sup>/day NOT 2400 mg/m<sup>2</sup> over 48 hours) to minimize medication errors.

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

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

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



## PRINCIPLES OF ADJUVANT THERAPY (2 of 2) - REFERENCES

- <sup>1</sup> Andre T, Louvet C, Maindrault-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.
- <sup>2</sup> 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.
- <sup>4</sup> Petrelli 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.
- <sup>4</sup> Cassidy 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.
- <sup>5</sup> Twelves 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.
- <sup>6</sup> 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. Haller DH, et al. *European Journal of Cancer Supplements* 2009;7(3):5 (abstr 5LBA).
- <sup>7</sup> 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.
- <sup>8</sup> 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.
- <sup>9</sup> Krishnan S, Janjan N, Skibber, J, et al. Phase II study of capecitabine and radiation plus concomitant boost in the treatment of locally advanced rectal cancer. *Int J Radiation Oncol Biol Phys* 2006;66:762-71.
- <sup>10</sup> Das P, Lin, E, Bhatia S, et al. Neoadjuvant Chemoradiation with Capecitabine versus Infusional 5-fluorouracil (5-FU) for Locally Advanced Rectal Cancer: a Matched Pair Analysis. *Int J Radiation Oncol Biol Phys* 2006;66:1378-83.

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### PRINCIPLES OF RADIATION THERAPY

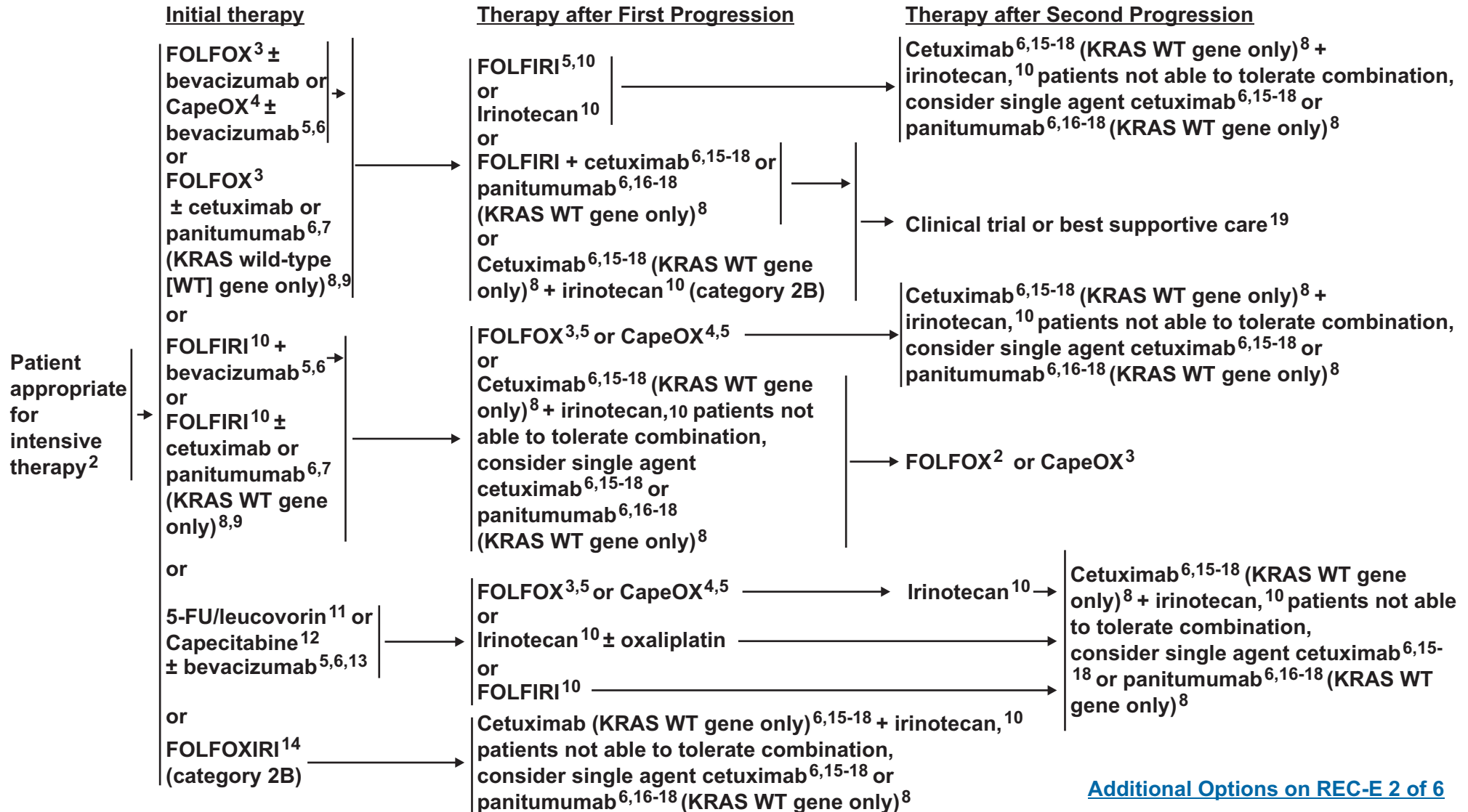
- Radiation therapy fields should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
- Multiple radiation therapy fields should be used (generally a 3 or 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.
- Radiation doses:
  - ▶ 45-50 Gy in 25-28 fractions to the pelvis.
  - ▶ For resectable cancers, after 45 Gy a tumor bed boost with a 2 cm margin of 5.4 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
  - ▶ Small bowel dose should be limited to 45 Gy.
- Intraoperative radiotherapy (IORT), if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. If IORT is not available, 10-20 Gy external beam radiation to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required, 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.
  - All male patients should be evaluated for erectile dysfunction and considered for early treatment intervention if necessary.

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**CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE: <sup>1</sup> (PAGE 1 of 6)**



[Additional Options on REC-E 2 of 6](#)

[See footnotes on page REC-E 3 of 6](#)

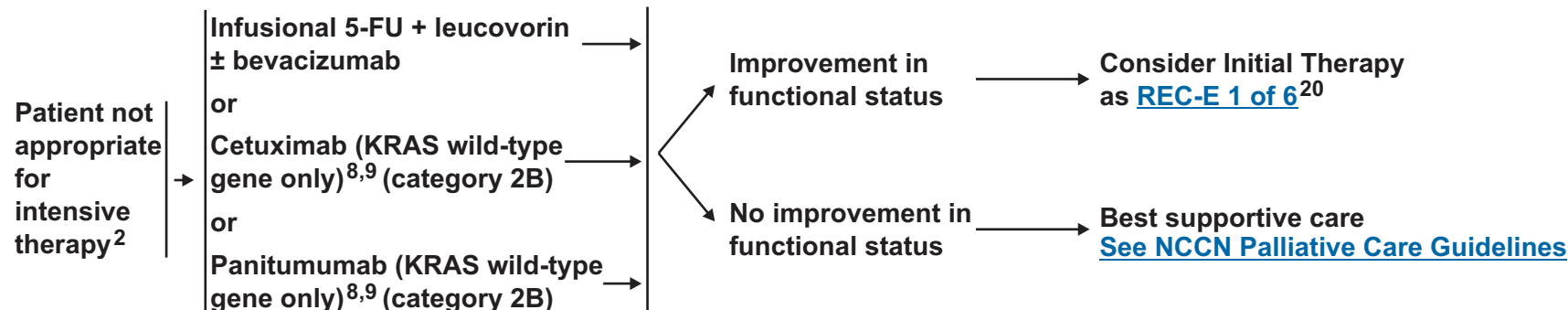
**Note:** All recommendations are category 2A unless otherwise indicated.  
**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



### CONTINUUM OF CARE - CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 2 of 6)

#### Initial therapy

#### Therapy after First Progression



[See footnotes on page REC-E 3 of 6](#)

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**CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 3 of 6)**

- <sup>1</sup>For chemotherapy references, [see Chemotherapy Regimens and References \(REC-E pages 4 - 6\)](#).
- <sup>2</sup>PET-CT should not be used to monitor progress of therapy. CT with contrast or MRI is recommended.
- <sup>3</sup>Discontinuation 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.
- <sup>4</sup>The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1250 mg/m<sup>2</sup> twice daily for 14 days, repeated every 21 days, is standard. Some data suggest that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine. The relative efficacy of CapeOx with lower starting doses of capecitabine has not been addressed in large scale randomized trials. For good performance status patients, the 1000 mg/m<sup>2</sup> twice daily dose is the recommended starting dose, with close monitoring in the first cycle for toxicity, and dose adjustments as indicated.
- <sup>5</sup>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 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.
- <sup>6</sup>Combination 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.
- <sup>7</sup>If cetuximab or panitumumab are used as initial therapy, then neither cetuximab nor panitumumab should be used in second or subsequent lines of therapy.
- <sup>8</sup>[See Principles of Pathologic Review \(REC-A 5 of 6\)](#) - KRAS and BRAF Mutation Testing.
- <sup>9</sup>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.
- <sup>10</sup>Irinotecan should be used with caution and with decreased doses in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for UGT1A1. Guidelines for use in clinical practice have not been established.
- <sup>11</sup>Infusional 5-FU is preferred.
- <sup>12</sup>Patients with diminished creatinine clearance may require dose modification of capecitabine.
- <sup>13</sup>A treatment option for patients not able to tolerate oxaliplatin or irinotecan.
- <sup>14</sup>Data are not mature for the addition of biologic agents to FOLFOXIRI.
- <sup>15</sup>Cetuximab is indicated in combination with irinotecan-based therapy or as single agent therapy for patients who cannot tolerate irinotecan.
- <sup>16</sup>EGFR testing has no demonstrated predictive value, and therefore routine EGFR testing is not recommended. No patient should be included or excluded from cetuximab or panitumumab therapy on the basis of EGFR test results.
- <sup>17</sup>There are no data, nor is there a compelling rationale, to support the use of panitumumab after clinical failure on cetuximab, or the use of cetuximab after clinical failure on panitumumab. As such, the use of one of these agents after therapeutic failure on the other is not recommended.
- <sup>18</sup>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.
- <sup>19</sup>Single agent or combination therapy with capecitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.
- <sup>20</sup>The use of single agent capecitabine as a salvage therapy after failure on a fluoropyrimidine-containing regimen has been shown to be ineffective, and this is therefore not recommended.

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**CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 4 of 6)**

**FOLFOX**

**mFOLFOX 6**

**Oxaliplatin 85 mg/m<sup>2</sup> IV over 2 hours, day 1**

**Leucovorin\* 400 mg/m<sup>2</sup> IV over 2 hours, day 1**

**5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, then 1200 mg/m<sup>2</sup>/day x 2 days (total 2400 mg/m<sup>2</sup> over 46-48 hours)<sup>†</sup> continuous infusion**

**Repeat every 2 weeks<sup>1</sup>**

**CapeOX<sup>1,2</sup>**

**Oxaliplatin 130 mg/m<sup>2</sup> day 1, Capecitabine 850-1000<sup>‡</sup> mg/m<sup>2</sup> twice daily for 14 days**

**Repeat every 3 weeks**

**FOLFIRI<sup>3</sup>**

**Irinotecan 180 mg/m<sup>2</sup> IV over 30-90 minutes, day 1**

**Leucovorin 400 mg/m<sup>2</sup> IV infusion to match duration of irinotecan infusion, day 1**

**5-FU 400 mg/m<sup>2</sup> IV bolus day 1, then 1200 mg/m<sup>2</sup>/day x 2 days (total 2400 mg/m<sup>2</sup> over 46-48 hours)<sup>†</sup> continuous infusion**

**Repeat every 2 weeks**

**Bevacizumab + 5-FU containing regimens:<sup>4-6</sup>**

**Bevacizumab 5 mg/kg IV every 2 weeks +**

**5-FU and Leucovorin**

**or FOLFOX<sup>7</sup>**

**or FOLFIRI**

**Bevacizumab 7.5 mg/kg IV every 3 weeks + CapeOX<sup>2</sup>**

**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)**

\*While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>.

<sup>†</sup>NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m<sup>2</sup>/day NOT 2400 mg/m<sup>2</sup> over 48 hours) to minimize medication errors.

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

[See Additional Chemotherapy Regimens REC-E 5 of 6](#)

[See footnotes on page REC-E 6 of 6](#)

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**CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 5 of 6)**

**Capecitabine<sup>8</sup>**

2000-2500 mg/m<sup>2</sup>/day PO in two divided doses, days 1-14,  
followed by 7 days rest  
Repeat every 3 weeks

**Bolus or infusional 5-FU/leucovorin**

**Roswell-Park regimen<sup>9</sup>**

Leucovorin 500 mg/m<sup>2</sup> IV over 2 hours, days 1, 8, 15, 22, 29, and 36  
5-FU 500 mg/m<sup>2</sup> 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)<sup>3</sup>**

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

**Weekly**

Leucovorin 20 mg/m<sup>2</sup> IV over 2 hours on day 1, 5-FU 500 mg/m<sup>2</sup> IV  
bolus injection 1h after the start of leucovorin. Repeat weekly.<sup>10</sup>  
5-FU 2600 mg/m<sup>2</sup> by 24 h infusion plus leucovorin 500 mg/m<sup>2</sup>  
Repeat every week<sup>11</sup>

**IROX<sup>12</sup>**

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

**FOLFOXIRI<sup>13</sup>**

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

**Irinotecan**

Irinotecan 125 mg/m<sup>2</sup> IV over 30-90 minutes, days 1, 8  
Repeat every 3 weeks<sup>14,15</sup>

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

**Cetuximab (KRAS wild-type gene only) ± irinotecan<sup>16</sup>**

Cetuximab 400 mg/m<sup>2</sup> 1st infusion, then 250 mg/m<sup>2</sup> IV weekly  
or

Cetuximab 500 mg/m<sup>2</sup> IV every 2 weeks<sup>16</sup>

±

Irinotecan 300-350 mg/m<sup>2</sup> IV every 3 weeks

or

Irinotecan 180 mg/m<sup>2</sup> IV every 2 weeks

or

Irinotecan 125 mg/m<sup>2</sup> on days 1, 8 and repeat every 3 weeks

**Cetuximab (KRAS wild-type gene only)<sup>17</sup>**

Cetuximab 400 mg/m<sup>2</sup> 1st infusion, then 250 mg/m<sup>2</sup> IV weekly

**Panitumumab<sup>18</sup> (KRAS wild-type gene only)**

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

\*While used in Europe, levoleucovorin is not approved for colorectal cancer in the United States. Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>.

<sup>†</sup>NCCN recommends limiting chemotherapy orders to 24 h units (ie, 1200 mg/m<sup>2</sup>/day NOT 2400 mg/m<sup>2</sup> over 48 hours) to minimize medication errors.

[See footnotes on page REC-E 6 of 6](#)

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**CHEMOTHERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES (PAGE 6 of 6)**

- <sup>1</sup>Cassidy 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.
- <sup>2</sup>European studies showing equivalent efficacy for CapeOX used at a higher dose; however, European patients consistently tolerate capecitabine with less toxicity than American patients.
- <sup>3</sup>Andre 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.
- <sup>4</sup>Kabbinavar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. *J Clin Oncol*. 2005;23:3706-3712.
- <sup>5</sup>Hurwitz HI, Fehrenbacher L, Hainsworth JD, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. *J Clin Oncol*. 2005;23:3502-3508.
- <sup>6</sup>Reidy DL, Chung KY, Timoney JP, et al. Bevacizumab 5 mg/kg can be infused safely over 10 minutes. *J Clin Oncol* 2007;25:2691-2695.
- <sup>7</sup>Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007;25:1539-44.
- <sup>8</sup>VanCutsem 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.
- <sup>9</sup>Wolmark 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.
- <sup>10</sup>Jäger 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.
- <sup>11</sup>Douillard 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.
- <sup>12</sup>Haller 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.
- <sup>13</sup>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(13):1670-1676.
- <sup>14</sup>Cunningham 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.
- <sup>15</sup>Fuchs 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.
- <sup>16</sup>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.
- <sup>17</sup>Van 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.
- <sup>18</sup>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.

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### PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care (1 of 2)

#### CRC Cancer Surveillance:

- History and Physical every 3-6 months for 2 years, then every 6 months for a total of 5 years.
- CEA every 3-6 months for 2 years, then every 6 months for a total of 5 years.
- CT scan of abdomen and pelvis annually for 3 years.
- Colonoscopy at 1 year, then as clinically indicated.

#### Cancer Screening Recommendations:<sup>1</sup>

##### • Breast Cancer:

- ▶ Periodic self breast exam (SBE) encouraged (optional)
- ▶ Clinical breast exam (CBE) every 1-3 years between ages 20 and 40
- ▶ Annual mammogram with clinical breast exam beginning at age 40.
- ▶ Women at high risk (greater than 20% lifetime risk) should get breast MRI and mammogram annually.
- ▶ See [NCCN Breast Cancer Screening and Diagnosis Guidelines](#)

##### • Cervical Cancer:

- ▶ Annual cervical cytology testing with conventional smears or every 2 years with liquid-based cytology for women up to age 30.
- ▶ After age 30, screening may be every 2-3 years if 3 negative/satisfactory annually cervical cytology tests documented.
- ▶ Alternatively, human papilloma virus (HPV) DNA testing for women age 30 and over, combined with cervical cytology.
- ▶ If cervical cytology and HPV DNA testing both negative, testing may be performed every 3 years.
- ▶ Counseling regarding HPV infection.
- ▶ Women over age 70 with no abnormal testing in last 10 years and 3 normal tests in a row may discontinue screening.
- ▶ Women without a cervix from a total abdominal hysterectomy do not need to be screened.
- ▶ See [NCCN Cervical Cancer Screening Guidelines](#)

##### • Prostate Cancer:

- ▶ Annual prostate specific antigen (PSA) testing and digital rectal exam (DRE) beginning at age 50
- ▶ For high risk men (African-American males and those with a family history of prostate cancer): PSA testing and DRE beginning at age 40.
- ▶ See [NCCN Prostate Cancer Early Detection Guidelines](#)

[Continued](#)

<sup>1</sup>American Cancer Society Guidelines for Early Detection of Cancer:

[http://www.cancer.org/docroot/PED/content/PED\\_2\\_3X\\_ACS\\_Cancer\\_Detection\\_Guidelines\\_36.asp](http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp), Accessed September 21, 2008.

**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 SURVIVORSHIP - Colorectal Long-term Follow-up Care (2 of 3)

### Management of Late Sequelae of Disease or Treatment:<sup>2</sup>

- **Chronic Diarrhea or Incontinence<sup>3-6</sup>**
  - ▶ Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, and protective undergarments.
- **Oxaliplatin-Induced Neuropathy**
  - ▶ Consider the use of analgesics or referral to a pain specialist, for painful, persistent neuropathy.
- **Bone Health After Pelvic Radiation<sup>7</sup>**
  - ▶ Consider monitoring of bone density or evaluation for pelvic fractures with pelvic pain if previously received pelvic radiation
- **Urogenital Dysfunction after Resection and/or Pelvic Radiation<sup>8,9</sup>**
  - ▶ 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.

### Immunizations:<sup>10</sup>

- Annual trivalent inactivated influenza vaccination
- Pneumococcal vaccination with revaccination as appropriate

### Routine Health Monitoring and Screening:

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

[Continued](#)

<sup>2</sup>Schneider EC, Malin JL, Kahn KL, et al. Surviving colorectal cancer. *Cancer* 2007;110:2075-82.

<sup>3</sup>Sprangers MAG, Taal BG, Aaronson NK, et al. Quality of life in colorectal cancer: stoma vs. nonstoma patients. *Dis Colon Rectum* 1995;38:361-369.

<sup>4</sup>Gami B, Harrington K, Blake P, et al. How patients manage gastrointestinal symptoms after pelvic radiotherapy. *Alimentary Pharmacology and Therapeutics* 2003;18:987-94.

<sup>5</sup>DeSnoo 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) 244-51.

<sup>6</sup>McGough C, Baldwin C, Frost C, Andreyev HJN. Role of nutritional intervention in patients treated with radiotherapy for pelvic malignancy. *British Journal of Cancer* 2004;90:2278-87.

<sup>7</sup>Baxter NN, Habermann EB, Tepper JE, et al. Risk of pelvic fractures in older women following pelvic irradiation. *JAMA* 2005;294:2587-93.

<sup>8</sup>Lange MM, Mass CP, Marijnen CAM, et al. Risk factors for sexual dysfunction after rectal cancer treatment. *Eur J Cancer* 2009;45:1578-88.

<sup>9</sup>Lange 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.

<sup>10</sup>Advisory Committee on Immunization Practices. Recommended adult immunization schedule: United States, October 2007–September 2008. *Ann Intern Med*. 2007;147:725-9.

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### PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care (3 of 3)

#### Counseling Regarding Healthy Lifestyle and Wellness:<sup>11-14</sup>

- Screening and counseling to maintain a healthy weight.
- Screening for physical activity and counseling to adopt a physically active lifestyle (Recommended activity: at least 30 minutes or more of moderate to vigorous physical activity at least 5 days of the week).
- Screening and counseling for alcohol use.
- Screening and counseling for tobacco use with emphasis on smoking cessation.
- Counseling regarding healthy diet adoption, with emphasis on plant sources.

#### Prescription for Survivorship and Transfer of Care to Primary Care Physician:<sup>15</sup>

(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.

<sup>11</sup>American Cancer Society Guidelines on Nutrition and Physical Activity for Cancer Prevention, [http://www.cancer.org/docroot/PED/content/PED\\_3\\_2X\\_Diet\\_and\\_Activity\\_Factors\\_That\\_Affect\\_Risks.asp?sitearea=PED](http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED), Accessed September 21, 2008.

<sup>12</sup>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.

<sup>13</sup>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.

<sup>14</sup>Dignam JL, 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;98:1647-54.

<sup>15</sup>Hewitt M, Greenfield S, Stovall E. *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, D.C.:The National Academies Press;2006.

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



**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 <sup>a</sup>
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 <sup>b</sup>
T4b	Tumor directly invades or is adherent to other organs or structures <sup>b,c</sup>

**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

**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
	T1-T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3-T4a	N2b	M0	C	C2
	T4b	N1-N2	M0	C	C3
IVA	Any T	Any N	M1a	-	-
IVB	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.

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## Discussion – Last updated 05/28/10

### NCCN Categories of Evidence and Consensus

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

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

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

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

**All recommendations are category 2A unless otherwise noted.**

### Overview

In 2009 an estimated 40,870 new cases of rectal cancer occurred in the United States (23,580 cases in men; 17,290 cases in women). During the same year, it is estimated that 49,920 people will have died from rectal and colon cancer.<sup>1</sup> 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 during the past 30 years. This decrease may be due to both earlier diagnosis through screening and better treatment modalities.

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

experience), that the recommendation is appropriate. The panel unanimously endorses patient participation in a clinical trial over standard or accepted therapy. This is especially true for cases of advanced disease and for patients with locally aggressive colorectal cancer who are receiving combined modality treatment. The clinical practice guidelines for managing rectal cancer overlap considerably with the [NCCN Colon Cancer Guidelines](#). First-degree relatives of patients with newly diagnosed adenomas<sup>2</sup> or invasive carcinoma<sup>3</sup> are at increased risk for colorectal cancer. Therefore, all rectal cancer patients should be counseled regarding their family history as outlined in the [NCCN Colorectal Screening Guidelines](#).

### TNM Staging

The 7th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual includes a number of modifications to the rectal cancer staging system.<sup>4,5</sup> Similar findings with respect to survival outcomes by TN stage were observed in analyses of colon cancer and rectal cancer databases<sup>6</sup>; hence, these 2 cancers share the same staging system.

In the previous version (6<sup>th</sup> edition) of the AJCC staging system for colon cancer, stage II disease, characterized by the absence of lymph node metastases (ie, N0 disease), was subdivided into IIA and IIB depending on whether the primary tumor was T3 or T4. Stage II disease is now subdivided into IIA (the primary tumor invades through the muscularis propria into pericolorectal tissues), IIB (T4a lesions which directly penetrate the visceral peritoneum) and IIC (T4b lesions where tumor directly invades or is adherent to other organs or structures).

Other changes relate to the classification of satellite tumor deposits. These are now defined by the new site-specific prognostic factor “tumor

deposits” which includes a description of their texture and number, although consideration of prognostic factors is not required for staging. In addition, satellite nodules are included in the definition of the new N1c category (see below).

These changes are supported by an analysis of 35,829 patients with invasive rectal cancer included in the Surveillance Epidemiology and End Results (SEER) colon cancer database from 1992-2004, as well as analyses of pooled data from 3791 patients with rectal cancer.<sup>6,7,8</sup> For example, the relative 5-year survival rate (ie, 5-year survival corrected by age-related morbidity) for node-negative patients with T4a tumors was considerably higher (69.2%) compared with tumors classified as T4b (53.6%).<sup>6</sup>

Based on the analyses described above, stage III disease, previously subdivided into IIIA (T1 to T2, N1, M0), IIIB (T3 to T4, N1, M0), and IIIC (any T, N2, M0), has now been revised to more accurately reflect the complex biologic relationship between the extent of tumor invasion and the number of affected lymph nodes. For example, due to the relatively high survival rates observed for patients with lesions with extensive nodal involvement but no tumor penetration beyond the muscularis propria, T1-2N2 lesions are now classified as either IIIA or IIIB. In addition, T4bN1 disease, formerly stage IIIB disease, is now included under stage IIIC since outcomes for patients with T4bN1 disease were found to be similar to those observed for patients with T3-4,N2 lesions.

The definitions of N1 and N2 disease have also been revised to reflect the prognostic impact of the number of involved regional lymph nodes. For example, N1 lesions (1 to 3 positive regional lymph nodes) have been subdivided into N1a (1 positive lymph node) and N1b (2-3 positive lymph nodes), whereas N2 tumors (4 or more positive regional nodes) is split into N2a (4-6 positive nodes) and N2b (7 or more positive

nodes). In addition, tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis is classified as N1c.

Staging of rectal cancer also includes an assessment of the presence or absence of distant metastases (M) with Stage IV disease characterized by the presence of one or more distant metastases and designated as M1. M1 disease is now dichotomized into M1a and M1b according to whether metastasis is confined to one or more organ(s)/site(s).

The 7<sup>th</sup> edition of the AJCC staging system specifies that the surgeon should score the completeness of the resection as: (1) R0 for complete tumor resection with all margins negative; (2) R1 for incomplete tumor resection with microscopic involvement of a margin; and (3) R2 for incomplete tumor resection with gross residual tumor remaining after resection.

### Pathology

Pathologic staging information is provided by examination of the surgical specimen. Some of the information that should be detailed in the report of the pathologic evaluation of rectal cancer includes: 1) gross description of the tumor and specimen 2) grade of the cancer; 3) depth of penetration and extension to adjacent structures (T); 4) number of regional lymph nodes evaluated and 5) number of positive regional lymph nodes (N); 6) the presence of distant metastases to other organs, the peritoneum of an abdominal structure, or non-regional lymph nodes (M) and 7) the status of proximal, distal, and circumferential (radial) margins.<sup>9,10,11</sup> The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.<sup>12</sup>



The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer.<sup>13</sup> 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, retroperitoneal) and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen which often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.<sup>14</sup> A positive CRM has been defined as tumor less than or equal to 1 mm from the transected margin.<sup>15-18</sup> Accurate pathologic assessment of the CRM of resected rectal tumor specimens is very important since the CRM has been shown to be a strong predictor of both local recurrence and overall survival, and is an important consideration when post-operative treatment decisions are made.<sup>12,19,20</sup> 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 who had received preoperative therapy when these patients were compared with patients undergoing surgery as initial therapy.<sup>21</sup> Additional components of the pathological evaluation of the surgical specimen following a total mesorectal excision (TME) are described under [Surgical Approaches](#).

The number of regional lymph nodes retrieved from a surgical specimen can vary with age of the patient, gender, and tumor grade or site.<sup>22-24</sup> The extent and quality of surgical resection and pathologic review of the specimen can also have an impact on the node harvest.<sup>25</sup> The Panel recommends examination of a minimum of 12 lymph nodes to accurately identify Stage II colorectal cancer. This recommendation is supported by previous statements from CAP,<sup>5</sup> as well as recommendations included in the 7<sup>th</sup> edition of the AJCC staging manual which specifies pathologic examination of a minimum of 10-14 lymph nodes.<sup>4</sup> Nevertheless, the literature lacks consensus regarding

the minimal number of lymph nodes needed to accurately identify stage II rectal cancer. Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Three studies confined only to rectal cancer have reported 14, >10 and 8 lymph nodes as the minimal number to accurately identify stage II rectal cancer.<sup>26-28</sup> Furthermore, the mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy has been reported to be significantly lower than those treated by surgery alone (13 vs 19,  $P < 0.05$ ; 7 vs 10,  $P \leq 0.0001$ ).<sup>29,30</sup> Of note, emerging evidence suggests that a greater number of nodes may need to be examined to provide an adequate assessment of disease stage in some situations.<sup>11</sup> A recent retrospective analysis of data from patients with T3/T4 and/or lymph node-positive rectal cancer enrolled in the Intergroup 0114 trial showed lymph node ratio (LNR), the number of positive lymph nodes divided by the total number, to be a strong predictor of survival.<sup>31</sup> Nevertheless, the panel does not consider determination of LNR to be a substitute for an adequate lymph node evaluation.

Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells, or identification of particular tumor antigens through immunohistochemical (IHC) analysis have been reported.<sup>32,33</sup> Although results of some of these studies seem promising, there is no uniformity in the definition of “true” clinically relevant metastatic carcinoma. Some studies have considered detection of single cells by IHC as well as isolated tumor cells (ITC) to be micrometastasis.<sup>34,35</sup> In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.<sup>36</sup> Presently, the use of sentinel lymph nodes and detection of cancer cells by IHC alone should be considered



investigational and the results should be used with caution in clinical management decisions.

Approximately 40% of colorectal cancers are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.<sup>37</sup> A sizable body of literature has demonstrated that these *KRAS* mutations predict for lack of response to cetuximab or panitumumab therapy.<sup>38-46</sup> The FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of colorectal cancer characterized by these mutations.<sup>47,48</sup> 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 the metastases.<sup>49,50</sup> 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.<sup>51</sup> No specific testing methodology is recommended.<sup>52</sup>

Approximately 5%-8% of colorectal cancers are characterized by a specific mutation in the *BRAF* gene (V600E).<sup>53,54</sup> *BRAF* mutations are, for all practical purposes, limited to those tumors that do not have *KRAS* exon 2 mutations.<sup>54</sup> There is retrospective evidence that a specific mutation in the *BRAF* gene (V600E) is another marker of resistance to anti-EGFR therapy,<sup>54-56</sup> and as of the date of this writing, all reported patients with tumors characterized by known *BRAF* V600E mutations who have received cetuximab or panitumumab in the chemotherapy-refractory setting have failed to respond. Other data from unplanned subset analyses, however, suggest that although a V600E *BRAF* mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this mutation received some benefit from the addition of cetuximab to front-line therapy,<sup>53</sup> nevertheless, the data regarding *BRAF* as a predictor of response (or lack thereof) to anti-EGFR therapy remain inconclusive. Although activation of the protein product of the non-mutated *BRAF* gene occurs downstream of activated k-ras protein in the EGFR pathway, the mutated *BRAF* protein product is believed to be constitutively active, thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab. For patients with *KRAS* wild-type tumors, the panel includes the option of *BRAF* genotyping of tumor tissue (either primary tumor or metastasis)<sup>57</sup> at the time of diagnosis of state IV disease. With respect to technical aspects of *BRAF* gene testing, the specific recommendations regarding tumor tissue sampling described above for *KRAS* gene testing apply. No specific testing methodology is recommended.

## Clinical Presentation and Treatment

### Management of Polypoid Cancer

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or villous adenoma, physicians should



review pathology and consult with the patient.<sup>58</sup> A malignant rectal polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore not considered to be capable of regional nodal metastasis.<sup>5</sup> 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.<sup>58</sup> Favorable histological features include lesions of grade 1 or 2, no angiolymphatic invasion and a negative resection margin.

However, in addition to the option of observation, the panel includes the option of rectal surgery in patients with a completely-removed, single-specimen, sessile polyp with favorable histological features and clear margins because it has been reported that patients with sessile polyps have a 10% risk of lymph node metastases.<sup>59</sup> For pedunculated and sessile polyps, unfavorable histopathological features are: grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. It should be noted that there is currently no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as the presence of tumor within 1-2 mm from the transected margin and the presence of tumor cells within the diathermy of the transected margin.<sup>58,60-62</sup> For a pedunculated or sessile polyp with fragmented specimen or margins that cannot be assessed or unfavorable pathology, either a transanal excision or a transabdominal resection is recommended (See section on [Surgical Approaches](#) used in the management of rectal cancer appropriate for resection). Results from a preoperative endoscopic ultrasound evaluation may provide additional information to guide choice of surgical approach, although

the accuracy of this method to detect residual cancer is limited (see section on Clinical Evaluation/Staging, below).<sup>63</sup> All patients who have resected polyps should undergo total colonoscopy to rule out other synchronous polyps, as well as appropriate follow-up surveillance endoscopy.<sup>64</sup>

### Management of Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge by rigid proctoscopy.<sup>65</sup> Some support for this definition comes from the study of Kapiteijn et al.<sup>66</sup> 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. 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.<sup>67</sup>

Determination of an optimal treatment plan for an individual patient with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative or palliative), consideration must also be given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence, and preserving genitourinary functions. For patients with distal rectal cancer, in particular, the simultaneous achievement of the goals of cure and minimal impact on quality of life can be challenging.<sup>68</sup> 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.<sup>69,70</sup> Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy for selected patients which combines chemoradiation (chemoRT) with operative treatment as part of the treatment regimen is recommended.

### **Clinical Evaluation/Staging**

The initial clinical workup of patients with rectal cancer provides important preoperative information on the clinical stage of disease. Since the clinical stage of the disease is used to direct decisions regarding choice of primary treatment, including surgical intent (eg, curative or palliative) and approaches, and whether to recommend preoperative chemoRT, the implications of either clinically understaging 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)-CT scan is not routinely indicated at baseline. In addition, the accessibility of rectal cancer to evaluation by certain imaging modalities, such as endoscopic ultrasound and magnetic resonance imaging (MRI), makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.<sup>71</sup>

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%).<sup>72</sup> 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.<sup>72,73</sup> 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.,<sup>72</sup> the sensitivities and specificities of the 3 imaging modalities for accurately evaluating lymph node involvement were: CT (55% and 74%); endoscopic ultrasound (67% and 78%); and MRI (66% and 76%). Results from another recent meta-analysis of 84 articles, indicated that none of the 3 imaging modalities were significantly superior to another method with respect to an accurate determination of tumor N-stage.<sup>74</sup> Disadvantages of endoscopic ultrasound and MRI include a high degree of operator dependence.<sup>72</sup> An advantage of MRI is its ability to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia. Hence, MRI evaluation of patients with more advanced rectal cancer has the potential to provide information useful in the prediction of the CRM prior to radical surgery.<sup>73-75</sup>

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.<sup>76</sup> These methods include local procedures, such as polypectomy, transanal excision and transanal microsurgery, and radical procedures involving a transabdominal resection (eg, low anterior resection [LAR], total mesorectal excision [TME] with coloanal anastomosis, or abdominoperineal resection [APR]).

Transanal excision may be appropriate for selected T1 cancers. Small (<3 cm), well to moderately differentiated small tumors that are within 8 cm of the anal verge and limited to less than 30% of the rectal circumference, and for which there is no evidence of nodal involvement (category 2A) can be approached with transanal excision with negative margins. Transanal endoscopic microsurgery (TEM) can facilitate excision of small tumors through the anus that are located higher up in the rectum. Both transanal excision and TEM involve a full thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (> 3 mm) deep and mucosal margins are required. Tumor fragmentation should be avoided. The excised specimen should be oriented and pinned before fixation and brought to the pathologist by the surgeon (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.<sup>68,77</sup> If pathologic examination reveals adverse features such as high grade, positive margins, lymphovascular invasion (LVI) or perineural invasion, a more radical resection is recommended.

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.<sup>78</sup> These observations may underlie the findings of a recent retrospective study of 282 patients undergoing either transanal excision or radical resection for T1 rectal cancer during 1985-2004 which showed respective local recurrence rates of 13.2% and 2.7% (P=0.001) for these 2 groups at a median follow-up of 5.6 years.<sup>79</sup> In addition, positive lymph nodes were found in 20% of the patients undergoing radical resection on pathologic examination of the surgical specimen.

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

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer are limited.<sup>80,81</sup> In the CLASICC trial comparing laparoscopically-assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.<sup>80</sup> 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 which may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically-assisted surgery for colorectal cancer have been described,<sup>82</sup> 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 total mesorectal excision (TME) with coloanal anastomosis is required. A TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a “tumor package” through sharp dissection and is designed to spare the autonomic nerves.<sup>68,83</sup> 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.<sup>84,85</sup> In addition, when a TME is performed, achievement of a mesorectal surgical plane has been reported to be a positive prognostic factor compared with other types of surgical planes (eg, intramesorectal or muscularis propria).<sup>13</sup> 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.<sup>85</sup>

An APR involves en bloc resection of the rectosigmoid, the rectum, and the anus, as well as the surrounding mesentery, mesorectum, and perianal soft tissue and necessitates creation of a colostomy.<sup>86</sup> An APR is necessary in cases where a margin-negative resection of the tumor would result in loss of anal sphincter function resulting in incontinence. Although preoperative chemoRT may result in tumor downsizing and a decrease in tumor bulk (see section on [Neoadjuvant/Adjuvant Therapy](#), below), tumor location is not altered.

Whereas sphincter preservation may become possible in cases where initial tumor bulk prevented consideration of such surgery but exposure to the tumor is improved by chemoRT, an APR should be performed when tumor directly involves the anal sphincter or the levator muscles. Recent comparisons of the outcomes of patients undergoing an APR versus a LAR in the treatment of rectal cancer have shown those treated with an APR to have worse local control and overall survival.<sup>87,88</sup> 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 3633 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.<sup>88</sup>

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.<sup>89</sup> The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.<sup>90</sup> A recent meta-analysis comparing extended lymphadenectomy with conventional surgery for rectal cancer showed a higher rate of urinary and sexual dysfunction in the former group but no difference in 5-year survival, although limitations of the meta-analysis (eg, inclusion of mostly observational studies) preclude a definitive determination of the impact of extended lymphadenectomy on survival.<sup>91</sup> 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.

### 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 (node-negative disease with tumor penetration through the muscle wall) or stage III rectal cancer (node-positive disease without distant metastasis). Use of perioperative pelvic RT in the treatment of patients with stage II/III rectal cancer continues to evolve. Concurrent fluoropyrimidine-based chemotherapy is recommended with radiation.

Ionizing radiation to the pelvis provides local tumoricidal therapy. Putative advantages to preoperative radiation are related to both tumor response and normal tissue.<sup>92,93</sup> Reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected). One disadvantage of using preoperative RT is the possibility of over-treating early-stage tumors which do not require adjuvant

radiation.<sup>93-95</sup> Improvements in preoperative staging techniques, such as endoscopic ultrasound and CT scans, allow for more accurate staging, although the risk of over-staging disease has not been eliminated.<sup>96</sup>

The results of the Swedish Rectal Cancer Trial evaluating the use of short course (5 day) RT administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence with this approach compared with surgery alone.<sup>97</sup> However, whereas a number of other studies investigating the effectiveness of preoperative RT or postoperative RT in patients with rectal cancer staged as T1-3 have demonstrated improvements in local control of disease, overall survival was not shown to be significantly affected.<sup>66,98,99</sup> In a multicenter, randomized study of 1350 patients with stage II/III rectal cancer comparing short-course preoperative RT with a postoperative approach which included chemoRT in selected patients (ie, those with a positive CRM following resection) and no RT in patients without evidence of residual disease following surgery indicated that patients in the preoperative RT arm had significantly lower local recurrence rates and a 6% absolute improvement in 3-year disease-free survival (DFS) (P=0.03).<sup>100</sup> No difference in overall survival has been observed between the 2 arms of the study. Advantages and disadvantages of preoperative short-course RT versus preoperative long-course chemoRT in the treatment of patients with stage II and stage III rectal cancer have been recently reviewed.<sup>101</sup> Currently, however, short-course RT for the treatment of rectal cancer is not widely practiced in the U.S.

A number of randomized trials have evaluated the effectiveness of chemoRT administered either preoperatively following clinical evaluation/staging (eg, T3-4 by endoscopic ultrasound) or postoperatively following pathologic staging of rectal cancer as T3



and/or N1-2. Putative benefits of addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (ie, eradication of micrometastases), whereas preoperative chemoRT also has the potential to increase rates of pathologic complete response and sphincter preservation. In a study of patients with T3/4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative RT alone or preoperative concurrent chemoRT with 5-FU/LV, no difference in overall survival or sphincter preservation was observed in the 2 groups, although patients receiving chemoRT were significantly more likely to exhibit a pathologic complete response (11.4% vs 3.6%;  $P < 0.05$ ) and grade 3/4 toxicity (14.6% vs 2.7%;  $P < 0.05$ ) and less likely to exhibit local recurrence of disease (8.1% vs 16.5%;  $P < 0.05$ ).<sup>102</sup> These conclusions have been supported in a recent systematic review which included 4 randomized controlled trials.<sup>103</sup>

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.<sup>93</sup> Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs 13%;  $P = 0.006$ ) and treatment-associated toxicity, although overall survival was similar in the 2 groups. Preliminary results of a phase III trial that included an evaluation of the addition of chemotherapy to preoperative RT in patients with T3-T4 resectable rectal cancer demonstrated that use of 5-FU/LV chemotherapy enhanced the tumorocidal effect of RT when the 2 approaches were used concurrently. Significant reductions in tumor size, pTN stage, and lymphatic, vascular and perineural invasion rates were observed with use of combined-modality therapy compared with use of RT and surgery without chemotherapy.<sup>104,105</sup> 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.<sup>106</sup> 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.<sup>107</sup> These findings may indicate that patients are more likely to benefit from adjuvant therapy if their disease can be downstaged by chemoRT.

In fact, emerging evidence strongly suggests that the pathologic stage of the surgical specimen following preoperative chemoRT is an important indicator of the likelihood of disease recurrence in patients with locally advanced rectal cancer.<sup>108-110</sup> Results from a number of studies have shown a pathologic complete response (pCR) following such therapy to be associated with a very favorable prognosis in patients with stage II or stage III rectal cancer.<sup>108-111</sup> Hence, use of more intense neoadjuvant chemoRT regimens (ie, regimens involving multiple cytotoxic agents and/or more intense doses of RT) for the purpose of increasing the pCR rate has been a central feature in the design of many of the more recent randomized clinical trials.<sup>112</sup>

Very recently, results from 2 phase III trials involving oxaliplatin-containing preoperative chemoRT regimens in the treatment of patients



with locally advanced rectal cancer have been reported.<sup>113,114</sup> The ACCORD-12 trial randomly assigned 598 patients to preoperative chemoRT with either capecitabine/45 Gy or capecitabine/oxaliplatin (CapeOX)/50 Gy<sup>113</sup> whereas the STAR-01 trial randomized 747 patients to preoperative continuous infusion 5-FU/50.4 Gy or preoperative continuous infusion 5-FU/oxaliplatin/50.4 Gy.<sup>114</sup> Neither trial showed statistically significant differences with respect to the pCR rate when the 2 arms were compared (ie, ypCR rates in ACCORD-12 were 13.9% in the capecitabine alone arm and 19.2% in the CapeOX arm (P=0.09), and 16% in both arms of the STAR-01 trial), although a significant reduction in the positive CRM rate was seen in the oxaliplatin arm of the ACCORD-12 trial. Importantly, both trials showed significant and substantial increases in the rate of grade 3/4 toxicity with the addition of oxaliplatin to preoperative chemoRT. Further follow-up of these studies is needed to determine whether the addition of oxaliplatin is associated with decreased likelihood of distant metastases and improvement in overall survival. The large, ongoing 4-arm NSABP R-04 trial is comparing preoperative RT with either capecitabine or continuous infusion 5-FU with or without oxaliplatin in the treatment of patients with operable rectal cancer. It is anticipated that results of this study will provide a definitive answer regarding the risks and benefits of oxaliplatin as a component of preoperative chemoRT in the treatment of patients with stage II/III rectal cancer. Until and unless these trials demonstrate a benefit, the consensus of the NCCN panel is that use of oxaliplatin with concurrent RT should be regarded as investigational.

Whereas reports from at least one randomized clinical trial has indicated that preoperative chemoRT is associated with increased rates of sphincter preservation in rectal cancer patients,<sup>93</sup> this conclusion has not been supported by 2 recent systematic reviews of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.<sup>115,116</sup>

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.<sup>14,117</sup> 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.<sup>14,118,119</sup> Nevertheless, there is retrospective evidence that the risk of locoregional recurrence is significantly higher in patients with pT3N0 rectal cancer not undergoing RT<sup>120</sup> and that the rate of positive lymph nodes following pathologic review of the surgical specimens is over 20% in patients clinically staged with T3N0 rectal cancer undergoing preoperative chemoRT.<sup>96,121</sup>

With respect to the type of chemotherapy administered concurrently with RT, results from the Intergroup 0114 trial, showed bolus 5-FU as part of adjuvant therapy for rectal cancer to be noninferior to bolus 5-FU plus LV.<sup>118</sup> 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 postoperative 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.<sup>122</sup> 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.<sup>123</sup> Most of the patients in this study had node-positive disease. Preliminary results from an ongoing phase III randomized clinical trial comparing capecitabine to 5-FU in preoperative chemoRT for patients with operable rectal cancer suggest that capecitabine/RT is noninferior to 5-FU/RT in this setting.<sup>124</sup> In addition, 2 large case-control studies have reported comparable results for capecitabine/RT and either continuous infusion 5-FU/RT or bolus 5-FU/LV/RT with respect to tumor downstaging and toxicity profile.<sup>125,126</sup> Finally, results from the ACCORD-12 trial as well as a cross trial comparison of findings from the STAR-01 and ACCORD-12 trials provide support for the efficacy of capecitabine in preoperative chemoRT with respect to local tumor control and safety.<sup>113,114</sup>

Postoperative chemoRT regimens commonly employ a “sandwich” approach – whereby chemotherapy (typically 5-FU based) is administered before and after the chemoRT regimen.<sup>118,122,123</sup> The use of FOLFOX or capecitabine chemotherapy before and after postoperative chemoRT is an extrapolation of the available data in colon cancer.<sup>127,128</sup>

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, with the exceptions of unresectable cancers where doses higher than 54 Gy may be required, and irradiation of the small bowel where the dose should be limited to 45 Gy. Intensity modulated radiotherapy (IMRT) which uses computer-imaging to focus RT to the tumor site and potentially decrease toxicity to normal tissue,<sup>129-131</sup> should be used in

the context of a clinical trial only. As an additional boost, intraoperative radiotherapy (IORT),<sup>132-134</sup> which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment should be considered preoperatively for patients with T4 tumors or recurrent cancers to facilitate resection.

Coordination of preoperative therapy, surgery and adjuvant chemotherapy is important. For patients treated with preoperative chemoRT, the panel recommends an interval of 5-10 weeks following completion of 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,<sup>135-137</sup> 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.<sup>138</sup>

Despite improvements in rates of local recurrence associated with preoperative chemoRT in patients with operable rectal cancer, the rate of distant metastases remains high in this population (ie, 30%-35%).<sup>111</sup> Adjuvant chemotherapy of approximately 4 months duration is recommended for all patients with stage II/III rectal cancer following neoadjuvant chemoRT/surgery regardless of the surgical pathology results (ie, 6 months total duration of pre- and post-operative chemotherapy),<sup>139</sup> although few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer and its role is not well defined.

Evaluation of adjuvant chemotherapy with 5-FU/LV alone versus postoperative RT followed by adjuvant chemotherapy with 5-FU/LV in patients with stage II/III rectal cancer in the National Surgical Breast

and Bowel Project (NSABP) R-02 trial showed a significant decrease in local recurrence rate in the group receiving adjuvant chemotherapy after RT compared to the group receiving adjuvant chemotherapy alone, but no difference in the incidence of distant disease was observed between the 2 groups.<sup>140</sup> Although addition of 5-FU-based chemotherapy to preoperative RT provided a significant local control benefit for patients with clinical stage T3 or T4 resectable rectal cancer enrolled in the European Organization for Research and Treatment of Cancer (EORTC) Radiotherapy Group Trial 22921, no survival differences were observed with the addition of chemotherapy either preoperatively or postoperatively to preoperative RT.<sup>106</sup> Similarly, administration of postoperative chemotherapy did not impact survival for patients receiving preoperative RT (+/- 5-FU-based chemotherapy)..

Most of the support for use of FOLFOX or capecitabine as adjuvant chemotherapy in rectal cancer is an extrapolation from the data available for colon cancer.<sup>127,128</sup> The phase III ECOG E3201 trial is investigating the effect of adding either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) to 5-FU/LV-based adjuvant chemotherapy administered to stage II/III rectal cancer patients following either preoperative or postoperative chemoRT. Early reports indicate that adjuvant FOLFOX can be safely used in this patient population.<sup>141</sup> Nevertheless, the duration of treatment with adjuvant FOLFOX in rectal cancer is still unclear.<sup>142,143</sup> In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX. Some justification for the use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) can be provided when preoperative chemoRT is administered. In addition, the NSABP-07 trial demonstrated similar DFS benefits to those reported in the MOSAIC trial with only 9 cycles of an oxaliplatin-containing adjuvant regimen.<sup>143</sup>

A summary of ongoing clinical trials in early-stage rectal cancer has been presented.<sup>144</sup>

### ***Treatment of Nonmetastatic Rectal Cancer***

#### *Recommendations for patients with T1 and T2 lesions*

Selected T1 and T2 lesions clinically staged as node negative without adverse pathologic features (eg, no lymphovascular invasion [LVI] or perineural invasion; size less than 3 cm; well to moderately differentiated) can be treated with transabdominal resection or transanal excision. No additional therapy is recommended for patients with well-differentiated T1 cancers with negative margins. If pathology review after local excision reveals a poorly differentiated histology, positive margins, or LVI, or the tumor is classified as a T2 lesion, then a transabdominal re-resection should be performed.

For patients with T1 lesions not amenable to local excision, a transabdominal resection is required. No adjuvant therapy is indicated for patients with pathologic findings of T1 or T2 lesions. Patients with pathologic lymph node-negative T3 lesions (pT3, N0, M0) or pathologic lymph node-positive lesions (pT1-3, N1-2) should receive a “sandwich regimen” consisting of adjuvant chemotherapy with 5-FU with or without LV, or FOLFOX, or capecitabine, followed by concurrent 5-FU/RT (continuous infusion or bolus infusion along with LV), or capecitabine/RT (category 2B), then 5-FU with or without LV or FOLFOX or capecitabine. The panel recommends approximately postoperative therapy for a total duration of approximately 6 months.

#### *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 (category 2A), or capecitabine/RT (category 2B). Patients who receive preoperative radiotherapy should undergo transabdominal resection 5-10 weeks following completion of neoadjuvant therapy. The panel recommends approximately 6 months total duration of pre- and postoperative chemotherapy (regardless of surgical pathology results) with 5-FU with or without LV (category 1 for T3, N0 or Tany, N1-2 tumors) or FOLFOX or capecitabine.

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

### *Recommendations for patients with T4 lesions and/or locally unresectable disease*

Patients with T4 and/or locally unresectable disease are treated with preoperative continuous infusional 5-FU/RT, or bolus 5-FU with LV/RT, or capecitabine/RT (category 2B). If possible, resection should be considered following preoperative chemoRT. Adjuvant therapy to

complete 6 months with either 5-FU with or without LV, FOLFOX, or capecitabine is recommended regardless of the surgical pathology results.

### ***Treatment of Metastatic or Recurrent Disease***

There is substantial overlap in the management of patients with metastatic rectal cancer and metastatic colon cancer. Please refer to the corresponding section in the NCCN Colon Cancer Guidelines – Principles of the Management of Metastatic Disease for background information on this topic ([MS-9-MS-14](#)).

It is important to note, however, that some of the treatment approaches for patients diagnosed with rectal cancer and potentially resectable synchronous lung or liver metastases differ relative to those for patients diagnosed with stage IV colon cancer characterized as potentially resectable metastatic disease. In particular, initial treatment options for potentially resectable rectal cancer may 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 three times more likely to develop distant metastases than local recurrence of disease after a median follow-up of over 5 years.<sup>106</sup>

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease.<sup>145</sup> In a single-center study at M D Anderson, rates of 5-year local recurrence were reported to be low (ie, 5-year locoregional control rate of 91%) for patients with rectal cancer treated with surgery and either RT or chemoRT, and 78% of recurrences occurred in the low pelvic and presacral regions.<sup>146</sup> Patients with disease recurrence at the anastomotic site are more likely than those with an isolated pelvic recurrence to be cured following re-resection.<sup>147,148</sup> 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.<sup>147</sup>

### *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. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS* gene, such testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see discussion of *KRAS* and *BRAF* testing on [MS-4](#)).

Initial treatment options for patients with stage IV disease (any T, any N, M1) with resectable liver or lung metastases include: combination chemotherapy for 2-3 months (eg, FOLFOX, CapeOX, or FOLFIRI regimens with or without bevacizumab, FOLFIRI or FOLFOX regimens with or without cetuximab or panitumumab (an EGFR inhibitor should be considered in *KRAS* wild-type tumors only); staged or synchronous resection of metastases and rectal lesion; treatment with continuous infusional 5-FU/pelvic RT, or bolus 5-FU with LV/pelvic RT, or

capecitabine/RT (category 2B). Upfront combination chemotherapy (for 2-3 months) with FOLFOX, CapeOX, or FOLFIRI regimens with or without bevacizumab or cetuximab (*KRAS* wild-type tumors only) can be followed by staged or synchronous resection of metastases and rectal lesion or by chemoRT followed by surgery. The impetus for inclusion of the latter option is upfront systemic treatment with a goal of early eradication of micrometastases followed by consolidating chemoRT for local control of disease prior to surgery. For the 3 groups of patients receiving neoadjuvant therapy, surgery should be performed 5-10 weeks following completion of such treatment.

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).<sup>122,123</sup> The panel acknowledged that not all patients with rectal cancer and resectable liver or lung metastases need to be treated with chemoRT. For example, in the population of patients with pT1-2,N0 disease, the competing risk of distant metastases is considered to be higher than that of locoregional recurrence. Therefore, the panel recommends that these patients receive an active adjuvant chemotherapy regimen (for 6 months) for advanced disease, with the exception of FOLFOXIRI. Adjuvant therapy recommendations for patients who have received neoadjuvant chemoRT only is as described for patients with pT1-2,N0 disease (except total duration of pre- plus postoperative chemotherapy should be 6 months), whereas patients who have undergone preoperative bevacizumab- or cetuximab (*KRAS* wild-type tumors only)-containing therapy should receive postoperative



chemoRT as described above for patients with pT3-4, Any N, or Any T, N1-2 disease (except total duration of pre- plus postoperative chemotherapy should be 6 months). Those patients undergoing preoperative bevacizumab- or cetuximab-containing therapy followed by preoperative chemoRT should not receive postoperative chemotherapy.

#### *Recommendations for Treatment of Synchronous Metastases/Unresectable Disease*

Patients with any unresectable or medically inoperable metastases are treated according to whether they are symptomatic or asymptomatic. Symptomatic patients are treated with chemotherapy alone or combined modality therapy with 5-FU/RT or capecitabine/RT (category 2B), resection of the involved rectal segment or laser canalization or diverting colostomy or stenting. 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 (eg, choice of FOLFIRI, FOLFOX, or CapeOX chemotherapy with or without bevacizumab, or FOLFOX or FOLFIRI regimens with or without cetuximab or panitumumab (an EGFR inhibitor should be considered in *KRAS* wild-type tumors only) or FOLFOXIRI alone (category 2B for FOLFOXIRI) 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,<sup>149</sup> 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 one to two weeks, and routine palliate resection of a synchronous primary lesion should not be done in the absence of overt, serious symptoms.<sup>150</sup> 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 [Treatment of Metastatic Disease](#)). Post-treatment follow-up for patients classified as stage IV and no evidence of disease (NED) is described in the section on [Post-Treatment Surveillance](#).

Patients with unresectable metastatic disease not responding to preoperative therapy should receive chemotherapy for advanced or metastatic disease 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 liver-directed therapies, such as arterial radioembolization therapy with yttrium-90 microspheres, due to limited evidence<sup>151</sup> and different



institutional practice patterns. For select patients with chemotherapy resistant/refractory disease characterized by predominant liver metastases and no obvious systemic disease, use of this intervention was supported by some panel members but not others (category 3). The consensus of the panel is that conformal external radiation therapy may be considered in highly selected cases or in the setting of a clinical trial; it should not be used indiscriminately in patients with potentially resectable disease.

#### *Recommendations for Treatment of Metachronous Metastases*

Routine use of PET-CT to monitor for disease recurrence is not recommended. It should be noted that the CT that accompanies a “PET-CT” is a non-contrast CT, and thus not of ideal quality for routine surveillance. Upon documentation on dedicated contrast-enhanced CT or MRI of metachronous metastases in which disease is or may become potentially resectable, characterization of the extent of disease by PET-CT scan may be considered. PET-CT 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.<sup>152</sup> As with other first identifications of metastatic disease, a tumor sample (metastases or original primary) should be sent for *KRAS* genotyping in order to define whether anti-EGFR agents can be considered in the list of potential options for this patient. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS* gene, such testing is currently optional and not a necessary part of decision-making regarding use of anti-EGFR agents (see discussion of *KRAS* and *BRAF* testing on [MS-4](#)). 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. Patients with resectable disease 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 2-3 months followed by resection and additional postoperative chemotherapy for a total duration of pre- plus postoperative chemotherapy for up to 6 months based on response to the neoadjuvant regimen; observation is also an option for patients without a response to neoadjuvant therapy. For example, the same chemotherapy regimen used in the neoadjuvant setting should be repeated postoperatively for patients with a preoperative disease response to such therapy. However either an alternative active chemotherapy regimen or observation is an option in the postoperative setting for patients not responding to neoadjuvant therapy.

Patients determined by cross-sectional imaging or PET-CT scan to have unresectable (including those considered to 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 or panitumumab (an EGFR inhibitor should be considered for *KRAS* wild type tumors only). Patients potentially convertible to resectability should be re-evaluated for disease conversion to a resectable status every 2 months; those

with chemotherapy-responsive disease who are converted to a resectable state should undergo resection followed by postoperative therapy as described above for patients with resectable disease and a history of previous chemotherapy. In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) 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 2-3 months. PET-CT scans are not recommended for routine monitoring of the progression of metastatic disease.

Isolated pelvic/anastomotic recurrence is optimally managed by preoperative RT and concurrent infusional 5-FU, if full course RT was not given previously. Resection followed by the option of IORT should be considered if it can be safely delivered.<sup>145,153</sup> However, debulking, resulting in gross residual cancer, is discouraged. Patients with unresectable lesions are treated 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.<sup>154,155</sup> 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.

### **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,<sup>147,148</sup> although the optimal timing for surveillance of the rectal anastomosis is not known.

Following curative-intent surgery, post-treatment surveillance of patients with colorectal cancer is performed to evaluate for possible therapeutic complications, discover a recurrence that is potentially resectable for cure, 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 studies<sup>156-158</sup> and in 3 recent meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.<sup>159-162</sup> Other recent studies impacting on the issue of post-treatment surveillance of colorectal cancer include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials which demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor,<sup>163</sup> and a population-based report indicating increased rates of resectability and survival in patients treated for local recurrence



and distant metastases of colorectal cancer, thereby providing support for more intensive post-treatment follow-up in these patients.<sup>164</sup> Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative colorectal cancer surgery.<sup>165,166</sup>

The following panel recommendations for post-treatment surveillance pertain to patients with stage I-stage III disease who have undergone successful treatment (i.e. no known residual disease): history and physical examination every 3-6 months for 2 years, and then every 6 months for a total of 5 years; and a CEA test at baseline and every 3-6 months for 2 years,<sup>167</sup> then every 6 months for the next 5 years for patients with disease staged as T2 or greater.<sup>162,167,168</sup> Colonoscopy is recommended at approximately 1 year following resection (or at approximately 6 months post resection if not performed preoperatively due to 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.<sup>169</sup> More frequent colonoscopies may be indicated in patients who present with colorectal cancer before age 50. 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. Chest, abdominal and pelvic CT scans are recommended annually for the first 3 to 5 years in Stage II and III patients.<sup>162,165</sup> Routine PET-CT scanning is not recommended and should 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 (i.e. can be seen once every 6 months). This principle also applies to CEA testing,<sup>170</sup> 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.<sup>167</sup> 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,<sup>171</sup> 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.<sup>169</sup> 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.<sup>162,165</sup> Furthermore, PET-CT scan is not routinely recommended to detect metastatic disease in the absence of other evidence of such disease.<sup>165</sup>

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. A survivorship care plan for patients with rectal cancer has recently been published.<sup>172</sup>

Other recommendations include monitoring for late sequelae of rectal cancer or the treatment of rectal cancer, such as: chronic diarrhea or incontinence (eg, patients with stoma)<sup>173</sup>; persistent neuropathy - a well known side effect of oxaliplatin treatment<sup>127</sup>; and pelvic pain/pelvic fractures; and urogenital dysfunction following resection or pelvic irradiation.<sup>174-177</sup> Specific management interventions to address these side effects are described in a recent review.<sup>178</sup> In addition, a summary of strategies for managing sexual dysfunction in survivors of colorectal cancer is available.<sup>179</sup>

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  $\geq 35$  kg/m<sup>2</sup> had an increased risk of disease recurrence and death.<sup>180</sup> 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.<sup>181</sup> 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.<sup>182</sup> In addition, a recent study of a large cohort of men treated for stage I-stage III colorectal cancer demonstrated an association between increased physical activity and lower rates of colorectal cancer-specific mortality and overall mortality.<sup>183</sup> A discussion of lifestyle characteristics which 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

Managing patients with an elevated CEA level after resection should include colonoscopy, chest, abdominal, and pelvic CT scans, and consideration of a PET-CT scan. If imaging study results are normal in the face of a rising CEA, a PET-CT scan should be considered 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-CT scan in the scenario of an elevated CEA with negative, good-quality CT scans was divided (ie, some panel members favored use of PET-CT in this scenario while others noted that the likelihood of PET-CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). Use of PET-CT scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called “blind” or “CEA-directed” laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,<sup>184</sup> 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. Selected patients with T1 tumors lesions that are node-negative by endorectal ultrasound or endorectal or pelvic MRI and who meet carefully defined criteria can be managed with a transanal excision. A



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

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

Recommendations for patients with previously untreated disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or

metastatic disease depend on whether or not the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOX, and FOLFOXIRI (category 2B). Addition of a biologic agent (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 or accepted therapy.

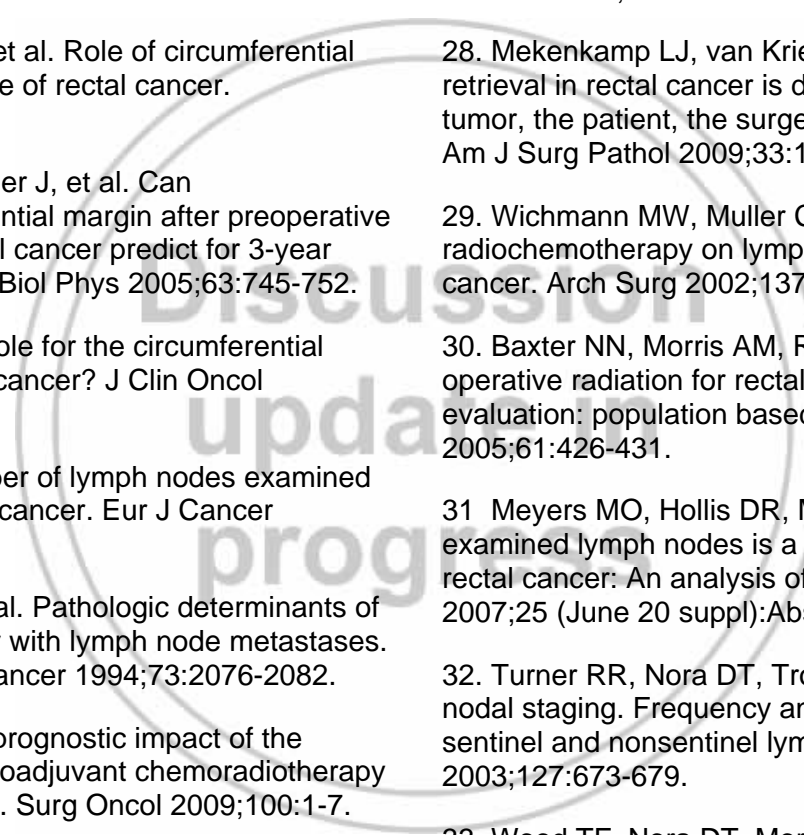


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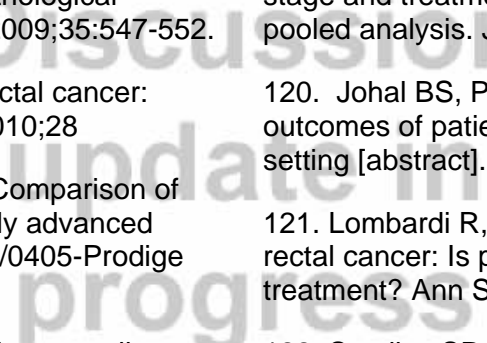
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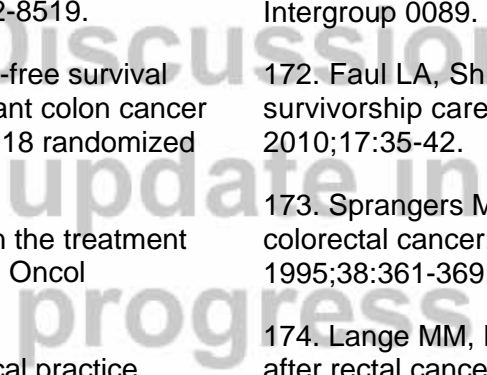
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