

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

# **Rectal Cancer**

Version 3.2017 — March 13, 2017

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## Rectal Cancer

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§ Radiotherapy/Radiation oncology	¶ Diagnostic/Interventional radiology
¶ Surgery/Surgical oncology	≠ Gastroenterology
≠ Pathology	¥ Patient advocate
‡ Hematology/Hematology oncology	* Discussion Section Writing Committee



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

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical\\_trials/physician.html](#).

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

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

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Updates in Version 3.2017 of the NCCN Guidelines for Rectal Cancer from Version 2.2017 include:

### [REC-8](#)

• The following footnotes removed:

- ▶ Meyerhardt JA, Mangu PB, et al. American Society of Clinical Oncology. J Clin Oncol 2013 Dec 10;31(35):4465-4470.
- ▶ CT scan may be useful for patients at high risk for recurrence (eg, lymphatic or venous invasion by tumor; poorly differentiated tumors).

### [REC-10](#)

• The following footnote removed: There are limited data to support a specific treatment regimen in this setting. (also applies to REC-11)

### [REC-11](#)

• Footnote “cc” modified: ~~Evidence increasingly suggests that~~ BRAF V600E mutation makes response to panitumumab or cetuximab, ~~as single agents or in combination with cytotoxic chemotherapy~~, highly unlikely. (also applies REC-E 6 of 10)

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

• The following footnote removed: NCCN recommends limiting chemotherapy orders to 24-hour units (ie, 1200 mg/m<sup>2</sup>/d NOT 2400 mg/m<sup>2</sup> over 48 hours) to minimize medication errors. (also applies to REC-E 7 of 10, REC-E 8 of 10, REC-E 9 of 10)

### [REC-E 1 of 10](#)

• Initial Therapy: 5-FU/leucovorin clarified with the addition of “infusional preferred”.

### [REC-E 6 of 10](#)

• The following footnotes removed:

- ▶ Discontinuation of oxaliplatin should be strongly considered from FOLFOX or CAPEOX after 3–4 months of therapy (or sooner if significant neurotoxicity develops ≥ 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 no data to support the routine use of Ca/Mg infusion to prevent oxaliplatin-related neurotoxicity and therefore it should not be done.
  - ▶ 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.
  - ▶ There is an increased risk of stroke and other arterial events, especially in those aged ≥65 years. The use of bevacizumab may interfere with wound healing.
  - ▶ 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.
  - ▶ There is a preponderance of data to suggest lack of activity of cetuximab and panitumumab in initial therapy for patients whose primary tumors originated on the right side of the colon.
  - ▶ Infusional 5-FU is preferred.
  - ▶ Patients with diminished creatinine clearance may require dose modification of capecitabine.
  - ▶ EGFR testing has no demonstrated predictive value; 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.
  - ▶ 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.
  - ▶ Single-agent or combination therapy with capecitabine, mitomycin, or gemcitabine has not been shown to be effective in this setting.
- Footnote “5” modified: 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.

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Updates in Version 2.2017 of the NCCN Guidelines for Rectal Cancer from Version 1.2017 include:

### [REC-7](#)

- Qualifier "(not recommended for T4 tumors)" add to "Short-course RT".

### [REC-9](#)

- Isolated pelvic/anastomotic recurrence: Capecitabine + RT added as a treatment option.

Updates in Version 1.2017 of the NCCN Guidelines for Rectal Cancer from Version 2.2016 include:

### General

- Imaging recommendations clarified with anatomy and contrast.
- Advanced or Metastatic Disease: "Chemotherapy" changed throughout to "Systemic therapy."
- T3-4, N0 or T any, N1-2, Medical contraindication to combined modality therapy (was REC-6) page was deleted.

### [MS-1](#)

- The discussion section was updated to reflect the changes in the algorithm.

### [REC-2](#)

- Workup: Pelvic MRI with contrast noted as "preferred."
- Workup: "Proctoscopy" removed.

### [REC-3](#)

- This page now addresses adjuvant treatment after local excision.
- The option for "transabdominal resection after chemo/RT" was removed and replaced with the options of "Consider observation if complete response or transabdominal resection or consider FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine."
- The following footnotes were added: (also applies to REC-4)
  - ▶ Footnote "o": "Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection." (Also applies to REC-5, REC-6, REC-10, and REC-11)
  - ▶ Footnote "p": "A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven."

### [REC-4](#)

- This page now addresses adjuvant treatment after transabdominal resection (previously on page REC-3)
- pT3-4, N0, M0: the following treatment options were added: "Observation or Chemotherapy: FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine."

### [REC-5](#)

- Adjuvant treatment following chemo/RT: FLOX removed as a treatment option.
- Footnote removed: "Postoperative therapy is indicated in all patients who receive preoperative therapy, regardless of the surgical pathology results."

### [REC-6](#)

- The combination regimens with bevacizumab, cetuximab, or panitumumab were removed, along with their corresponding footnotes.
- Neoadjuvant Treatment
  - ▶ Short-course RT was added as a treatment option except for T4 tumors. Further therapy includes staged or synchronous resection (preferred) and/or local therapy for metastases and resection of rectal lesion followed by "FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine."

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Updates in Version 1.2017 of the NCCN Guidelines for Rectal Cancer from Version 2.2016 include:

### [REC-6](#)

- **Primary Treatment:** Short-course RT added as a treatment option except for T4 tumors.
- **Adjuvant Treatment following Chemo/RT and resection:**
  - Recommendations changed from "Chemotherapy as per REC-E" to "FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine."
- **Footnote "u" clarified:** "Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver *or lung* oligometastases." (also applies to REC-10)

### [REC-7](#)

- **Primary treatment:** "Laser recanalization" removed.
- "Short-course RT" added as a treatment option.

### [REC-8](#)

- **Surveillance options differentiated based on stage.**
  - The following added: "Stage I with full surgical staging" with colonoscopic surveillance
- **Other stages:** "routinely" removed from PET/CT scan is not recommended.
- **Footnote "w":** reference updated to "Meyerhardt JA, Mangu PB, et al. American Society of Clinical Oncology. J Clin Oncol 2013 Dec 10;31(35):4465-4470."

### [REC-10](#)

- **Primary Treatment**
  - **No previous chemotherapy:** Neoadjuvant chemotherapy with FLOX or Capecitabine or 5-FU/leucovorin changed from a category 2A to a category 2B.
  - **Previous chemotherapy:** Neoadjuvant chemotherapy recommendations changed from "Chemotherapy as per REC-E" to "FOLFOX (preferred) or CAPEOX (preferred) or FLOX or Capecitabine or 5-FU/leucovorin."
- **Adjuvant Treatment**
  - **No growth on neoadjuvant chemotherapy:** "Observation" added as an option.
  - **Growth on neoadjuvant chemotherapy:** "~~Systemic chemotherapy~~ *Systemic chemotherapy ± biologic therapy (REC-E) (category 2B for biologic therapy).*"
  - **Previous chemotherapy:** Adjuvant therapy after resection clarified as "~~Systemic chemotherapy~~ *Systemic chemotherapy ± biologic therapy (REC-E) (category 2B for biologic therapy).*"
- **Surveillance added with a link to REC-8.** (also applies to REC-11)
- **Footnote "dd" added:** "There are limited data to support a specific treatment regimen in this setting." (also applies to REC-11)

### [REC-11](#)

- **Adjuvant treatment clarified as** "~~Systemic chemotherapy~~ *Systemic chemotherapy ± biologic therapy (REC-E) (category 2B for biologic therapy).*"
- **For patients with deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) tumors,** nivolumab or pembrolizumab were added as treatment options in subsequent therapy for patients appropriate for intensive therapy.
- **Surveillance moved to REC-8.**





# NCCN Guidelines Version 3.2017 Updates

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Updates in Version 1.2017 of the NCCN Guidelines for Rectal Cancer from Version 2.2016 include:

### [REC-A 1 of 6](#)

- Endoscopically Removed Malignant Polyps, bullet 3 modified with addition of 3rd sentence: "In several studies, tumor budding has been shown to be an adverse histological feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps."

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

- Pathologic Stage, sub-bullet 4 modified: "Status of proximal, distal, ~~and circumferential (radial) margins~~, and mesenteric margins.
- Pathologic Stage, sub-bullet 10 modified: ~~Extranodal~~ Tumor deposits. (also applies to REC-A 3 of 6)
- Pathologic stage, sub-bullet removed: "A positive circumferential resection margin (CRM) has been defined as  $\leq 1$  mm."

### [REC-A 4 of 6](#)

- Lymph node evaluation, first sentence modified: "The AJCC and CAP recommend examination of a minimum of 12 lymph nodes to accurately identify stage II colorectal cancer."

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

- Microsatellite Instability (MSI) and Mismatch Repair (MMR) Testing
  - ▶ Bullet 1 changed from "Lynch syndrome tumors screening (ie, IHC for MMR or PCR for MSI)\* should be performed for all patients with colorectal cancer diagnosed at age  $\leq 70$  y and also those  $>70$  y who meet the Bethesda guidelines. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal" to "Universal MMR or MSI testing is recommended in all patients with a personal history of colon or rectal cancer. [See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#)"
  - ▶ Bullet 3 modified: ~~"MMR or MSI testing should also be performed for all patients with stage II disease, because Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy."~~
  - ▶ Bullet 4 added: "MMR or MSI testing should be performed only in CLIA-approved laboratories."
  - ▶ Bullet removed: "MMR or MSI testing should also be performed for all patients with metastatic disease."

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

- Liver, bullet 7 changed from "Some institutions use arterially directed embolic therapy (category 3) in highly selected patients with chemotherapy-resistant/-refractory disease, without obvious systemic disease, with predominant hepatic metastases" to "Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases."
- Lung, bullet 5 added: "Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection."

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

- CAPEOX dosing modified with the removal of timing for oxaliplatin over 2 hours.
- Footnote "\*" modified with updated reference.
- Footnote "#" added for capecitabine: "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."



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Updates in Version 1.2017 of the NCCN Guidelines for Rectal Cancer from Version 2.2016 include:

### [REC-D](#)

- Bullet 7, first sentence modified: "Intraoperative radiation therapy (IORT), if available, ~~should~~*may* be considered for very close or positive margins after resection, as an additional boost, especially patients with T4 or recurrent cancers."
- Bullet 10 added: "Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases."
- Bullet 11, first sentence modified: "In patients with a limited number of liver or lung metastases, radiotherapy *to the metastatic site* 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 3-D conformal radiation therapy, IMRT, or stereotactic body radiation therapy (SBRT) ~~(category 3).~~"

### [REC-E](#)

- The pages for the Continuum of Care - Systemic ~~Chemo~~Therapy for Advanced or Metastatic Disease reorganized to address first-line therapy and then subsequent therapy based on previous therapy.
- For patients with deficient mismatch repair (dMMR) or microsatellite instability-high (MSI-H) tumors, nivolumab or pembrolizumab were added as treatment options in subsequent therapy for patients appropriate for intensive therapy.

### [REC-E 2 of 10](#)

- This page now addresses subsequent therapy options for patients receiving oxaliplatin-based therapy without irinotecan as initial therapy.

### [REC-E 3 of 10](#)

- This page now addresses subsequent therapy options for patients receiving irinotecan-based therapy without oxaliplatin as initial therapy.

### [REC-E 4 of 10](#)

- This page now addresses subsequent therapy options for patients receiving FOLFOXIRI as initial therapy.

### [REC-E 5 of 10](#)

- This page now addresses subsequent therapy options for patients receiving fluoropyrimidine without oxaliplatin or irinotecan as initial therapy.

### [REC-E 6 of 10](#)

- Footnote "2" modified: "~~CT with contrast or MRI is recommended.~~ *Chest/Abdominal/Pelvic CT with contrast or Chest CT and Abdominal/Pelvic MRI with contrast* to monitor progress of therapy. PET/CT should not be used."
- Footnote "9" added: "There is a preponderance of data to suggest lack of activity of cetuximab and panitumumab in initial therapy for patients whose primary tumors originated on the right side of the colon."
- Footnote "17" modified: "*Cetuximab or panitumumab are recommended* ~~is indicated~~ in combination with irinotecan-based therapy or as a single-agent for patients who cannot tolerate irinotecan."
- Footnote "20" modified: "Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens ~~(eg, KRAS/NRAS mutant or KRAS/NRAS WT with previous exposure to anti-EGFR inhibitor.)~~"





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Updates in Version 1.2017 of the NCCN Guidelines for Rectal Cancer from Version 2.2016 include:

### [REC-E 7 of 10](#)

- Regimen added: mFOLFOX7 (Oxaliplatin 85 mg/m<sup>2</sup> IV day 1; Leucovorin 400 mg/m<sup>2</sup> IV day 1; 5-FU 1200 mg/m<sup>2</sup>/d x 2 days [total 2400 mg/m<sup>2</sup> over 46–48 hours]) IV continuous infusion. Repeat every 2 weeks.
- CAPEOX dosing modified with the removal of 850 mg for capecitabine and removal of timing for oxaliplatin over 2 hours.
- Footnote “\*” modified with updated reference. (also applies to REC-E 8 of 10)
- Footnote “‡” modified with the removal of the following sentence: "The relative efficacy of CAPEOX with lower starting doses of capecitabine has not been addressed in large-scale randomized trials."

### [REC-E 9 of 10](#)

- Dosing recommendations were added for pembrolizumab and nivolumab.

### [REC-E 10 of 10](#)

- References 4, 30, 31 added. Reference 18 updated.

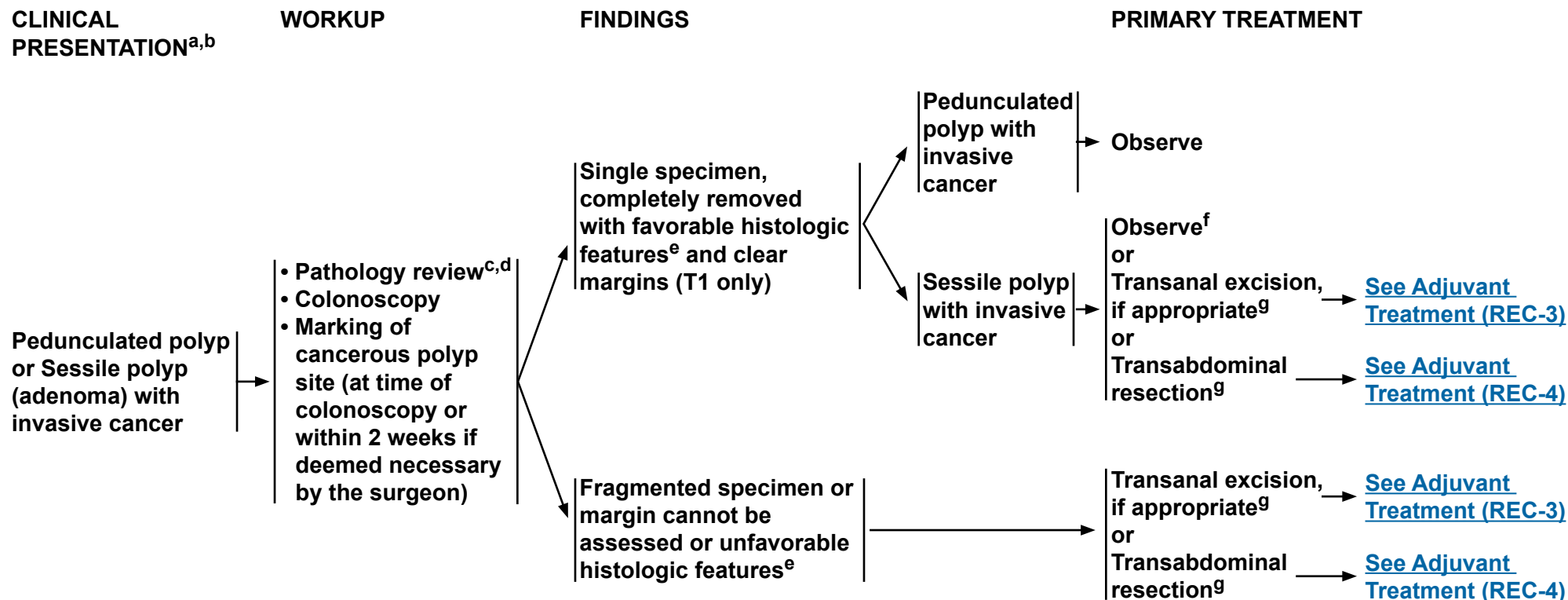
### [REC-F 1 OF 2](#)

- Management of Late Sequelae of Disease or Treatment
  - Link added to the NCCN Guidelines for Survivorship.
  - "Pelvic floor rehabilitation" added as an intervention for chronic diarrhea or incontinence.
  - "Oxaliplatin-induced neuropathy" added with intervention: "Consider duloxetine for painful neuropathy."
  - "Fatigue" added with intervention: "Encourage physical activity, energy conservation measures."
  - "Potential for pelvic fractures/decreased bone density after pelvic radiation" added with intervention: "Consider bone density monitoring."
- "Survivorship Care Planning" added with the following revisions:
  - Addition: "The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to patient."
  - Removal: "Prescription for Survivorship and Transfer of Care to Primary Care Physician (If primary physician will be assuming cancer surveillance responsibilities):"
  - Addition: "Develop survivorship care plan that includes:"
    - ◊ Sub-bullet 1 modified: ~~"Include Overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received."~~
    - ◊ Sub-bullet 2 modified: ~~"Description of possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment."~~
    - ◊ Sub-bullet 3 modified: ~~"Include Surveillance recommendations."~~
    - ◊ Sub-bullet 5 added: "Health behavior recommendations."
- Counseling Regarding Healthy Lifestyle and Wellness
  - Bullet 3 modified: "Consume a healthy diet with emphasis on plant sources. *Diet recommendations may be modified based on severity of bowel dysfunction.*"
  - Bullet 4 added: "Consider low-dose aspirin."



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<sup>a</sup>All patients with rectal cancer should be counseled for family history. Patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

<sup>b</sup>For melanoma histology, see the [NCCN Guidelines for Melanoma](#).

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

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

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

<sup>g</sup>[See Principles of Surgery \(REC-B\)](#).

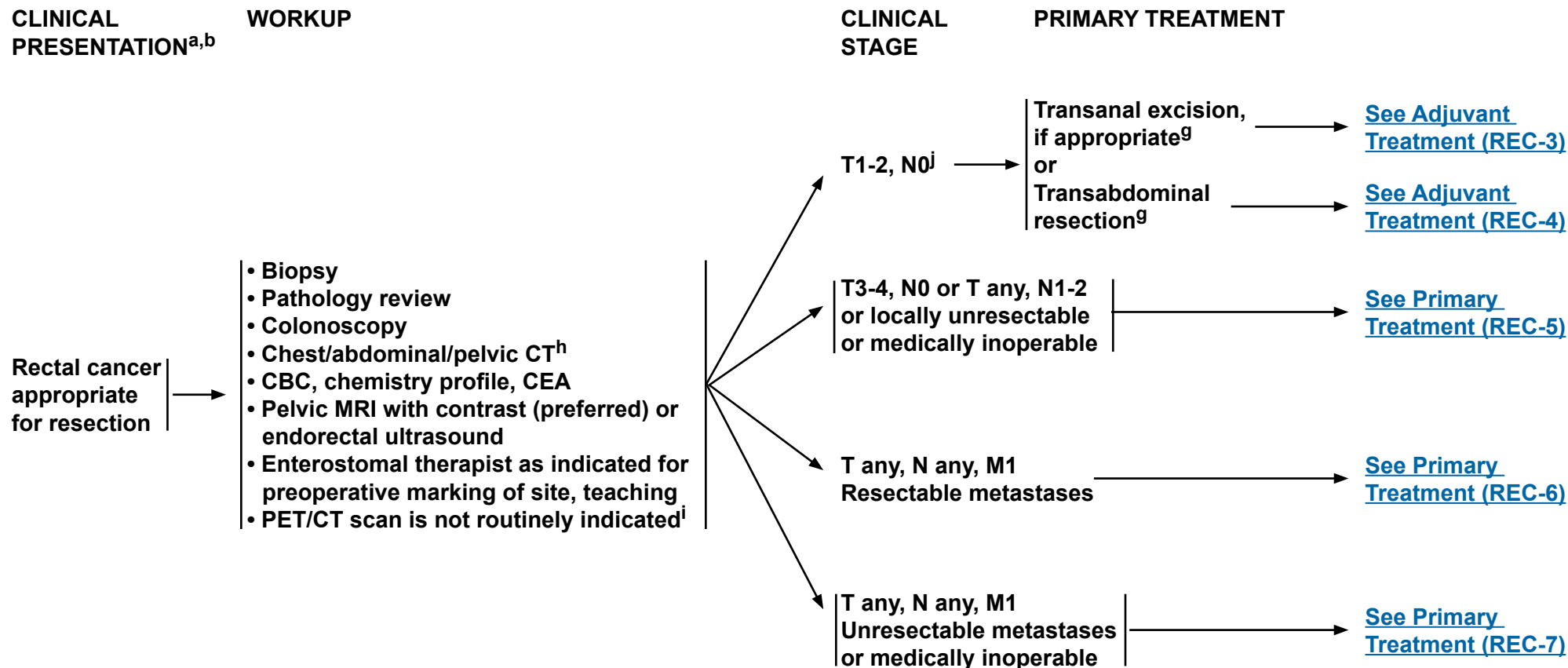
**Note:** All recommendations are category 2A unless otherwise indicated.

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



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<sup>b</sup>For melanoma histology, see the [NCCN Guidelines for Melanoma](#).

<sup>g</sup>See [Principles of Surgery \(REC-B\)](#).

<sup>h</sup>CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

<sup>i</sup>PET/CT does not supplant a contrast-enhanced diagnostic CT scan. PET/CT should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or in patients with strong contraindications to IV contrast.

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

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

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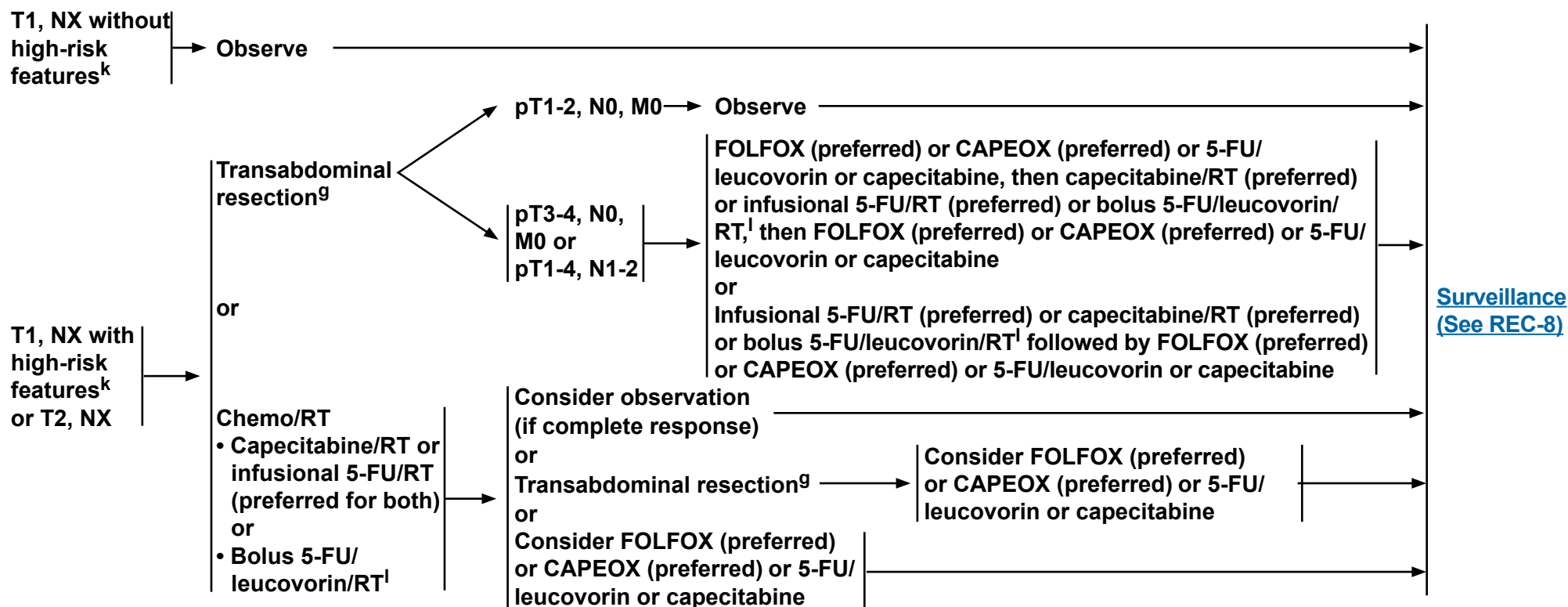


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### FINDINGS AFTER TRANSANAL EXCISION

### ADJUVANT TREATMENT<sup>m,n,o</sup> (6 MO PERIOPERATIVE TREATMENT PREFERRED)<sup>p</sup>


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

<sup>k</sup>High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion.

<sup>l</sup>Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

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

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

<sup>o</sup>Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.

<sup>p</sup>A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

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# NCCN Guidelines Version 3.2017

## Rectal Cancer

### FINDINGS AFTER TRANSABDOMINAL RESECTION FOR cT1-2, N0

### ADJUVANT TREATMENT<sup>m,n,o</sup> (6 MO PERIOPERATIVE TREATMENT PREFERRED)<sup>p</sup>

pT1-2, N0, M0

Observe

pT3-4, N0, M0

Observation  
or  
Chemotherapy:  
FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine  
or  
FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine, then  
capecitabine/RT (preferred) or infusional 5-FU/RT (preferred) or bolus 5-FU/leucovorin/RT,<sup>l</sup>  
then FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine  
or  
Infusional 5-FU/RT (preferred) or capecitabine/RT (preferred) or bolus 5-FU/leucovorin/RT<sup>l</sup>  
followed by FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine

pT1-4, N1-2

FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine, then  
capecitabine/RT (preferred) or infusional 5-FU/RT (preferred) or bolus 5-FU/leucovorin/  
RT,<sup>l</sup> then FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine  
or  
Infusional 5-FU/RT (preferred) or capecitabine/RT (preferred) or bolus 5-FU/leucovorin/  
RT<sup>l</sup> followed by FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or  
capecitabine

[Surveillance  
\(See REC-8\)](#)

<sup>l</sup>Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

<sup>m</sup>See [Principles of Adjuvant Therapy \(REC-C\)](#).

<sup>n</sup>See [Principles of Radiation Therapy \(REC-D\)](#).

<sup>o</sup>Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.

<sup>p</sup>A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.

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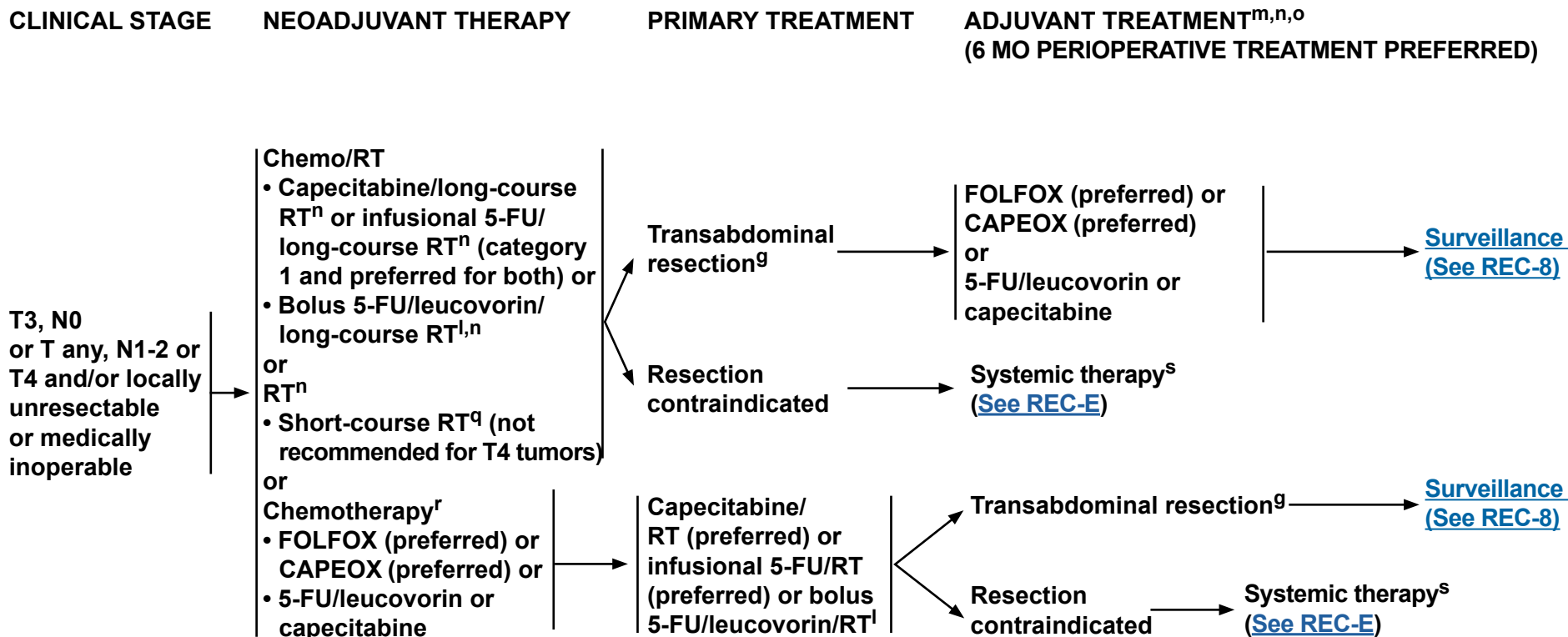


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# NCCN Guidelines Version 3.2017

## Rectal Cancer

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<sup>g</sup>[See Principles of Surgery \(REC-B\).](#)

<sup>l</sup>Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

<sup>m</sup>[See Principles of Adjuvant Therapy \(REC-C\).](#)

<sup>n</sup>[See Principles of Radiation Therapy \(REC-D\).](#)

<sup>o</sup>Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.

<sup>q</sup>Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.

<sup>r</sup>Fernandez-Martos C, Pericay C, Aparicio J, et al: Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 2010;28:859-865.

Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. J Natl Compr Canc Netw 2014;12:513-519.

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

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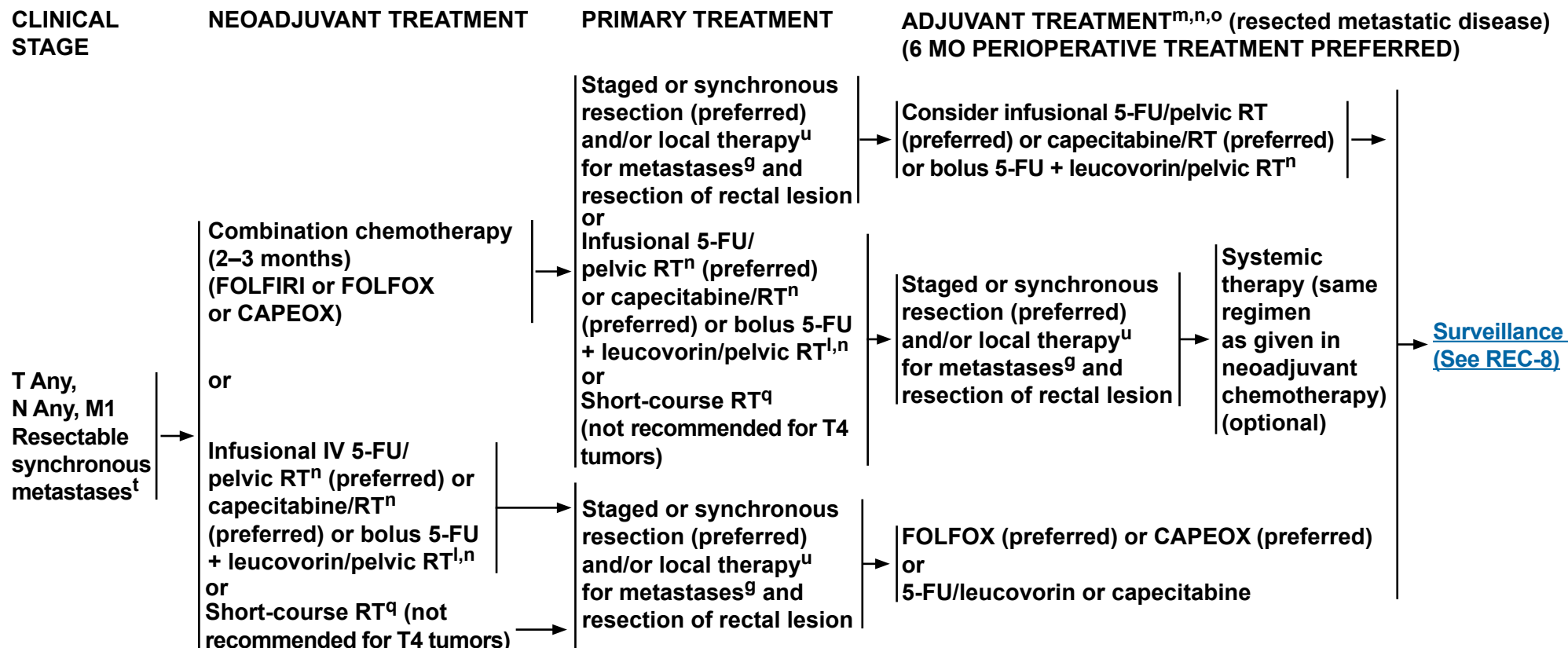


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## Rectal Cancer

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<sup>g</sup>See [Principles of Surgery \(REC-B\)](#).

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<sup>m</sup>See [Principles of Adjuvant Therapy \(REC-C\)](#).

<sup>n</sup>See [Principles of Radiation Therapy \(REC-D\)](#).

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<sup>q</sup>Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.

<sup>t</sup>Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See [Principles of Pathologic Review \(REC-A 5 of 6\)](#) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

<sup>u</sup>Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases ([REC-B](#) and [REC-D](#)).

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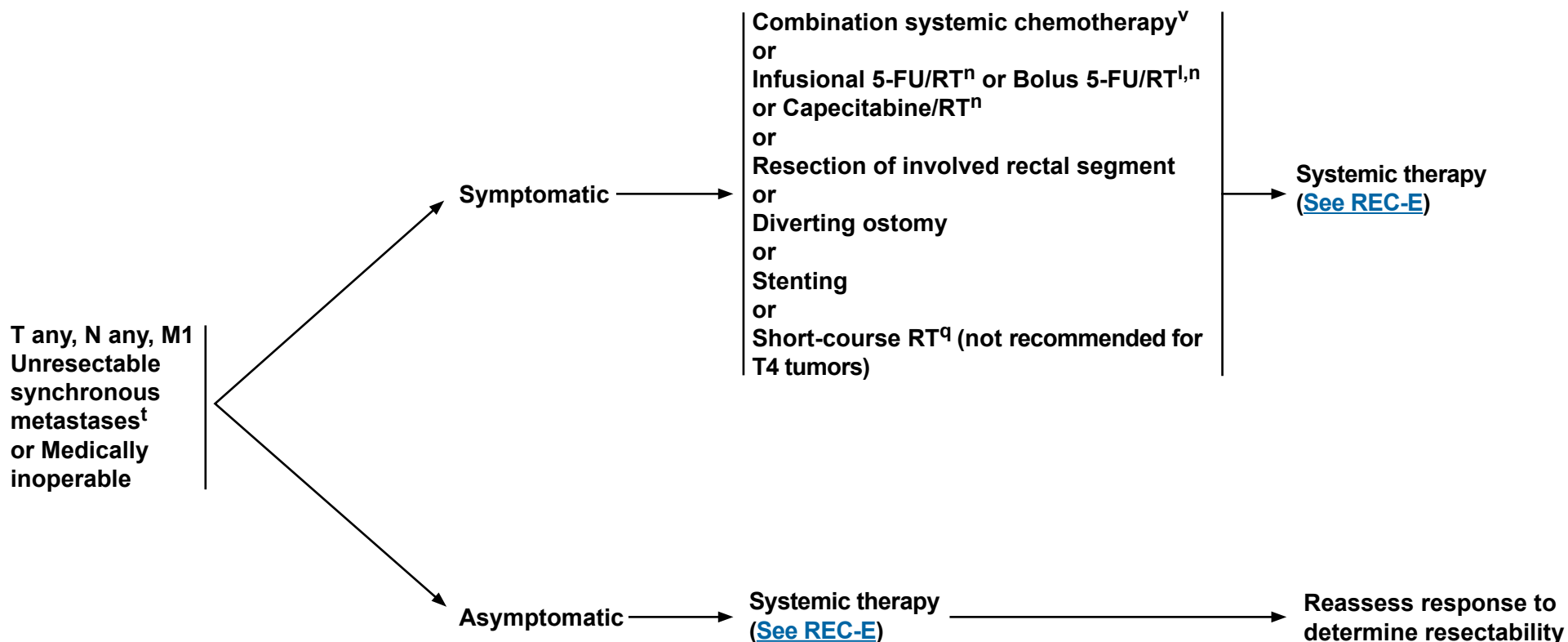


# NCCN Guidelines Version 3.2017

## Rectal Cancer

### CLINICAL STAGE

### PRIMARY TREATMENT



<sup>l</sup>Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

<sup>n</sup>[See Principles of Radiation Therapy \(REC-D\).](#)

<sup>q</sup>Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for down-staging and the possibility of long-term toxicity.

<sup>t</sup>Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). [See Principles of Pathologic Review \(REC-A 5 of 6\)](#) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

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

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# NCCN Guidelines Version 3.2017

## Rectal Cancer

### SURVEILLANCE

Stage I with full  
surgical staging

- Colonoscopy at 1 y**
- ▶ If advanced adenoma, repeat in 1 y
  - ▶ If no advanced adenoma,<sup>w</sup> repeat in 3 y, then every 5 y<sup>x</sup>

Stage II, III

- History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA<sup>y</sup> every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdominal/pelvic CT<sup>h</sup> every 6–12 mo (category 2B for frequency <12 mo) for a total of 5 y
- 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>w</sup> repeat in 3 y, then every 5 y<sup>x</sup>
- Proctoscopy (with EUS or MRI with contrast) every 3–6 mo for the first 2 y, then every 6 mo for a total of 5 y (for patients treated with transanal excision only)
- PET/CT scan is not recommended
- See [Principles of Survivorship \(REC-F\)](#)

Stage IV

- History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA<sup>y</sup> every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdominal/pelvic CT<sup>h</sup> every 3–6 mo (category 2B for frequency <6 mo) x 2 y, then every 6–12 mo for a total of 5 y
- 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>w</sup> repeat in 3 y, then every 5 y<sup>x</sup>
- Proctoscopy (with EUS or MRI with contrast) every 3–6 mo for the first 2 y, then every 6 mo for a total of 5 y (for patients treated with transanal excision only)
- PET/CT scan is not recommended
- See [Principles of Survivorship \(REC-F\)](#)

Serial CEA  
elevation or  
documented  
recurrence

[See Workup  
and Treatment  
\(REC-9\)](#)

<sup>h</sup>CT should be with IV and oral contrast. Consider abdominal/pelvic MRI with MRI contrast plus a non-contrast chest CT if either CT of abd/pelvis is inadequate or if patient has a contraindication to CT with IV contrast.

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

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

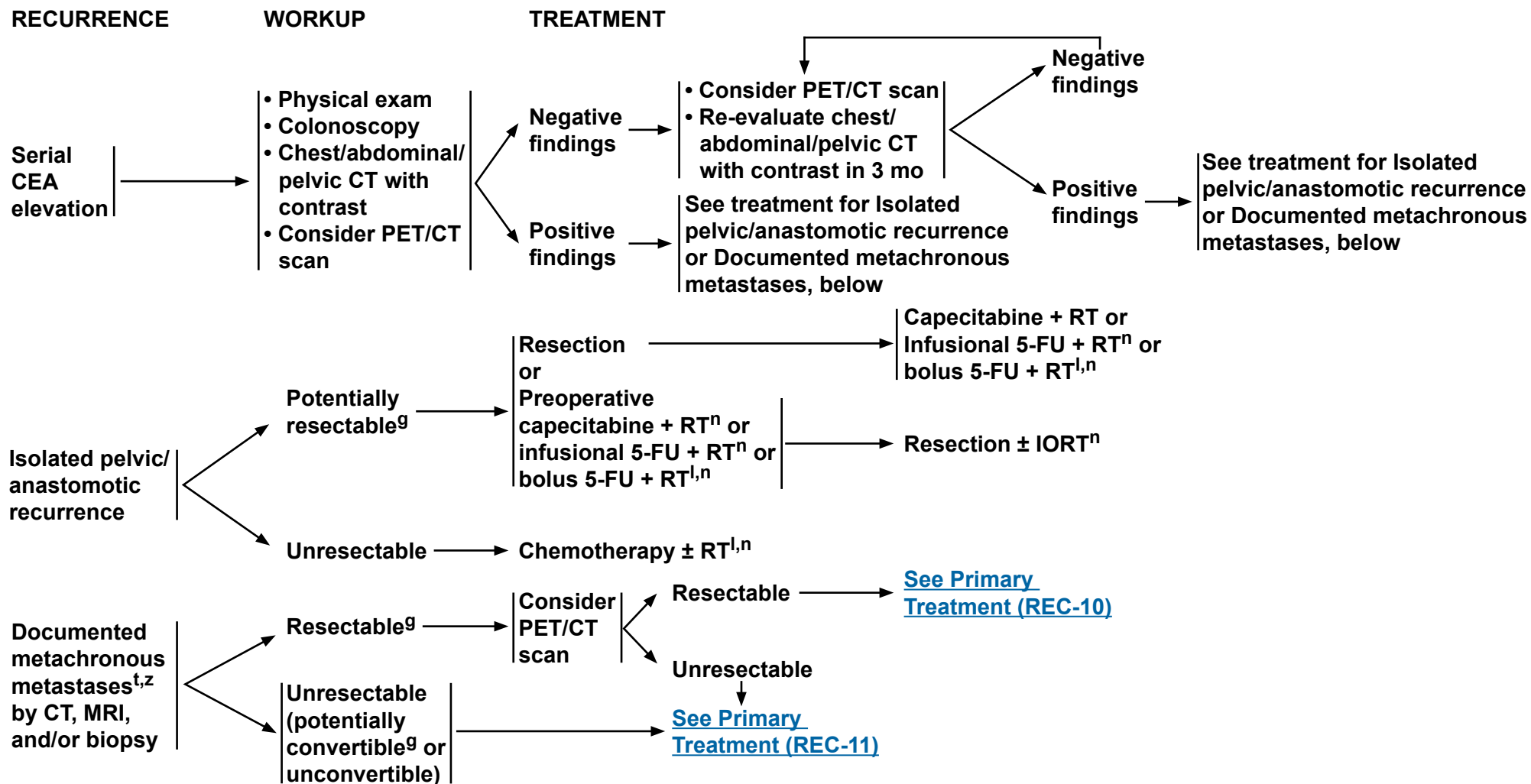
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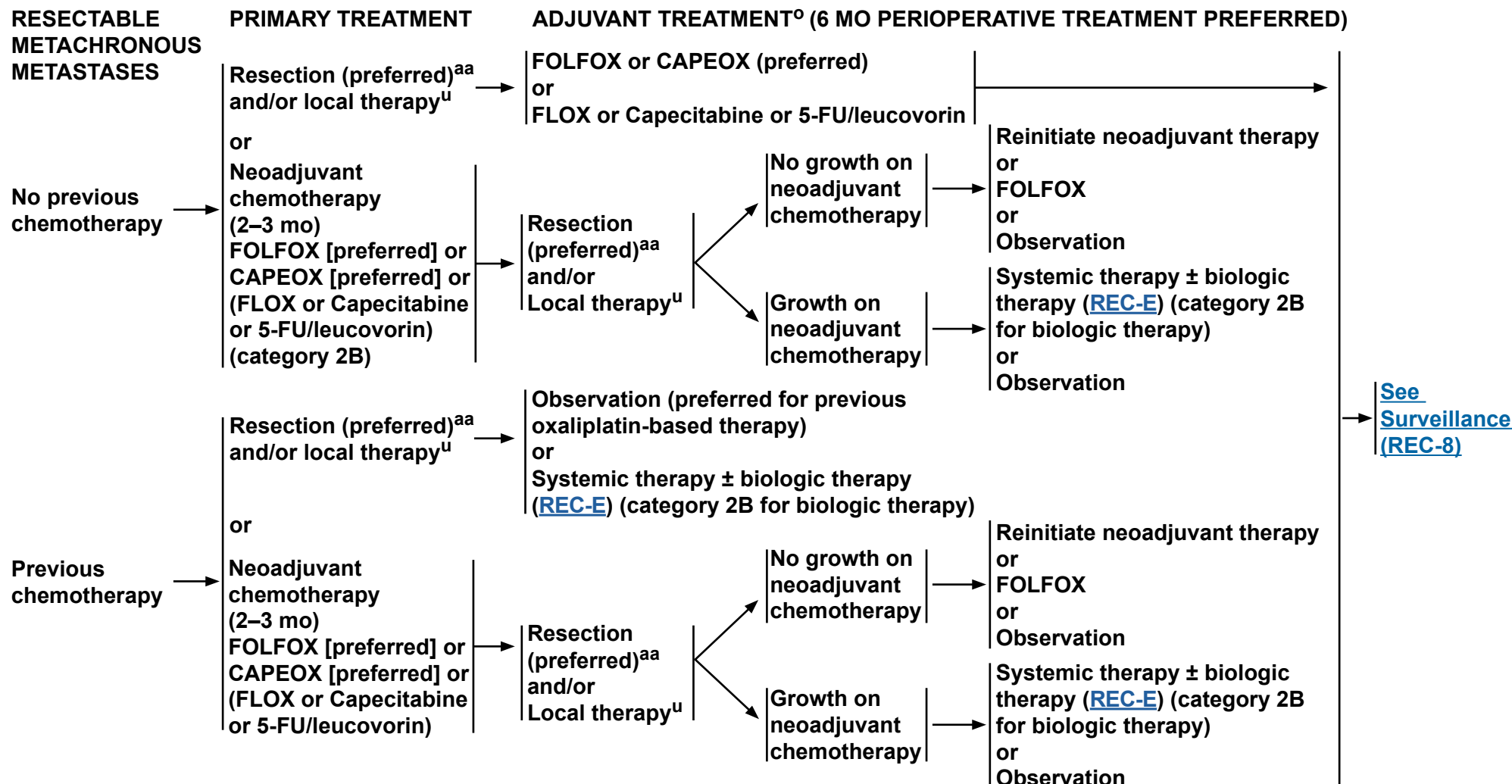
## Rectal Cancer

<sup>g</sup>See Principles of Surgery (REC-B).<sup>l</sup>Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.<sup>n</sup>See Principles of Radiation Therapy (REC-D).<sup>t</sup>Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (REC-A 5 of 6) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.<sup>z</sup>Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



# NCCN Guidelines Version 3.2017

## Rectal Cancer



<sup>o</sup>Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.

<sup>u</sup>Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases ([REC-B](#) and [REC-D](#)).

<sup>aa</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.

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# NCCN Guidelines Version 3.2017

## Rectal Cancer

### UNRESECTABLE METACHRONOUS METASTASES

### PRIMARY TREATMENT

### ADJUVANT TREATMENT<sup>o</sup> (6 MO PERIOPERATIVE TREATMENT PREFERRED)

- Previous adjuvant FOLFOX/CAPEOX within past 12 months

FOLFIRI ± (bevacizumab [preferred] or ziv-aflibercept or ramucirumab)<sup>cc</sup>  
or  
Irinotecan ± (bevacizumab [preferred] or ziv-aflibercept or ramucirumab)<sup>bb</sup>  
or  
FOLFIRI + (cetuximab or panitumumab) (KRAS/NRAS WT gene only)<sup>t,cc</sup>  
or  
Irinotecan ± (Cetuximab or panitumumab) (KRAS/NRAS WT gene only)<sup>t,cc</sup>  
or  
(Nivolumab or pembrolizumab) (dMMR/MSI-H only)

- Previous adjuvant FOLFOX/CAPEOX >12 months
- Previous 5-FU/LV or capecitabine
- No previous chemotherapy

Systemic therapy ([REC-E](#))

Re-evaluate for conversion to resectable<sup>g</sup> every 2 mo if conversion to resectability is a reasonable goal

Converted to resectable

→ Resection<sup>aa</sup>

Remains unresectable

→ Systemic therapy ([REC-E](#))

Systemic therapy ± biologic therapy ([REC-E](#)) (category 2B for biologic therapy) or Observation

See [Surveillance \(REC-8\)](#)

<sup>g</sup>See [Principles of Surgery \(REC-B\)](#).

<sup>o</sup>Imaging (Chest/Abdomen/Pelvic CT with contrast) to be performed prior to adjuvant treatment to assess response to primary therapy or resection.

<sup>t</sup>Determination of tumor gene status for RAS (KRAS and NRAS) and BRAF. Determination of tumor MMR or MSI status (if not previously done). See [Principles of Pathologic Review \(REC-A 5 of 6\)](#) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

<sup>aa</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>bb</sup>Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

<sup>cc</sup>BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely.

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# NCCN Guidelines Version 3.2017

## Rectal Cancer

### 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 to be a “malignant polyp.”
- Favorable histopathologic 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; and 3) tumor cells present within the diathermy of the transected margin.<sup>1-4</sup>
- Unfavorable histologic features grade 3 or 4, angiolymphatic invasion, or a “positive margin.” See above for definition of a positive margin. In several studies, tumor budding has been shown to be an adverse histological feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcome (residual disease, recurrent disease, mortality, or hematogenous metastasis, but not lymph node metastasis) than do 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 histopathologic features: <3 cm size, T1, grade I or II, no lymphatic or venous invasion, or negative margins.<sup>8,9</sup>
- Unfavorable histopathologic features: >3 cm in size, T1, with grade III, or lymphovascular invasion, positive margin, or sm3 depth of tumor invasion.<sup>8-10</sup>

#### Rectal Cancer Appropriate for Resection

- Histologic confirmation of primary malignant rectal neoplasm.

[See Pathologic Stage on REC-A 2 of 6](#)

[See Lymph Node Evaluation on REC-A 4 of 6](#)

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

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

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### PRINCIPLES OF PATHOLOGIC REVIEW (2 of 6)

#### Pathologic Stage

• The following parameters should be reported:

- ▶ Grade of the cancer
- ▶ Depth of penetration (T), the T stage, is based on viable tumor. Acellular mucin pools are not considered to be residual tumor in those cases treated with neoadjuvant therapy.
- ▶ Number of lymph nodes evaluated and number positive (N). Acellular mucin pools are not considered to be residual tumor in those cases treated with neoadjuvant therapy.
- ▶ Status of proximal, distal, circumferential (radial), and mesenteric margins.<sup>11-12</sup>
- ▶ Circumferential resection margin (CRM)<sup>13-17</sup>
- ▶ Neoadjuvant treatment effect<sup>15,16,18,19</sup>
- ▶ Lymphovascular invasion<sup>15,16,20</sup>
- ▶ Perineural invasion (PNI)<sup>21-23</sup>
- ▶ Tumor deposits<sup>24-25</sup>

• CRM - 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, it should be stated in the pathology report. A positive CRM is a more powerful predictor of local recurrence in patients treated with neoadjuvant therapy. A positive CRM secondary to lymph node metastasis in some studies has been associated with lower recurrence rates than by direct extension.<sup>13-17</sup>

• Neoadjuvant treatment effect - The most recent College of American Pathologists (CAP) Guidelines on examination specimens of the rectum and the AJCC Cancer Staging Manual, Seventh Edition require commenting on treatment effect after neoadjuvant therapy. The minimum requirement is:

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

The system used to grade tumor response as recommended by the AJCC Cancer Staging Manual, 7th Edition and the CAP Guidelines is that as modified from Ryan R, et al. *Histopathology* 2005;47:141-146.

- ▶ 0 - Complete response: No remaining viable cancer cells.
- ▶ 1 - Moderate response: Only small clusters or single cancer cells remaining.
- ▶ 2 - Minimal response: Residual cancer remaining, but with predominant fibrosis.
- ▶ 3 - Poor response: Minimal or no tumor kill; extensive residual cancer.

According to CAP, it is optional to grade the tumor response to treatment. However, the NCCN Rectal Cancer Guidelines Panel recommends grading tumor response. Other grading systems that are used are referenced.<sup>15,16,18,19</sup>

[See Pathologic Stage continued on REC-A 3 of 6](#)

[See Endoscopically Removed Malignant Polyps, Rectal Cancer Appropriate for Resection on REC-A 1 of 6](#)

[See Lymph Node Evaluation on REC-A 4 of 6](#)

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

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

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### PRINCIPLES OF PATHOLOGIC REVIEW (3 of 6)

#### Pathologic Stage (continued)

- **Perineural invasion (PNI)** - The presence of PNI is associated with a significantly worse prognosis. In multivariate analysis, PNI has been shown to be an independent prognostic factor for cancer-specific, overall, and 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% [ $P = .0005$ ]). In stage III rectal cancer, those with PNI have a significantly worse prognosis.<sup>21-23</sup>
- **Tumor deposits** - Irregular discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered to be tumor deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. Most examples are due to lymphovascular invasion or, more rarely, PNI. Because these tumor deposits are associated with reduced disease-free and overall survival, their number should be recorded in the surgical pathology report.

[See Endoscopically Removed Malignant Polyps, Rectal Cancer Appropriate for Resection on REC-A 1 of 6](#)

[See Pathologic Stage on REC-A 2 of 6](#)

[See Lymph Node Evaluation on REC-A 4 of 6](#)

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

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

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# NCCN Guidelines Version 3.2017

## Rectal Cancer

### PRINCIPLES OF PATHOLOGIC REVIEW (4 of 6)

#### Lymph Node Evaluation

- The AJCC and CAP recommend examination of a minimum of 12 lymph nodes to accurately stage rectal cancer.<sup>11,12,26</sup> Sampling of 12 lymph nodes may not be achievable in patients who received preoperative chemotherapy. The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, and >30.<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 fewer than 12 lymph nodes are initially identified, it is recommended that the pathologist go back to the specimen and resubmit more tissue of potential lymph nodes. If 12 lymph nodes are still not identified, a comment in the report should indicate that an extensive search for lymph nodes was undertaken. The mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs. 19,  $P < .05$ , 7 vs. 10,  $P < .001$ ).<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 histologic and/or immunohistochemical investigation to detect the presence of metastatic carcinoma. Studies in the literature have been reported using multiple H & E sections and/or immunohistochemistry (IHC) to detect cytokeratin-positive cells.<sup>37-39</sup> The AJCC Cancer Staging Manual, Seventh Edition<sup>40</sup> considers “tumor clusters” <0.2 mm to be isolated tumor cells (pN0) and not metastatic carcinoma. However, some investigators believe that size should not affect the diagnosis of metastatic cancer. They believe that tumor foci that show evidence of growth (eg, glandular differentiation, distension of sinus, stromal reaction) should be diagnosed as a lymph node metastasis regardless of size.<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 to be micrometastases.<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 should be used with caution in clinical management decisions.<sup>37-39,43-47</sup>

[See Endoscopically Removed Malignant Polyps, Rectal Cancer Appropriate for Resection on REC-A 1 of 6](#)

[See Pathologic Stage on REC-A 2 of 6](#)

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

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

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### PRINCIPLES OF PATHOLOGIC REVIEW (5 of 6)

#### ***KRAS*, *NRAS*, and *BRAF* Mutation Testing**

- All patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.<sup>48-50</sup> *BRAF V600E* mutation makes response to panitumumab or cetuximab highly unlikely.<sup>51-53</sup>
- Testing for *KRAS*, *NRAS*, and *BRAF* mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform *high complexity* clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).
- 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*, *NRAS*, and *BRAF* mutations are similar in both specimen types.<sup>54</sup>

#### **Evaluation of Mesorectum (TME)**

- The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).<sup>55-57</sup>

#### **Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing**

- Universal MMR\* or MSI\* testing is recommended in all patients with a personal history of colon or rectal cancer. [See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#)
- The presence of a *BRAF V600E* mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome.
- Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.<sup>58</sup>
- MMR or MSI testing should be performed only in CLIA-approved laboratories.

\*IHC for MMR and PCR for MSI are different assays measuring the same biological effect.

[See Endoscopically Removed Malignant Polyps, Rectal Cancer Appropriate for Resection on REC-A 1 of 6](#)

[See Pathologic Stage on REC-A 2 of 6](#)

[See Lymph Node Evaluation on REC-A 4 of 6](#)

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

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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 invasion or PNI
- ▶ Well to moderately differentiated
- ▶ No evidence of lymphadenopathy on pretreatment imaging

• When the lesion can be adequately identified in the rectum, transanal endoscopic microsurgery (TEM) may be used. TEM for more proximal lesions may be technically feasible.

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

##### • Management principles

- ▶ The treating surgeon should perform a rigid proctoscopy before initiating treatment.
- ▶ Remove primary tumor with adequate margins.
- ▶ Treat draining lymphatics by total mesorectal excision.
- ▶ Restore organ integrity, if possible.
- ▶ Surgery should be 5–12 weeks following full-dose 5.5-week neoadjuvant chemoradiation.

##### • Total mesorectal excision

- ▶ Reduces positive radial margin rate.
- ▶ Extend 4–5 cm below distal edge of tumors for an adequate mesorectal excision. In distal rectal cancers (ie, <5 cm from anal verge), negative distal bowel wall margin of 1–2 cm may be acceptable; this must be confirmed to be tumor free by frozen section.
- ▶ Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.

- Some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery,<sup>2,3</sup> whereas other studies have shown that laparoscopy is associated with higher rates of circumferential margin positivity and incomplete TME.<sup>4,5</sup> Therefore, minimally invasive resection may be considered based on the following principles:
  - ▶ The surgeon should have experience performing minimally invasive proctectomy with total mesorectal excision.
  - ▶ It is not indicated for locally advanced disease with a threatened or high-risk circumferential margin based on staging. For these high-risk tumors, open surgery is preferred.
  - ▶ It is not indicated for acute bowel obstruction or perforation from cancer.
  - ▶ Thorough abdominal exploration is required.
- Lymph node dissection<sup>6,7</sup>
  - ▶ Biopsy or remove clinically suspicious nodes beyond the field of resection if possible.
  - ▶ Extended resection is not indicated in the absence of clinically suspected nodes.

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

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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>8</sup>
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.<sup>9,10</sup>
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.<sup>11-13</sup> Plan for a debulking resection (R1/R2 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>8</sup> All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- Conformal external beam radiation therapy (category 3) 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.
- Re-resection can be considered in selected patients.<sup>14</sup>

##### Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.<sup>15-18</sup>
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.<sup>19-22</sup>
- Re-resection can be considered in selected patients.<sup>23</sup>
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- 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>24-27</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>28</sup> Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.<sup>29</sup>

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

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# NCCN Guidelines Version 3.2017

## Rectal Cancer

### PRINCIPLES OF ADJUVANT THERAPY (1 of 2)

Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy.

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

#### Postoperative Adjuvant Chemotherapy:

- mFOLFOX 6<sup>1,2,3</sup>

Oxaliplatin 85 mg/m<sup>2</sup> IV, day 1,\* leucovorin 400 mg/m<sup>2</sup> IV day 1,\*\* 5-FU 400 mg/m<sup>2</sup> IV bolus on day 1, then 1200 mg/m<sup>2</sup>/d x 2 days (total 2400 mg/m<sup>2</sup> over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.

- Simplified biweekly infusional 5-FU/LV (sLV5FU2)<sup>4</sup>

Leucovorin 400 mg/m<sup>2</sup> IV day 1, followed by 5-FU bolus 400 mg/m<sup>2</sup> and then 1200 mg/m<sup>2</sup>/d x 2 days (total 2400 mg/m<sup>2</sup> over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.

- Capecitabine<sup>5</sup>

Capecitabine<sup>#</sup> 1000–1250 mg/m<sup>2</sup> twice daily days 1–14 every 3 weeks to a total of 6 months perioperative therapy.

- CAPEOX<sup>6,7</sup>

Oxaliplatin 130 mg/m<sup>2</sup> day 1.\* Capecitabine<sup>#</sup> 1000 mg/m<sup>2</sup> twice daily days 1–14 every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.

- 5-FU 500 mg/m<sup>2</sup> IV bolus weekly x 6 + leucovorin 500 mg/m<sup>2</sup> IV weekly x 6, each 8-week cycle. Repeat every 8 weeks to a total of 6 months perioperative therapy.<sup>8</sup>

#### Dosing Schedules for Concurrent Chemotherapy/RT:

- XRT + continuous infusion 5-FU<sup>9</sup>

5-FU 225 mg/m<sup>2</sup> over 24 hours 5 or 7 days/week during XRT

- XRT + Capecitabine<sup>11,12</sup>

Capecitabine<sup>#</sup> 825 mg/m<sup>2</sup> twice daily 5 d/wk + XRT x 5 weeks

- XRT + 5-FU/leucovorin<sup>10‡</sup>

5-FU 400 mg/m<sup>2</sup> IV bolus + leucovorin 20 mg/m<sup>2</sup> IV bolus for 4 days during week 1 and 5 of XRT

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

\*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m<sup>2</sup>/min. Leucovorin infusion should match infusion time of oxaliplatin.

Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m<sup>2</sup>/min. J Oncol Pract 2016;12:e548-553.

\*\*Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>.

‡Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

#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.

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

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- <sup>2</sup>Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br J Cancer* 2002;87:393-399.
- <sup>3</sup>Maindault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. *Ann Oncol* 2000;11:1477-1483.
- <sup>4</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>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.
- <sup>7</sup>Haller DG, Tabernero J, Maroun J, et al. Capecitabine Plus Oxaliplatin Compared With Fluorouracil and Folinic Acid As Adjuvant Therapy for Stage III Colon Cancer. *J Clin Oncol* 2011;29:1465-1471.
- <sup>8</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>9</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>10</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>11</sup>O'Connell MJ, Colangelo LH, Beart RW, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project trial R-04. *J Clin Oncol* 2014;32:1927-1934.
- <sup>12</sup>Hofheinz R, Wenz FK, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: A randomized, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol* 2012;13:579-588.

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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 radiation therapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations such as reirradiation of previously treated patients with recurrent disease or unique anatomical situations.
- 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.
- Short-course radiation therapy (25 Gy in 5 fractions) with surgery within 1 to 2 weeks of completion of therapy can also be considered for patients with ultrasound or pelvic MRI stage T3 rectal cancer.<sup>1</sup>
- Intraoperative radiation therapy (IORT), if available, may be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers. If IORT is not available, 10–20 Gy external beam radiation and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
- For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
- Fluoropyrimidine-based chemotherapy should be delivered concurrently with radiation therapy.
- Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- In patients with a limited number of liver or lung metastases, radiotherapy to the metastatic site 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 3-D conformal radiation therapy, IMRT, or stereotactic body radiation therapy (SBRT).
- Side effect management:
  - Female patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.
  - Male patients should be counseled on infertility risks and given information regarding sperm banking.
  - Female patients should be counseled on infertility risks and given information regarding oocyte, egg, or ovarian tissue banking prior to treatment.

<sup>1</sup>Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012;30:3827-3833.

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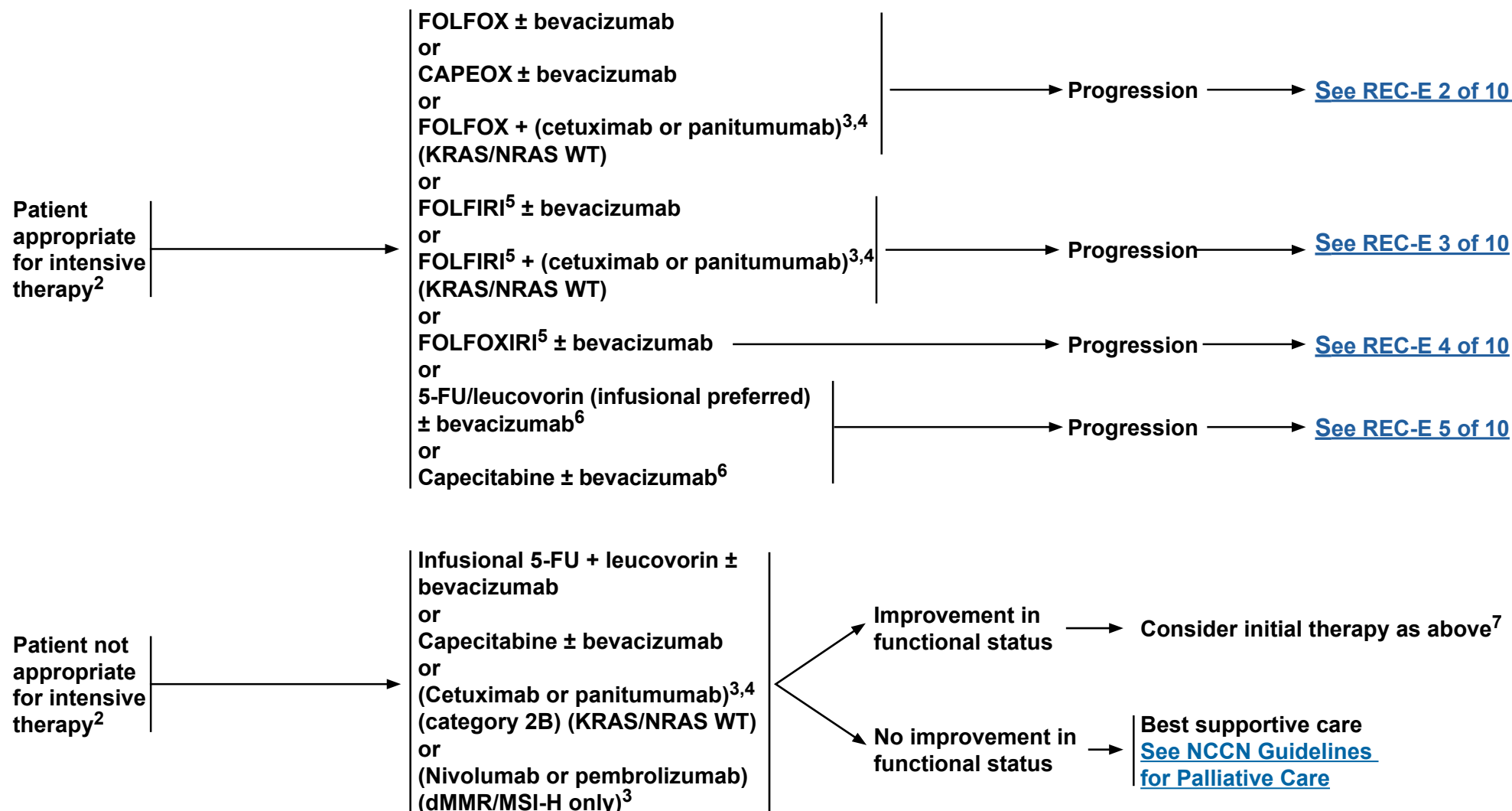


# NCCN Guidelines Version 3.2017

## Rectal Cancer

### CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 1 of 10)

#### Initial Therapy



[See footnotes on REC-E 6 of 10](#)

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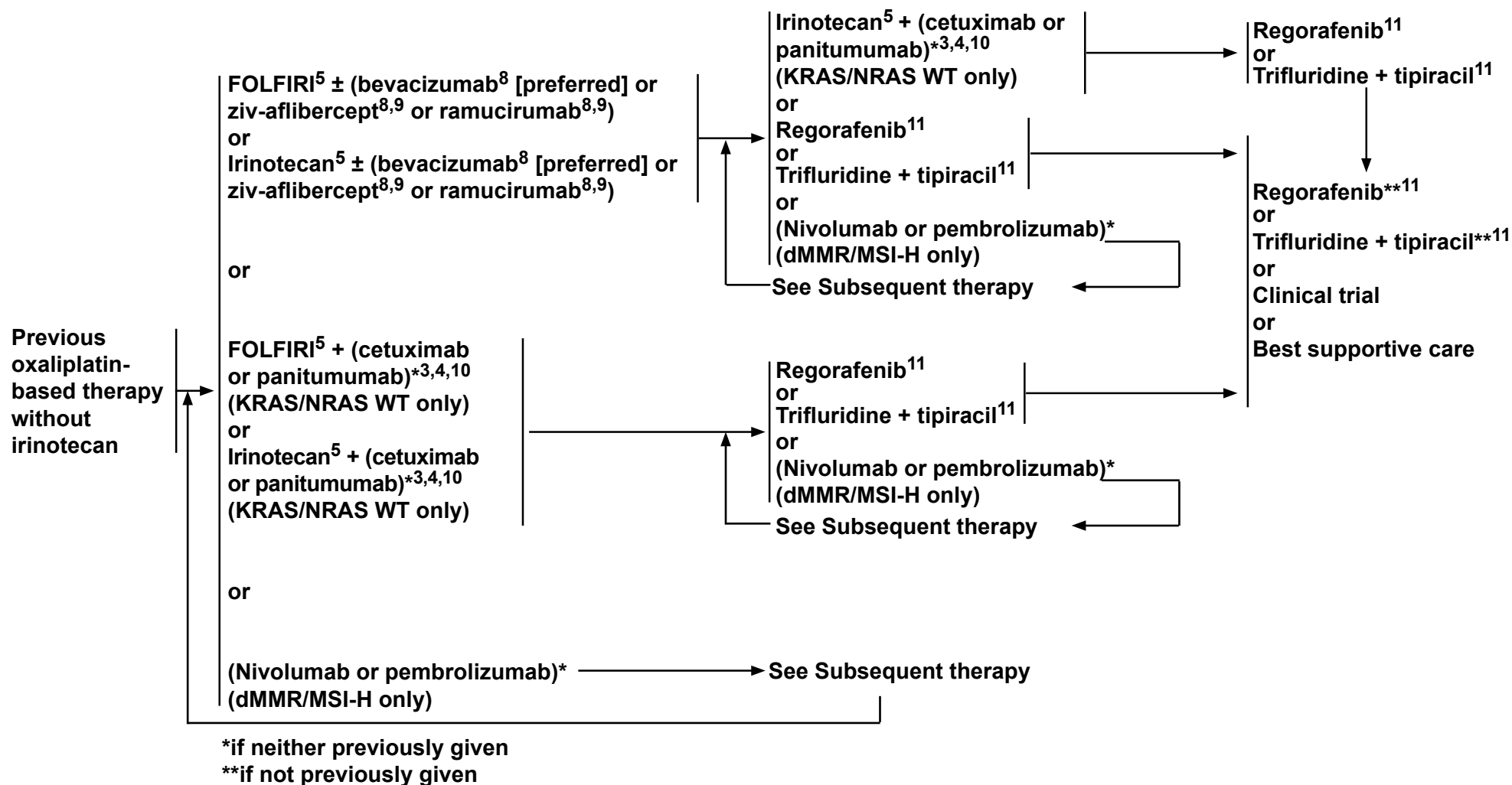


# NCCN Guidelines Version 3.2017

## Rectal Cancer

### CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 2 of 10)

#### Subsequent Therapy


[See footnotes on REC-E 6 of 10](#)

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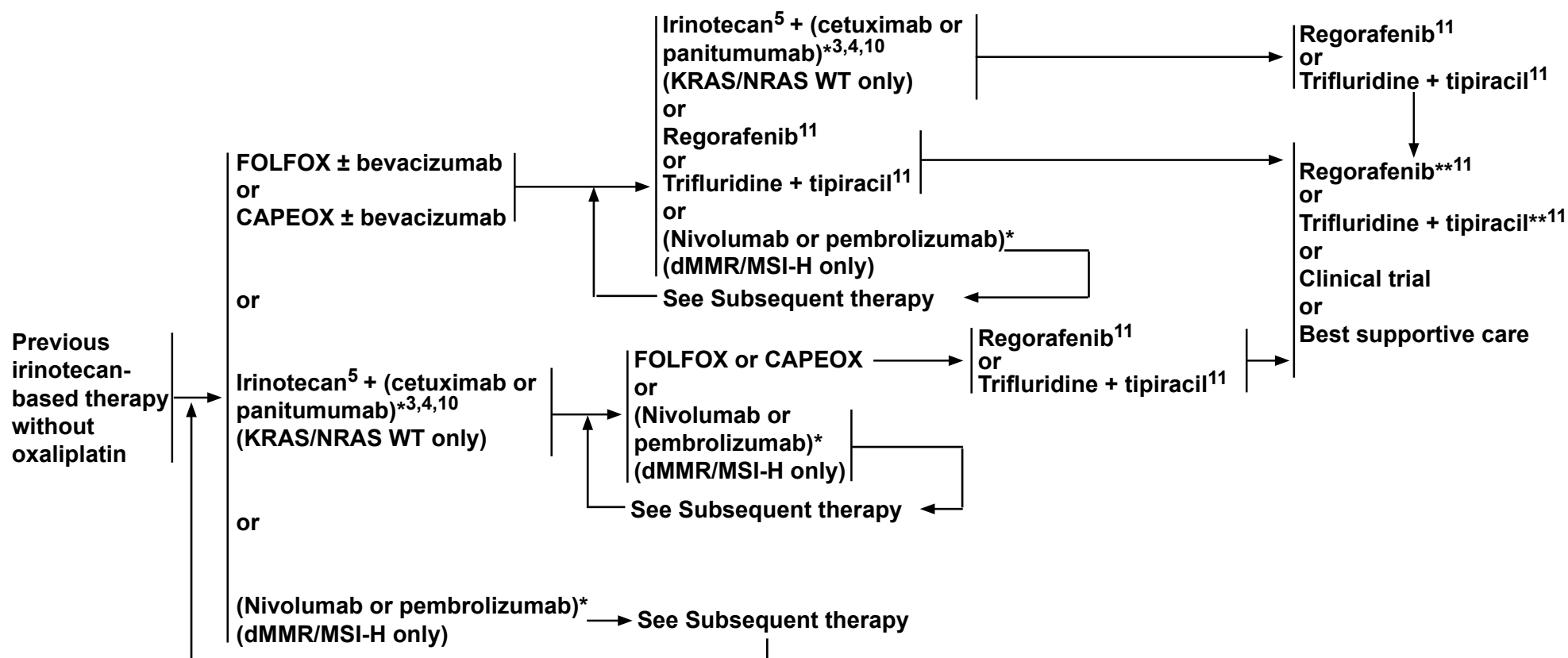


# NCCN Guidelines Version 3.2017

## Rectal Cancer

### CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 3 of 10)

#### Subsequent Therapy



\*if neither previously given

\*\*if not previously given

[See footnotes on REC-E 6 of 10](#)

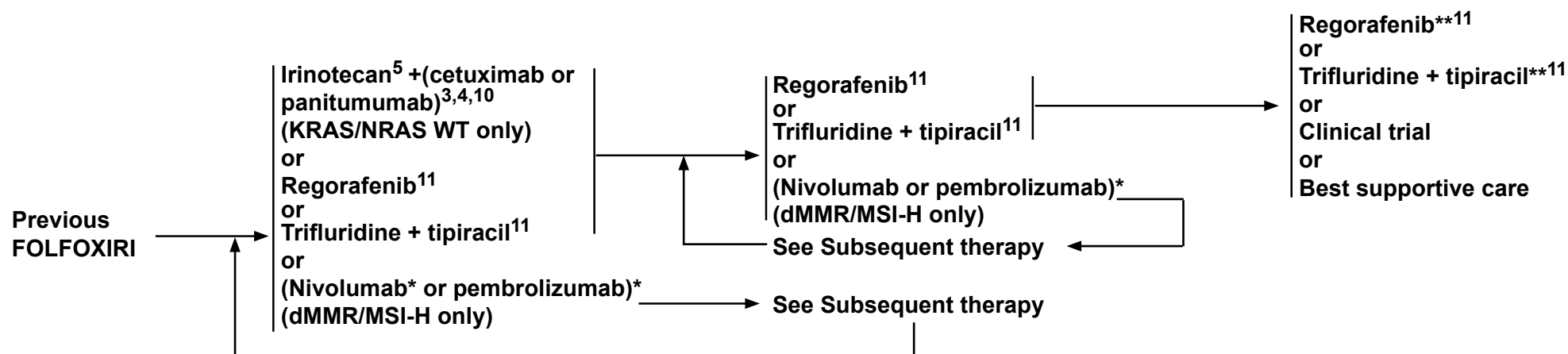
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### CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 4 of 10)

#### Subsequent Therapy



\*if neither previously given

\*\*if not previously given

[See footnotes on REC-E 6 of 10](#)

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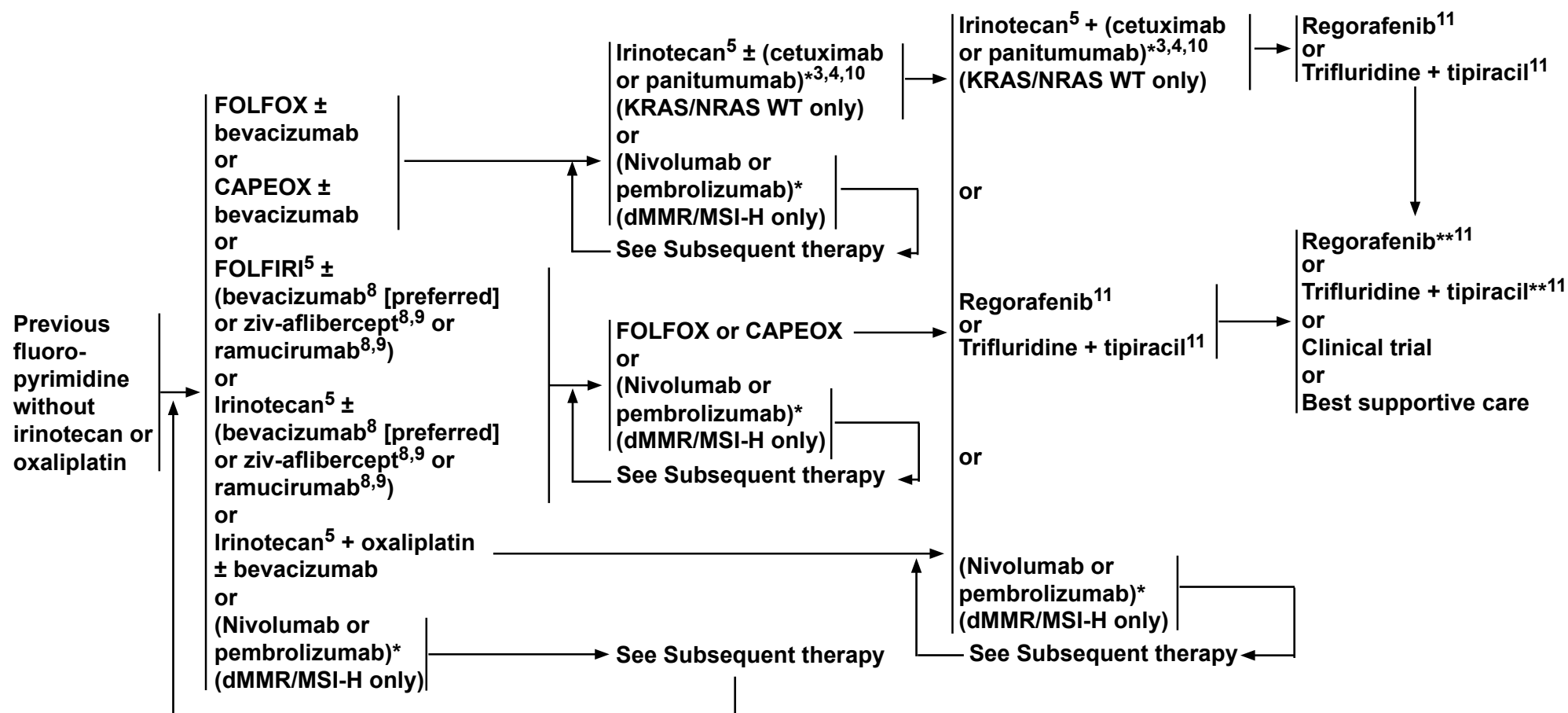


# NCCN Guidelines Version 3.2017

## Rectal Cancer

### CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE:<sup>1</sup> (PAGE 5 of 10)

#### Subsequent Therapy



\*if neither previously given

\*\*if not previously given

[See footnotes on REC-E 6 of 10](#)

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# NCCN Guidelines Version 3.2017

## Rectal Cancer

### SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (PAGE 6 of 10)

<sup>1</sup>For chemotherapy references, [see Chemotherapy Regimens and References \(REC-E 7-10\)](#).

<sup>2</sup>Chest/Abdominal/Pelvic CT with contrast or Chest CT and Abdominal/Pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used.

<sup>3</sup>[See Principles of Pathologic Review \(REC-A 5 of 6\)](#).

<sup>4</sup>BRAF V600E mutation makes response to panitumumab or cetuximab highly unlikely.

<sup>5</sup>Irinotecan should be used with caution 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>6</sup>A treatment option for patients not able to tolerate oxaliplatin or irinotecan.

<sup>7</sup>The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.

<sup>8</sup>Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

<sup>9</sup>There are no data to suggest activity of FOLFIRI-ziv-aflibercept or FOLFIRI-ramucirumab in a patient who has progressed on FOLFIRI-bevacizumab, or vice versa. Ziv-aflibercept and ramucirumab have only shown activity when given in conjunction with FOLFIRI in FOLFIRI-naïve patients.

<sup>10</sup>Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.

<sup>11</sup>Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.

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### SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 7 of 10)

#### mFOLFOX 6<sup>1,2,3¶</sup>

Oxaliplatin 85 mg/m<sup>2</sup> IV day 1\*

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

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

Repeat every 2 weeks

#### mFOLFOX7<sup>4</sup>

Oxaliplatin 85 mg/m<sup>2</sup> IV day 1\*

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

5-FU 1200 mg/m<sup>2</sup>/d x 2 days (total 2400 mg/m<sup>2</sup> over 46–48 hours)  
IV continuous infusion

Repeat every 2 weeks

#### FOLFOX + bevacizumab<sup>5</sup>

Bevacizumab 5 mg/kg IV, day 1

Repeat every 2 weeks

#### FOLFOX + panitumumab<sup>6</sup> (KRAS/NRAS WT only)

Panitumumab 6 mg/kg IV over 60 minutes, day 1

Repeat every 2 weeks

#### FOLFOX + cetuximab<sup>7</sup> (KRAS/NRAS WT only)

Cetuximab 400 mg/m<sup>2</sup> IV over 2 hours first infusion,  
then 250 mg/m<sup>2</sup> IV over 60 minutes weekly

or Cetuximab 500 mg/m<sup>2</sup> IV over 2 hours, day 1, every 2 weeks

#### CAPEOX<sup>8</sup>

Oxaliplatin 130 mg/m<sup>2</sup> IV day 1\*

Capecitabine 1000<sup>‡</sup> mg/m<sup>2</sup> twice daily PO for 14 days

Repeat every 3 weeks

#### CAPEOX + bevacizumab<sup>8¶</sup>

Oxaliplatin 130 mg/m<sup>2</sup> IV day 1\*

Capecitabine 1000<sup>‡</sup> mg/m<sup>2</sup> PO twice daily for 14 days

Bevacizumab 7.5 mg/kg IV day 1

Repeat every 3 weeks

[See References on REC-E 10 of 10](#)

\*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m<sup>2</sup>/min. Leucovorin infusion should match infusion time of oxaliplatin.

Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m<sup>2</sup>/min. J Oncol Pract 2016;12:e548-553.

\*\*Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</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.

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

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### SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 8 of 10)

#### FOLFIRI<sup>9,10</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>/d x 2 days (total 2400 mg/m<sup>2</sup> over 46–48 hours) continuous infusion  
Repeat every 2 weeks

#### FOLFIRI + bevacizumab<sup>11,¶</sup>

Bevacizumab 5 mg/kg IV, day 1  
Repeat every 2 weeks

#### FOLFIRI + cetuximab (*KRAS/NRAS* WT only)

Cetuximab 400 mg/m<sup>2</sup> IV over 2 hours first infusion, then 250 mg/m<sup>2</sup> IV over 60 minutes weekly<sup>12</sup>  
or Cetuximab 500 mg/m<sup>2</sup> IV over 2 hours, day 1, every 2 weeks<sup>13</sup>

#### FOLFIRI + panitumumab<sup>14</sup> (*KRAS/NRAS* WT only)

Panitumumab 6 mg/kg IV over 60 minutes, day 1  
Repeat every 2 weeks

#### FOLFIRI + ziv-aflibercept<sup>15</sup>

Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1  
Repeat every 2 weeks

#### FOLFIRI + ramucirumab<sup>16</sup>

Ramucirumab 8 mg/kg over 60 minutes, day 1  
Repeat every 2 weeks

#### FOLFOXIRI<sup>17</sup>

Irinotecan 165 mg/m<sup>2</sup> IV day 1, oxaliplatin 85 mg/m<sup>2</sup> IV day 1,\*  
leucovorin 400\*\* mg/m<sup>2</sup> day 1, fluorouracil 1600 mg/m<sup>2</sup>/d x 2 days (total 3200 mg/m<sup>2</sup> over 48 hours) continuous infusion starting on day 1.

Repeat every 2 weeks

The dose of 5-FU listed here was used in European studies. U.S. patients have been shown to have poorer tolerance for 5-FU. A starting dose of 5-FU consistent with the dose recommended in FOLFOX or FOLFIRI should be strongly considered for U.S. patients.

#### FOLFOXIRI + bevacizumab<sup>18</sup>

Bevacizumab 5 mg/kg IV, day 1  
Repeat every 2 weeks

#### IROX<sup>19</sup>

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

[See References on REC-E 10 of 10](#)

\*Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m<sup>2</sup>/min. Leucovorin infusion should match infusion time of oxaliplatin.

Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m<sup>2</sup>/min. J Oncol Pract 2016;12:e548-553.

\*\*Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>.

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

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### SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS (PAGE 9 of 10)

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

##### Roswell Park regimen<sup>20</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, and 36  
Repeat every 8 weeks

##### Simplified biweekly infusional 5-FU/LV (sLV5FU2)<sup>9</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>/d x 2 days  
(total 2400 mg/m<sup>2</sup> over 46–48 hours) 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 1 hour after the start of leucovorin. Repeat weekly.<sup>21</sup>  
5-FU 2600 mg/m<sup>2</sup> by 24-hour infusion plus leucovorin 500 mg/m<sup>2</sup>  
Repeat every week<sup>21</sup>

#### Capecitabine<sup>8</sup>

Capecitabine 850–1250 mg/m<sup>2</sup> PO twice daily, days 1–14  
Repeat every 3 weeks

#### Capecitabine + Bevacizumab<sup>22,†</sup>

Bevacizumab 7.5 mg/kg IV, day 1  
Repeat every 3 weeks

#### Irinotecan

Irinotecan 125 mg/m<sup>2</sup> IV over 30–90 minutes, days 1 and 8  
Repeat every 3 weeks<sup>23,24</sup>  
or Irinotecan 180 mg/m<sup>2</sup> IV over 30–90 minutes, day 1

#### Repeat every 2 weeks

or Irinotecan 300–350 mg/m<sup>2</sup> IV over 30–90 minutes, day 1

#### Repeat every 3 weeks

#### Irinotecan + cetuximab (*KRAS/NRAS* WT only)

Cetuximab 400 mg/m<sup>2</sup> first infusion, then 250 mg/m<sup>2</sup> IV weekly<sup>25</sup>  
or Cetuximab 500 mg/m<sup>2</sup> IV over 2 hours, day 1, every 2 weeks<sup>13</sup>

#### Cetuximab (*KRAS/NRAS* WT only)

Cetuximab 400 mg/m<sup>2</sup> first infusion, then 250 mg/m<sup>2</sup> IV weekly<sup>25</sup>  
or Cetuximab 500 mg/m<sup>2</sup> IV over 2 hours, day 1, every 2 weeks<sup>13</sup>

#### Panitumumab<sup>26</sup> (*KRAS/NRAS* WT only)

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

#### Regorafenib<sup>27</sup>

Regorafenib 160 mg<sup>§</sup> PO daily days 1–21  
Repeat every 28 days

#### Trifluridine + tipiracil<sup>28</sup>

Trifluridine + tipiracil 35 mg/m<sup>2</sup> up to a maximum dose of 80 mg per  
dose (based on the trifluridine component)  
PO twice daily days 1–5 and 8–12  
Repeat every 28 days

#### Pembrolizumab<sup>29</sup>

Pembrolizumab 2 mg/kg every 3 weeks

#### Nivolumab<sup>30</sup>

Nivolumab 3 mg/kg every 2 weeks  
or Nivolumab 240 mg IV every two weeks

[See References on REC-E 10 of 10](#)

\*\*Leucovorin 400 mg/m<sup>2</sup> is the equivalent of levoleucovorin 200 mg/m<sup>2</sup>.

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

§It is common practice to start at a lower dose of regorafenib (80 or 120 mg) and escalate, as tolerated.

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# NCCN Guidelines Version 3.2017

## Rectal Cancer

### SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES (PAGE 10 of 10)

- <sup>1</sup>deGramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced rectal cancer. *J Clin Oncol* 2000;18:2938-2947.
- <sup>2</sup>Cheeseman SL, Joel SP, Chester JD, et al. A 'modified de Gramont' regimen of fluorouracil, alone and with oxaliplatin, for advanced colorectal cancer. *Br J Cancer* 2002;87:393-399.
- <sup>3</sup>Maindault-Goebel F, deGramont A, Louvet C, et al. Evaluation of oxaliplatin dose intensity in bimonthly leucovorin and 48-hour 5-fluorouracil continuous infusion regimens (FOLFOX) in pretreated metastatic colorectal cancer. *Ann Oncol* 2000;11:1477-1483.
- <sup>4</sup>Hochster HS, Grothey A, Hart L, et al. Improved time to treatment failure with an intermittent oxaliplatin strategy: results of CONCePT. *Ann Oncol* 2014;25:1172-1178.
- <sup>5</sup>Emmanouilides C, Sfakiotaki G, Androulakis N, et al. Front-line bevacizumab in combination with oxaliplatin, leucovorin and 5-fluorouracil (FOLFOX) in patients with metastatic colorectal cancer: a multicenter phase II study. *BMC Cancer* 2007;7:91.
- <sup>6</sup>Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol* 2010;28:4697-4705.
- <sup>7</sup>Venook AP, Niedzwiecki D, Lenz H-J, et al. CALGB/SWOG 80405: Phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab or cetuximab for patients with KRAS wild-type untreated metastatic adenocarcinoma of the colon or rectum [abstract]. *ASCO Meeting Abstracts* 2014;32:LBA3.
- <sup>8</sup>Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;26:2013-2019.
- <sup>9</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.
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- <sup>11</sup>Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomized, open-label, phase 3 trial. *Lancet Oncol* 2014.
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- <sup>13</sup>Martín-Martorell P, Roselló S, Rodríguez-Braun E, et al. Biweekly cetuximab and irinotecan in advanced colorectal cancer patients progressing after at least one previous line of chemotherapy: results of a phase II single institution trial. *Br J Cancer* 2008;99:455-458.
- <sup>14</sup>Peeters M, Price TJ, Cervantes A, et al. Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 2010;28:4706-4713.
- <sup>15</sup>Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of Afibercept to Fluorouracil, Leucovorin, and Irinotecan Improves Survival in a Phase III Randomized Trial in Patients With Metastatic Colorectal Cancer Previously Treated With an Oxaliplatin-Based Regimen. *J Clin Oncol* 2012;30:3499-3506.
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**Note:** All recommendations are category 2A unless otherwise indicated.

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



### PRINCIPLES OF SURVIVORSHIP - Colorectal Long-term Follow-up Care

#### Colorectal Cancer Surveillance:

- See [REC-8](#)
- Long-term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years.

#### Management of Late Sequelae of Disease or Treatment:<sup>1-5</sup>

##### [See NCCN Guidelines for Survivorship](#)

- Chronic diarrhea or incontinence
  - ▶ Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, pelvic floor rehabilitation, and protective undergarments.
- For oxaliplatin-induced neuropathy
  - ▶ Consider duloxetine for painful neuropathy
- For fatigue
  - ▶ Encourage physical activity, energy conservation measures
- Urogenital dysfunction after resection and/or pelvic radiation<sup>6,7</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.
- Potential for pelvic fractures/decreased bone density after pelvic radiation
  - ▶ Consider bone density monitoring

#### Survivorship Care Planning:

The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to patient.<sup>8</sup>

- Develop survivorship care plan that includes:
  - ▶ Overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received.
  - ▶ Description of possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.

- ▶ Surveillance recommendations.
- ▶ Delineate appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist.
- ▶ Health behavior recommendations.

#### Cancer Screening Recommendations:

These recommendations are for average-risk patients.

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

- Breast Cancer: [NCCN Guidelines for Breast Cancer Screening](#)
- Prostate Cancer: [NCCN Guidelines for Prostate Early Detection](#)

#### Counseling Regarding Healthy Lifestyle and Wellness:<sup>9</sup>

##### [See NCCN Guidelines for Survivorship](#)

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

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

##### [See NCCN Guidelines for Survivorship](#)

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





# NCCN Guidelines Version 3.2017 Staging Rectal Cancer

**Table 1. Definitions for T, N, M****Primary Tumor (T)**

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria <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

<sup>a</sup>Tis includes cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa.

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

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

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit [www.springer.com](http://www.springer.com).) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

**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 (eg, 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

### NCCN Categories of Evidence and Consensus

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

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

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

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

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

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### Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2016, an estimated 39,220 new cases of rectal cancer will occur in the United States (23,110 cases in men; 16,110 cases in women). During the same year, it is estimated that 49,190 people will die from rectal and colon cancer combined.<sup>1</sup> Despite these statistics, the incidence per 100,000 population of colon and rectal cancers decreased from 60.5 in 1976 to 46.4 in 2005.<sup>2</sup> In fact, the incidence of colorectal cancer decreased at a rate of approximately 3% per year or greater between 2003 and 2012.<sup>1</sup> The incidence rate for colorectal cancer reported by the CDC for 2011 is 40.0 per 100,000 persons.<sup>3</sup> In addition, mortality from colorectal cancer decreased by almost 35% from 1990 to 2007,<sup>4</sup> and is currently down by about 50% from peak mortality rates.<sup>1</sup> These improvements in incidence of and mortality from colorectal cancer are thought to be a result of cancer prevention and earlier diagnoses through screening and of better treatment modalities.

Despite the observed improvements in the overall colorectal cancer incidence rate, a retrospective cohort study of the SEER CRC registry found that the incidence of colorectal cancer in patients younger than 50 years has been increasing.<sup>5</sup> The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients 20 to 34 years by 2030. The cause of this trend is currently unknown.

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for managing rectal cancer. These guidelines begin with the clinical presentation of the patient to the primary care physician or gastroenterologist and address diagnosis, pathologic staging, neoadjuvant treatment, surgical management,

adjuvant treatment, management of recurrent and metastatic disease, patient surveillance, and survivorship. These guidelines overlap considerably with the NCCN Guidelines for Colon Cancer, especially in the treatment of metastatic disease. The recommendations in these guidelines are classified as category 2A except where noted. The panel unanimously endorses patient participation in a clinical trial over standard or accepted therapy, especially for cases of advanced disease and for patients with locally aggressive colorectal cancer who are receiving combined modality treatment.

### Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Rectal Cancer, an electronic search of the PubMed database was performed to obtain key literature in the field of colorectal cancer published between June 12, 2015 and June 12, 2016, using the following search terms: (colon cancer) OR (colorectal cancer) OR (rectal cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.<sup>6</sup>

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 375 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting



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abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website ([www.NCCN.org](http://www.NCCN.org)).

### Risk Assessment

Approximately 20% of cases of colorectal cancer are associated with familial clustering, and first-degree relatives of patients with colorectal adenomas or invasive colorectal cancer<sup>7-11</sup> are at increased risk for colorectal cancer. Genetic susceptibility to colorectal cancer includes well-defined inherited syndromes, such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC])<sup>12,13</sup> and familial adenomatous polyposis (FAP).<sup>14</sup> Therefore, it is recommended that all patients with colorectal cancer be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening (to view the most recent version of these guidelines, visit the NCCN website at [www.NCCN.org](http://www.NCCN.org)). Results from a recent randomized controlled trial suggest that most individuals without a personal history of colorectal cancer and with one first-degree relative with colorectal cancer diagnosed before age 50 years or two first-degree relatives with colorectal cancer diagnosed at any age can safely be screened with colonoscopy every 6 years.<sup>15</sup>

### Lynch Syndrome

Lynch syndrome is the most common form of genetically determined colorectal cancer predisposition, accounting for 2% to 4% of all colorectal cancer cases.<sup>12,13,16,17</sup> This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Although identifying a germline mutation in

an MMR gene through sequencing is definitive for Lynch syndrome, patients usually undergo selection by considering family history and performing an initial test on tumor tissue before sequencing. One of two different initial tests can be performed on colorectal cancer specimens to identify individuals who might have Lynch syndrome: immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation, or analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.<sup>18</sup> Testing the *BRAF* gene for mutation is indicated when immunohistochemical analysis shows that *MLH1* expression is absent in the tumor. The presence of a *BRAF* mutation indicates that *MLH1* expression is down-regulated through somatic methylation of the promoter region of the gene and not through a germline mutation.<sup>18</sup>

Many NCCN Member Institutions and other comprehensive cancer centers now perform immunohistochemistry and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.<sup>19-22</sup> The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for colorectal cancer, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the CDC.<sup>23-25</sup> The US Multi-Society Task Force on Colorectal Cancer also recommends universal genetic testing of tumors of all patients with newly diagnosed colorectal cancer, as does the American Gastroenterological Association.<sup>26,27</sup> The Cleveland Clinic recently reported on its experiences implementing such a screening approach.<sup>28</sup>





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The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome. This testing is also relevant for treatment selection in stage IV disease (see *Predictive Marker for Pembrolizumab and Nivolumab: MSI Status*, below). Furthermore, MMR/MSI status may be a prognostic marker for rectal cancer, with 5-year rectal cancer-specific survival rates of 100% reported for patients with stage I/II dMMR tumors.<sup>29</sup> An infrastructure needs to be in place to handle the screening results in either case. A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening (available online at [www.NCCN.org](http://www.NCCN.org)).

### Molecular Classification of Colon and Rectal Cancer

Colorectal cancer is a heterogeneous disease. An international consortium has recently reported a molecular classification, defining four different subtypes: CMS1 (MSI Immune), hypermutated, microsatellite unstable (see *Lynch Syndrome*, above), with strong immune activation; CMS2 (Canonical), epithelial, chromosomally unstable, with marked WNT and MYC signalling activation; CMS3 (Metabolic), epithelial, with evident metabolic dysregulation; and CMS4 (Mesenchymal), prominent transforming growth factor  $\beta$  activation, stromal invasion, and angiogenesis.<sup>30</sup> However, this classification is not yet recommended in clinical practice.

### Other Risk Factors for Colorectal Cancer

It is well recognized that individuals with inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease) are at an increased risk for colorectal cancer.<sup>31-33</sup> Other possible risk factors for the development of colorectal cancer include smoking, the consumption of red and processed meats, alcohol consumption, diabetes mellitus, low levels of physical activity, metabolic syndrome, and obesity/high body mass

index (BMI).<sup>32,34-54</sup> In fact, in the EPIC cohort of almost 350,000 individuals, those who adhered to 5 healthy lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, healthy diet) had a hazard ratio (HR) for the development of colorectal cancer of 0.63 (95% CI, 0.54–0.74) compared with those who adhered to  $\leq 1$  of the factors. Other large studies support the conclusion that adherence to healthy lifestyle factors can reduce the risk of colorectal cancer.<sup>55,56</sup>

Some data suggest that consumption of dairy may lower risk for the development of colorectal cancer.<sup>57,58</sup> However, a recent systematic review and meta-analysis of 15 cohort studies (>900,000 subjects; >5200 cases of colorectal cancer) only found an association between risk for colon cancer in men and the consumption of nonfermented milk.<sup>59</sup> No association was seen for rectal cancer in men or for colon or rectal cancer in women, and no association was seen for either cancer in either gender with consumption of solid cheese or fermented milk. Large cohort studies and meta-analyses suggest that other dietary factors may also lower the risk for colorectal cancer, including the consumption of fish and legumes.<sup>60-62</sup> Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs may also decrease the risk for colorectal cancer.<sup>63-68</sup>

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption is associated with a poor prognosis.<sup>37,69-72</sup> Conversely, post-diagnosis fish consumption may be associated with a better prognosis.<sup>73</sup> A family history of colorectal cancer increases risk while improving prognosis.<sup>74</sup> Data on the effect of dairy consumption on prognosis after diagnosis of colorectal cancer are conflicting.<sup>75,76</sup>



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The relationship between diabetes and colorectal cancer is complex. Whereas diabetes and insulin use may increase the risk of developing colorectal cancer, treatment with metformin appears to decrease risk, at least in women.<sup>77-84</sup> Results of a small randomized study suggest that 1 year of low-dose metformin in non-diabetic patients with previously resected colorectal adenomas or polyps may reduce the likelihood of subsequent adenomas or polyps.<sup>85</sup> In addition, although patients with colorectal cancer and diabetes appear to have a worse prognosis than those without diabetes,<sup>86</sup> patients with colorectal cancer treated with metformin seem to have a survival benefit.<sup>87</sup> The data regarding the effects of metformin on colorectal cancer incidence and mortality, however, are not completely consistent, with some studies seeing no effect.<sup>88,89</sup>

### TNM Staging

The NCCN Guidelines for Rectal Cancer adhere to the current TNM (tumor, node, metastases) staging system of the AJCC Cancer Staging Manual (Table 1 of the guidelines).<sup>90</sup> The TNM categories reflect very similar survival outcomes for rectal and colon cancer; these diseases therefore share the same staging system.

The 8<sup>th</sup> edition of the AJCC Staging Manual was released in 2016, with implementation scheduled for January 1, 2018.<sup>90</sup> In this edition, T1 tumors involve the submucosa; T2 tumors penetrate through the submucosa into the muscularis propria; T3 tumors penetrate through the muscularis propria; T4a tumors directly penetrate to the surface of the visceral peritoneum; and T4b tumors directly invade or are adherent to other organs or structures.<sup>90</sup>

Regional lymph node classification includes N1a (1 positive lymph node); N1b (2–3 positive lymph nodes), N2a (4–6 positive nodes); and N2b (7 or more positive nodes). In addition, tumor deposit(s) in the

subserosa, mesentery, or non-peritonealized pericolic or perirectal tissues without regional nodal metastasis (ie, satellite tumor nodules) have been classified as N1c. Within each T stage, survival is inversely correlated with N stage (N0, N1a, N1b, N2a, and N2b).<sup>90</sup>

Metastatic disease is classified as M1a when metastases are to only one site/solid organ (including to lymph nodes outside the primary tumor regional drainage area). M1b is used for metastases to multiple distant sites or solid organs, exclusive of peritoneal carcinomatosis. The 8<sup>th</sup> edition of the AJCC Cancer Staging Manual includes the M1c category for peritoneal carcinomatosis with or without blood-borne metastasis to visceral organs.<sup>90</sup> Patients with peritoneal metastases have a shorter PFS and OS than those without peritoneal involvement.<sup>91</sup>

The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.<sup>90</sup>

### 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; 5) number of positive regional lymph nodes (N); 6) the presence of distant metastases to other organs or sites including non-regional lymph nodes (M); 7) the status of proximal, distal, circumferential (radial), and mesenteric margins<sup>92-96</sup>; 8) neoadjuvant treatment effect<sup>97,98</sup>; 9) lymphovascular invasion (LVI)<sup>99</sup>; 10) perineural invasion (PNI)<sup>100-102</sup>; and 11) the number of tumor deposits.<sup>103-107</sup>





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### Margins

The 8<sup>th</sup> edition of the AJCC Cancer Staging Manual includes the suggestion that the surgeon mark the area of the specimen with the deepest tumor penetration so that the pathologist can directly evaluate the status of the resection margins.<sup>90</sup>

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer.<sup>108</sup> The radial margin for resected segments of the colon that are completely encased by a peritonealized (serosal) surface is also referred to as the peritoneal margin. The CRM is very important in segments of the colon or rectum that are either not encased or only partially encased in peritoneum.<sup>108</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, the retroperitoneal or subperitoneal aspect of the tumor) or from the edge of a lymph node and should be measured in millimeters.

Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen that often requires inking of the outer surfaces and “bread-loaf” slicing of the specimen.<sup>109</sup>

The panel defines a positive CRM as tumor within 1 mm from the transected margin.<sup>94,96,110</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 (OS),<sup>108,110-112</sup> including in patients undergoing neoadjuvant therapy,<sup>95,113</sup> and is an important consideration when postoperative treatment decisions are made. Furthermore, in a retrospective study of over 17,000 patients with rectal cancer, CRM was found to be a better predictor of local recurrence for patients undergoing surgery as initial therapy than for those who had received preoperative therapy.<sup>95</sup> CRM positivity based

solely on intranodal tumor should be noted as such; some studies have shown that positive intranodal CRM is associated with lower recurrence rates than a positive CRM by direct tumor extension. Additional components of the pathologic evaluation of the surgical specimen following a total mesorectal excision (TME) are described under *Surgical Approaches*, below.

### Lymph Nodes

The AJCC and the College of American Pathologists (CAP) recommend evaluation of 12 lymph nodes to accurately identify early-stage colorectal cancers, respectively.<sup>90,108,114</sup> The number of lymph nodes that can be retrieved varies with age and gender of the patient and on tumor grade or site.<sup>115</sup> The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify early-stage rectal cancer.<sup>116</sup> Most of these studies have combined rectal and colon cancers 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>117,118</sup> A more recent analysis of patients with stage I or II rectal cancer in the SEER database found that OS improved with greater numbers of lymph nodes retrieved.<sup>119</sup> Furthermore, the mean number of lymph nodes retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than those treated by surgery alone (13 vs. 19,  $P < .05$ ; 7 vs. 10,  $P \leq .0001$ ).<sup>120-122</sup> In fact, retrieval of fewer lymph nodes may be a marker of a higher tumor response and better prognosis following neoadjuvant treatment.<sup>123,124</sup>

Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells and the identification of particular tumor antigens through immunohistochemical analysis have been



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reported.<sup>125,126</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 immunohistochemistry or by H&E, so-called isolated tumor cells (ITCs), to be micrometastasis.<sup>126,127</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>128</sup> Furthermore, in a recent study involving 156 patients with colon cancer and 44 patients with rectal cancer, this “ultra-staging” of lymph nodes only changed the staging for 1% of patients.<sup>129</sup> Others have noted that micrometastasis found in node-negative patients did not predict outcome.<sup>130</sup> In contrast, a recent meta-analysis found that the presence of micrometastases increases the likelihood of disease recurrence, whereas the presence of ITCs does not.<sup>131</sup>

There is also potential benefit of assessing regional lymph nodes for ITCs. One study of 312 consecutive patients with pN0 disease found that positive cytokeratin staining was associated with a higher risk of recurrence.<sup>132</sup> Relapse occurred in 14% of patients with positive nodes compared to 4.7% of those with negative nodes (HR, 3.00; 95% CI, 1.23–7.32;  $P = .013$ ). A recent systematic review and meta-analysis came to a similar conclusion, finding decreased survival in patients with pN0 disease with immunohistochemical or reverse transcriptase polymerase chain reaction (RT-PCR) evidence of tumor cells in regional nodes.<sup>133</sup>

### Response to Treatment

The most recent CAP Guidelines require that the pathology report comment on treatment effects of neoadjuvant therapy.<sup>114</sup> The tumor response should be graded on a scale of 0 (complete response – no

viable cancer cells observed) to 3 (poor response – minimal or no tumor kill; extensive residual cancer).<sup>97,98,114,134</sup>

### Perineural Invasion

Several studies have demonstrated that the presence of PNI is associated with a significantly worse prognosis.<sup>100-102,135-137</sup> For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at one institution found a 4-fold greater 5-year survival in patients without PNI versus patients whose tumors invaded nearby neural structures.<sup>101</sup> Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year disease-free survival (DFS) compared to those without PNI (29% vs. 82%;  $P = .0005$ ).<sup>102</sup> Similar results were seen for patients with stage III disease.<sup>100</sup> A meta-analysis that included 58 studies and 22,900 patients also found that PNI is associated with a worse 5-year OS (Relative risk [RR], 2.09; 95% CI, 1.68–2.61) and 5-year DFS (RR, 2.35; 95% CI, 1.66–3.31).<sup>136</sup> PNI is therefore included as a high-risk factor for systemic recurrence.

### Tumor Deposits

Tumor deposits, or satellite nodules, are irregular discrete tumor deposits in the perirectal fat that are away from the leading edge of the tumor and show no evidence of residual lymph node tissue, but that are within the lymphatic drainage of the primary tumor. They are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to be due to LVI or occasionally PNI. The number of tumor deposits should be recorded in the pathology report, since they have been shown to be associated with reductions in DFS and OS.<sup>103-107,137</sup>

Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5% 5-year survival rate compared to 37.0% for patients with pN0 tumors and the presence



of satellite nodules ( $P < .0001$ ).<sup>107</sup> Another retrospective study found a similar difference in 5-year OS rates (80.3% vs. 34.9%, respectively;  $P < .001$ ).<sup>138</sup> The association of tumor deposits with decreased survival also holds in patients with rectal cancer who had neoadjuvant chemoradiation (chemoRT).<sup>139,140</sup> Tumor deposits are classified as pN1c.<sup>90</sup>

## The Role of Vitamin D in Colorectal Cancer

Prospective studies have suggested that vitamin D deficiency may contribute to colorectal cancer incidence and/or that vitamin D supplementation may decrease colorectal cancer risk.<sup>141-145</sup>

Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with colorectal cancer.<sup>146-149</sup> In fact, a systematic review and meta-analysis of 5 studies totaling 2330 patients with colorectal cancer compared the outcomes of patients in the highest and lowest categories of vitamin D levels and found better OS (HR, 0.71; 95% CI, 0.55–0.91) and disease-specific mortality (HR, 0.65; 95% CI, 0.49–0.86) in those with higher vitamin D levels.<sup>150</sup> Another meta-analysis determined that the relationship between vitamin D levels and mortality is linear.<sup>151</sup>

Results of a recent randomized, double-blind, placebo-controlled trial, however, showed that supplementation with vitamin D and/or calcium had no effect on the recurrence of colorectal adenomas within 3 to 5 years after removal of adenomas in 2259 participants.<sup>152</sup> Furthermore, no study has yet examined whether vitamin D supplementation improves outcomes in patients with colorectal cancer. In a 2010 report, the Institute of Medicine concluded that data supporting a role for vitamin D were only conclusive in bone health, not in cancer and other diseases.<sup>153</sup> Citing this report and the lack of level 1 evidence, the panel does not currently recommend routine screening for vitamin D

deficiency or supplementation of vitamin D in patients with colorectal cancer.

## Clinical Presentation and Treatment of Nonmetastatic Disease

### Management of Polypoid Cancer

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or villous adenoma, physicians should review pathology<sup>154</sup> and consult with the patient. A malignant rectal polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1).<sup>155</sup> Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis.<sup>108</sup> The panel recommends marking the cancerous polyp site at the time of colonoscopy or within 2 weeks if deemed necessary by the surgeon.

In patients with pedunculated or sessile polyps (adenomas), no additional surgery is required if the polyp has been completely resected with favorable histologic features.<sup>154,156</sup> Favorable histologic features include lesions of grade 1 or 2 without angiolymphatic invasion and with a negative resection margin.<sup>154</sup> For patients with a completely removed, single-specimen, sessile polyp (pT1) with favorable histologic features and clear margins, observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than with polypoid malignant polyps. Also see the section on *Endoscopically Removed Malignant Polyps* in *Principles of Pathologic Review* in the algorithm. Rectal surgery is also an option for these patients.

Rectal surgery is also recommended for patients with polyps with unfavorable histologic features or when the specimen is fragmented or



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margins cannot be assessed. Unfavorable histologic features for adenomas are grade 3 or 4, angiolymphatic invasion, or a positive margin of resection. In such cases, risk of nodal involvement is higher. It should be noted that no consensus currently exists as to the definition of what constitutes a positive margin of resection. A positive margin for an endoscopically removed polyp has been defined as the presence of tumor within 1 to 2 mm from the transected margin or by the presence of tumor cells within the diathermy of the transected margin.<sup>154,157-159</sup> In addition, several studies have shown that tumor budding is an adverse histological feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.<sup>160-163</sup>

For a polyp with fragmented specimen or margins that cannot be assessed, either a transanal excision or a transabdominal resection is recommended. In patients with unfavorable pathologic features, transabdominal resection should be considered in order to include lymphadenectomy. Results from a preoperative endoscopic ultrasound (EUS) 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>164</sup> All patients who have malignant polyps removed by transanal excision or transabdominal resection should undergo total colonoscopy to rule out other synchronous polyps and should undergo surveillance as described in the guidelines.

### Management of Localized Rectal Cancer

Rectal cancer has been defined as a cancerous lesion located within 12 cm of the anal verge by proctoscopy.<sup>165</sup> Some support for this definition comes from the study by Kapiteijn et al,<sup>166</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.<sup>166</sup> A 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 proctoscopy or colonoscopy.<sup>167</sup>

The determination of an optimal treatment plan for an individual patient with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative or palliative), consideration must also be given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence and preserving genitourinary functions. For patients with distal rectal cancer, in particular, the simultaneous achievement of the goals of cure and of minimal impact on quality of life can be challenging.<sup>168</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>169-171</sup> Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoRT with operative treatment for selected patients is recommended.<sup>172</sup>

### 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 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,





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the implications of either clinically understaging or overstaging rectal cancer can be substantial.

Patients who present with rectal cancer appropriate for resection require a complete staging evaluation, including total colonoscopy to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum. They also require a complete physical examination, including carcinoembryonic antigen (CEA) determination and assessment of performance status to determine operative risk. In addition, the accessibility of rectal cancer to evaluation by pelvic MRI with contrast (preferred) or endorectal ultrasound makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.<sup>173</sup>

Additional information regarding the extent of disease and the occurrence of distant metastases can be determined preoperatively through CT scans. Thus, pelvic MRI (preferred) or endorectal ultrasound and CT scans of the chest, abdomen, and pelvis are recommended for the preoperative staging of rectal cancer. CT should be with IV and oral contrast, and if the CT of the abdomen and pelvis is inadequate or if CT with IV contrast is contraindicated, an abdominal/pelvic MRI with contrast plus a non-contrast chest CT should be considered. The chest CT can identify lung metastases, which occur in approximately 4% to 9% of patients with colon and rectal cancer.<sup>174-176</sup> A series of 378 patients found that resection of pulmonary metastases resulted in 3-year recurrence-free survival of 28% and 3-year OS of 78%.<sup>177</sup>

The consensus of the panel is that a PET scan is not indicated. PET/CT, if done, does not supplant a contrast-enhanced diagnostic CT scan. PET/CT should only be used to evaluate an equivocal finding on

a contrast-enhanced CT scan or in patients with a strong contraindication to IV contrast.

Results from a meta-analysis of 90 studies involving the accuracy of EUS, MRI, and CT for preoperative staging of rectal cancer demonstrated that EUS and MRI have similarly high sensitivities for evaluating the depth of tumor penetration into the muscularis propria (94%), although EUS was found to be more specific than MRI in the evaluation of local tumor invasion (86% vs. 69%).<sup>178</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>178,179</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>178</sup> the sensitivities and specificities of the 3 imaging modalities for accurately evaluating lymph node involvement were comparable: CT (55% and 74%); EUS (67% and 78%); and MRI (66% and 76%). However, only CT and MRI can evaluate iliac and mesenteric or retroperitoneal nodes.<sup>178</sup> 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>180</sup> A disadvantage of EUS is a high degree of operator dependence.<sup>178</sup> An advantage of MRI is its ability to provide accurate images of soft tissue structures in the mesorectum, including the mesorectal fascia so as to provide information useful in the prediction of the CRM prior to radical surgery.<sup>179-182</sup> Recently published 5-year follow-up results of the MERCURY trial show that high-resolution MRI can accurately assess the CRM preoperatively, differentiating patients with low-risk and high-risk disease.<sup>183</sup> Patients with MRI-clear CRM had a 5-year OS of 62.2% compared with 42.2% in patients with MRI-involved CRM (HR, 1.97; 95% CI, 1.27–3.04;  $P < .01$ ). The preoperative MRI



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imaging also predicted DFS (HR, 1.65; 95% CI, 1.01–2.69;  $P < .05$ ) and local recurrence (HR, 3.50; 95% CI, 1.53–8.00;  $P < .05$ ). A group of experts developed consensus guidelines for standardized imaging of rectal cancer by MRI.<sup>184</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.

### *Restaging / Assessing Treatment Response*

Restaging after neoadjuvant treatment is done to plan the surgical approach and, increasingly, to determine if additional therapy or resection can be avoided for select patients. Future and ongoing trials will help to answer these questions (see *Wait-and-See Nonoperative Approach for Clinical Complete Responders* and *Preoperative Chemotherapy Without Chemoradiation*, below). MRI, CT, and EUS are the most commonly used modalities for restaging after neoadjuvant treatment, but the accuracy of these techniques for determining T stage and lymph node involvement is limited.<sup>185-193</sup> Advanced functional MRI techniques (eg, dynamic contrast-enhanced MRI, diffusion-weighted MRI) allow for the measurement of microcirculation, vascular permeability, and tissue cellularity and thus may be useful for determining response to neoadjuvant treatment and restaging patients with rectal cancer.<sup>192,194-196</sup> FDG-PET/CT is also being investigated for its ability to accurately determining response to neoadjuvant treatment.<sup>195,197</sup>

### ***Surgical Approaches***

A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions.<sup>198,199</sup> These methods include local procedures, such as polypectomy, transanal excision, and transanal endoscopic microsurgery (TEM), and more invasive procedures involving a transabdominal resection (eg, low anterior resection [LAR], proctectomy with TME and coloanal anastomosis, abdominoperineal resection [APR]).<sup>198,199</sup>

### *Transanal Excision*

Transanal excision is only appropriate for selected T1, N0 early-stage cancers. Small (<3 cm), well to moderately differentiated tumors that are within 8 cm of the anal verge and limited to less than 30% of the rectal circumference and for which there is no evidence of nodal involvement can be approached with transanal excision with negative margins.<sup>200</sup>

TEM can facilitate excision of small tumors through the anus when lesions can be adequately identified in the rectum. TEM may be technically feasible for more proximal lesions. Although data are limited, a 2015 meta-analysis found that TEM may achieve superior oncologic outcomes compared with transanal excision.<sup>201</sup> Both transanal excision and TEM involve a full-thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Negative (>3 mm) deep and mucosal margins are required, and tumor fragmentation should be avoided.

The locally excised specimen should be oriented and pinned before fixation and brought to the pathologist by the surgeon to facilitate an oriented histopathologic evaluation of the specimen. If pathologic examination reveals adverse features such as positive margins, LVI,





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poor differentiation, or invasion into the lower third of the submucosa (sm3 level),<sup>202,203</sup> a more radical resection is recommended.

Data are limited on long-term patient outcomes, including risk of local recurrence, for patients undergoing local excision for T2 tumors.<sup>204</sup> Results of a multi-institutional, single-arm, open-label, non-randomized, phase II trial suggest that chemoradiotherapy with CapeOx followed by local excision may be a safe alternative to transabdominal resection in patients with T2N0 distal rectal cancer.<sup>205</sup> A meta-analysis also suggests that this approach of neoadjuvant chemoRT followed by local excision may be a safe and effective alternative for patients with any T and any N stage of rectal cancer who refuse or are unfit for transabdominal resection.<sup>206</sup> Further studies in this area are needed.

Advantages of a local procedure include minimal morbidity (eg, a sphincter-sparing procedure) and mortality and rapid postoperative recovery.<sup>168,204</sup> Limitations of a local excision include the absence of pathologic staging of nodal involvement. Further, evidence indicates that lymph node micrometastases are both common in early rectal lesions and unlikely to be identified by endorectal ultrasound.<sup>207</sup> These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.<sup>204,208,209</sup> A retrospective study of 282 patients undergoing either transanal excision or radical resection for T1 rectal cancer from 1985 to 2004 showed respective local recurrence rates of 13.2% and 2.7% for these 2 groups ( $P = .001$ ).<sup>209</sup> A similar retrospective study of 2124 patients showed local recurrence rates of 12.5% and 6.9% for patients undergoing local excision versus standard resection, respectively ( $P = .003$ ).<sup>204</sup> More recently, an analysis of >164,000 individuals from the National Cancer Data Base with resected, invasive, nonmetastatic rectal cancer diagnosed from 1998 to 2010 found that positive margins were more likely after local excision compared to

transabdominal excision in both the T1 and T2 populations (95% vs. 76% in T1/T2 combined;  $P < .001$ ).<sup>210</sup> In the T1N0 population, a small but significant decrease in OS was also noted in the local excision group. Interestingly, limited data suggest that TEM might have superior oncologic outcomes in patients with stage I rectal cancer compared with radical resection,<sup>208,211</sup> although not all studies have seen such results.<sup>212</sup>

Thus, careful patient selection for local excision of T1N0 rectal cancer is important, as is the careful examination of the resection specimen with subsequent transabdominal resection in patients found to have T2 disease or high-risk features, as described above.

### *Transabdominal Resection*

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

In transabdominal resections, TME is recommended. A TME involves an en bloc removal of the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and mesorectal fascia as a “tumor package” through sharp dissection and is designed to spare the autonomic nerves.<sup>168,199,213</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>214</sup> The TME approach is



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designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.<sup>215</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. In cases where anal function is intact and distal clearance is adequate, the TME may be followed by creation of a coloanal anastomosis.

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

An APR with TME should be performed when the tumor directly involves the anal sphincter or the levator muscles. An APR is also necessary in cases where a margin-negative resection of the tumor would result in loss of anal sphincter function and incontinence. An APR involves en bloc resection of the rectosigmoid, the rectum, and the anus, as well as the surrounding mesentery, mesorectum (TME), and perianal soft tissue, and it necessitates creation of a colostomy.<sup>216</sup> In the NSABP R-04 trial, patients who had an APR reported worse body image, worse micturition symptoms, and less sexual enjoyment at 1-year post surgery than those who had sphincter-sparing surgery.<sup>217</sup> An extralevator APR may have benefits over a conventional APR approach, including lower rates of CRM involvement and local recurrence.<sup>218</sup>

Pathologists play a key role following TME in evaluating the surgical specimen, including a macroscopic assessment of both its external appearance/completeness and the CRM.<sup>219,220</sup> The panel defines a

positive CRM as tumor within 1 mm from the transected margin (see *Pathology*, above).<sup>94,96,110</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>94</sup>

Recent retrospective comparisons of the outcomes of patients undergoing an APR versus an LAR in the treatment of rectal cancer have shown that those treated with an APR have worse local control and OS.<sup>221,222</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>221</sup> Importantly, quality of life between patients with or without a permanent colostomy appears to be fairly comparable.<sup>223,224</sup>

### *Laparoscopic Resection*

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer have been maturing in recent years.<sup>225-228</sup>

One large prospective multicentre study, which included 4405 patients with rectal cancer but was not randomized, found no differences in recurrence or survival, although complications and other measures of quality indicated a benefit to the laparoscopic approach.<sup>229</sup> The phase III COLOR II trial, powered for non-inferiority, also randomized patients with localized rectal cancer to laparoscopic or open surgery. Short-term secondary endpoints were met, with patients in the laparoscopic arm losing less blood, having shorter hospital stays, and having a quicker



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return of bowel function, but with longer operation times.<sup>230</sup> No differences were seen in completeness of resection, percentage of patients with positive CRM, morbidity, or mortality between the arms. The primary endpoint of locoregional recurrence at 3 years was identical in the 2 groups, at 5.0%, and no statistically significant differences were seen in DFS or OS.<sup>225</sup>

In the CLASICC trial comparing laparoscopically assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.<sup>231</sup> No significant differences in local recurrence, DFS, or OS were observed between the 2 groups of patients with colon or rectal cancer based on surgical approach. A 5-year follow-up of the CLASICC trial showed that this lack of difference in local recurrence, DFS, or OS was maintained for patients with rectal cancer, despite a trend towards better 5-year OS after laparoscopic surgery (52.9% and 60.3% for open and laparoscopic surgery, respectively;  $P = .132$ ).<sup>232</sup>

The COREAN trial randomized patients with stage II or III low- to mid-rectal cancer to an open or laparoscopic resection, with short-term benefits seen to the laparoscopic approach.<sup>233</sup> The primary endpoint, 3-year DFS, did not differ between the 2 groups at 72.5% (95% CI, 65.0–78.6) for open surgery and 79.2% (95% CI, 72.3–84.6) for the laparoscopic group.<sup>226</sup> Factors that may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically assisted surgery for colorectal cancer have been described,<sup>234</sup> and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Two other trials, ACOSOG Z6051 and ALaCaRT, have reported pathologic outcomes.<sup>227,228</sup> In Z6051, the primary endpoint was a composite of CRM >1 mm, negative distal margin, and TME completeness.<sup>227</sup> No significant differences were observed between the

arms in these 3 measures or in the composite of successful resection. For example, complete or nearly complete TME was achieved in 92.1% (95% CI, 88.7–95.5) in the laparoscopic resection arm and 95.1% (95% CI, 92.2–97.9) in the open resection arm, for a difference of –3.0 (95% CI, –7.4–1.5;  $P = .20$ ). However, the criteria for non-inferiority of the laparoscopic approach were not met. In ALaCaRT, the primary endpoint was also a composite of resection quality measures.<sup>228</sup> Successful resections were achieved in 82% of the laparoscopic resection arm and 89% of the open resection arm, for a difference of –7.0% (95% CI, –12.4% to infinity). A negative CRM was achieved in 93% and 97%, respectively (risk difference, –3.7%; 95% CI, –7.6%–0.1%;  $P = .06$ ). As in Z6051, the criteria for non-inferiority of the laparoscopic approach were not met in ALaCaRT. Longer follow-up with oncologic outcomes of these trials are needed.

Reviews and meta-analyses including these and additional small trials have also been published.<sup>226,235-248</sup> They consistently find the laparoscopic approach to be safe and feasible. In addition, an analysis of results from >18,000 individuals in the National Cancer Data Base undergoing LAR for rectal cancer found short-term oncologic outcomes to be similar between the open and laparoscopic approaches.<sup>249</sup>

In conclusion, some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery,<sup>225,226</sup> whereas other studies have shown the laparoscopic approach to be associated with higher rates of CRM positivity and incomplete TME.<sup>227,228</sup> Therefore, the panel defined principles by which laparoscopic resection of rectal cancer can be considered: the procedure can be considered by an experienced surgeon, should include thorough abdominal exploration, and should be limited to lower-risk tumors, as outlined in the guidelines. An international group of



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experts has defined standards for the technical details of laparoscopic TME.<sup>250</sup>

### ***Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease***

Neoadjuvant/adjuvant therapy of stage II (T3-4, node-negative disease with tumor penetration through the muscle wall) or stage III (node-positive disease without distant metastasis) rectal cancer often includes locoregional treatment 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.

Although radiation therapy (RT) has been associated with decreased rates of local recurrence of rectal cancer, it is also associated with increased toxicity (eg, radiation-induced injury, hematologic toxicities) relative to surgery alone.<sup>109,251,252</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>109,253,254</sup> However, 22% of 188 patients clinically staged with T3, N0 rectal cancer by either EUS or MRI who subsequently received preoperative chemoRT had positive lymph nodes following pathologic review of the surgical specimens according to results of a retrospective multicenter study,<sup>255</sup> suggesting that many patients are under-staged and would benefit from chemoRT. Therefore, the guidelines recommend preoperative chemoRT for patients with T3, N0 disease.

Combined-modality therapy consisting of surgery, concurrent fluoropyrimidine-based chemotherapy with ionizing radiation to the pelvis (chemoRT), and chemotherapy is recommended for the majority of patients with stage II or stage III rectal cancer. Use of perioperative pelvic RT in the treatment of patients with stage II/III rectal cancer continues to evolve. In these patients, the current guidelines recommend 2 possible sequences of therapy: 1) chemoRT preoperatively and chemotherapy postoperatively; or 2) chemotherapy followed by chemoRT followed by resection. The total duration of perioperative therapy, including chemoRT and chemotherapy, should not exceed 6 months.

### ***Preoperative Versus Postoperative Radiation***

Several studies have compared the administration of radiation preoperatively versus postoperatively for stage II/III rectal cancer.<sup>256,257</sup> A large prospective, randomized trial from the German Rectal Cancer Study Group (the CAO/ARO/AIO-94 trial) compared preoperative versus postoperative chemoRT in the treatment of clinical stage II/III rectal cancer.<sup>256</sup> Results of this study indicated that preoperative therapy was associated with a significant reduction in local recurrence (6% vs. 13%;  $P = .006$ ) and treatment-associated toxicity (27% vs. 40%;  $P = .001$ ), although OS was similar in the 2 groups. Long-term follow-up of this trial was later published.<sup>258</sup> The improvement in local control persisted, with the 10-year cumulative incidence of local recurrence at 7.1% and 10.1% in the preoperative and postoperative treatment arms, respectively ( $P = .048$ ). OS at 10 years was again similar between the groups (59.6% and 59.9%, respectively;  $P = .85$ ), as was DFS and the occurrence of distant metastases.

Interestingly, a recent SEER database analysis of 4724 patients with T3N0 rectal cancer found that radiation given after resection was associated with a significant decrease in risk for cancer death compared





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to surgery without any radiation (HR, 0.69; 95% CI, 0.58–0.82;  $P < .001$ ), while radiation given before resection was not (HR, 0.86; 95% CI, 0.72–1.04;  $P = .13$ ).<sup>259</sup>

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue.<sup>256,257,260</sup> First of all, reducing tumor volume may facilitate resection and increase the likelihood of a sphincter-sparing procedure. Although some studies have indicated that preoperative radiation or chemoRT is associated with increased rates of sphincter preservation in patients with rectal cancer,<sup>256,257</sup> this conclusion is not supported by 2 meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.<sup>261,262</sup> Second, irradiating tissue that is surgery-naïve and thus better oxygenated may result in increased sensitivity to RT. Third, preoperative radiation can avoid the occurrence of radiation-induced injury to small bowel trapped in the pelvis by post-surgical adhesions. Finally, preoperative radiation that includes structures that will be resected increases the likelihood that an anastomosis with healthy colon can be performed (ie, the anastomosis remains unaffected by the effects of RT because irradiated tissue is resected).

One disadvantage of using preoperative RT is the possibility of over-treating early-stage tumors that do not require adjuvant radiation.<sup>256,263</sup>

Improvements in preoperative staging techniques, such as MRI or CT scans, have allowed for more accurate staging, but the risk of over-staging disease has not been eliminated.<sup>255</sup> Weighing these advantages and disadvantages, the panel recommends preoperative chemoRT for patients with stage II/III rectal cancer. Postoperative chemoRT is recommended when stage I rectal cancer is upstaged to stage II or III after pathologic review of the surgical specimen. Postoperative chemoRT regimens commonly employ a “sandwich” approach –

whereby chemotherapy (typically 5-FU–based) is administered before and after the chemoRT regimen.<sup>254,264,265</sup>

### *Concurrent Chemotherapy with Radiation*

A number of randomized trials have evaluated the effectiveness of the addition of chemotherapy to radiation administered either preoperatively following clinical evaluation/staging (eg, T3-4 by EUS) or postoperatively following pathologic staging of rectal cancer as pT3 and/or N1-2.<sup>266</sup> Putative benefits of the addition of chemotherapy concurrent with either pre- or postoperative RT include local RT sensitization and systemic control of disease (ie, eradication of micrometastases). Preoperative chemoRT also has the potential to increase rates of pathologic complete response and sphincter preservation.

In a study of patients with T3-4 rectal cancer without evidence of distant metastases who were randomly assigned to receive either preoperative RT alone or preoperative concurrent chemoRT with 5-FU/LV, no difference in OS 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%;  $P < .05$ ) and grade 3/4 toxicity (14.6% vs. 2.7%;  $P < .05$ ) and less likely to exhibit local recurrence of disease (8.1% vs. 16.5%;  $P < .05$ ).<sup>266</sup>

Preliminary results of a phase III trial that included an evaluation of the addition of chemotherapy to preoperative RT in patients with T3-4 resectable rectal cancer demonstrated that use of 5-FU/LV chemotherapy enhanced the tumoricidal effect of RT when the 2 approaches were used concurrently.<sup>267</sup> Significant reductions in tumor size, pTN stage, and lymphatic, vascular, and PNI rates were observed with use of combined-modality therapy compared with use of RT and surgery without chemotherapy.<sup>267</sup> More mature results from this trial,



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which included 4 treatment groups (preoperative RT; preoperative chemoRT; preoperative RT plus postoperative chemotherapy; and preoperative chemoRT plus postoperative chemotherapy), however, indicated that no significant differences in OS were associated with adding 5-FU-based chemotherapy preoperatively or postoperatively.<sup>268</sup>

The conclusions of these trials have been supported in a 2009 systematic review that included 4 randomized controlled trials.<sup>269</sup> In addition, a recent Cochrane review of 6 randomized controlled trials found that chemotherapy added to preoperative radiation in patients with stage III, locally advanced rectal cancer reduced the risk of local recurrence, but had no effect on OS, 30-day mortality, sphincter preservation, and late toxicity.<sup>270</sup> Similarly, a separate Cochrane review of stage II and III resectable disease found that the addition of chemotherapy to preoperative radiation enhances pathologic response and improves local control, but has no effect on DFS or OS.<sup>271</sup> Another recent meta-analysis of 5 randomized controlled trials comparing neoadjuvant chemoRT with neoadjuvant radiotherapy came to similar conclusions.<sup>252</sup>

With respect to the type of chemotherapy administered concurrently with RT,<sup>254</sup> the equivalence of bolus 5-FU/LV and infusional 5-FU in concurrent chemoRT for rectal cancer is supported by the results of a phase III trial (median follow-up of 5.7 years) in which similar outcomes with respect to OS and relapse-free survival were observed when an 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>265</sup> On the other hand, results from an earlier trial from the North Central Cancer Treatment Group (NCCTG) showed that postoperative administration of infusional 5-FU during pelvic irradiation was associated with longer OS when compared to bolus 5-FU.<sup>264</sup> Most of the patients in this study had node-positive

disease. The panel considers bolus 5-FU/LV/RT as an option for patients not able to tolerate capecitabine or infusional 5-FU (both preferred in the chemoRT setting).

Recent studies have shown that capecitabine is equivalent to 5-FU in perioperative chemoRT therapy.<sup>272,273</sup> The randomized NSABP R-04 trial compared the preoperative use of infusional 5-FU with or without oxaliplatin to capecitabine with or without oxaliplatin in 1608 patients with stage II or III rectal cancer.<sup>273,274</sup> No differences in locoregional events, DFS, OS, complete pathologic response, sphincter-saving surgery, or surgical downstaging were seen between the regimens, while toxicity was increased with the inclusion of oxaliplatin.

Similarly, a phase III randomized trial in which 401 patients with stage II or III rectal cancer received capecitabine– or 5-FU–based chemoRT either pre- or postoperatively showed that capecitabine was non-inferior to 5-FU with regard to 5-year OS (capecitabine 75.7% vs. 5-FU 66.6%;  $P = .0004$ ), with capecitabine showing borderline significance for superiority ( $P = .053$ ).<sup>272</sup> Furthermore, in this trial capecitabine demonstrated a significant improvement in 3-year DFS (75.2% vs. 66.6%;  $P = .034$ ).<sup>272</sup> Because of these studies, capecitabine given concurrently with RT is now listed in the guidelines as a category 2A recommendation. The panel feels that capecitabine is an acceptable alternative to infusional 5-FU in those patients who are able to manage the responsibilities inherent in self-administered, oral chemotherapy.

**Addition of oxaliplatin:** In attempts to improve on the outcomes achieved with neoadjuvant 5-FU/RT or capecitabine/RT, several large randomized phase III trials (ACCORD 12, STAR-01, R-04, CAO/ARO/AIO-04, and FOWARC) addressed the addition of oxaliplatin to the regimens. In a planned interim report of primary tumor response in the STAR-01 trial, grade 3 and 4 adverse events occurred more





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frequently in patients receiving infusional 5-FU/oxaliplatin/RT than in those receiving infusional 5-FU/RT (24% vs. 8%,  $P < .001$ ), while there was no difference in pathologic response between the arms of the study (16% pathologic complete response in both arms).<sup>275</sup> Recently reported results of the NSABP R-04 trial also showed that the addition of oxaliplatin did not improve clinical outcomes including the endpoints of locoregional events, DFS, OS, pathologic complete response, sphincter-saving surgery, and surgical downstaging, while it increased toxicity.<sup>273,274</sup> Further follow-up of these trials is necessary to see if there is a difference in local recurrence rates and progression-free survival (PFS) over time. The primary endpoints of OS for the STAR-01 trial will be reported in the future.

Similar results were seen in the ACCORD 12/0405-Prodige 2 trial, in which capecitabine/RT (45 Gy) was compared to CapeOx/RT (50 Gy) and the primary endpoint was pathologic complete response.<sup>276</sup> The pathologic complete response rates were similar at 19.2% and 13.9% ( $P = .09$ ) for the oxaliplatin-containing arm and the control arm, respectively. Although patients treated with oxaliplatin and the higher radiation dose in the ACCORD 12 trial had an increased rate of minimal residual disease at the time of surgery (39.4% vs. 28.9%,  $P = .008$ ), this did not translate to improved local recurrence rates, DFS, or OS at 3 years.

Results of the German CAO/ARO/AIO-04 trial have been published.<sup>277,278</sup> This trial also assessed the addition of oxaliplatin to a fluorouracil RT regimen. In contrast to STAR-01, R-04, and ACCORD 12, higher rates of pathologic complete response were seen in the oxaliplatin arm (17% vs. 13%,  $P = .038$ )<sup>278</sup>, but this result could be because of differences in the fluorouracil schedule between the arms.<sup>279</sup> The primary endpoint of this trial, the 3-year DFS rate, was 75.9% (95% CI, 72.4%–79.5%) in the oxaliplatin arm versus 71.2% (95% CI, 67.6%–

74.9%) in the control group ( $P = .03$ ).<sup>277</sup> Importantly, oxaliplatin was also added to the adjuvant therapy in the AIO-04 trial but not in the other trials, so cross-trial comparisons are limited.

In line with CAO/ARO/AIO-04, the Chinese FOWARC phase III open-label, multicenter trial, which randomized patients with locally advanced rectal cancer to neoadjuvant treatment consisting of infusional 5-FU/LV-RT, FOLFOX-RT, or FOLFOX, found that FOLFOX-RT resulted in higher rates of pathologic complete response and downstaging than the other regimens.<sup>280</sup>

Based on the results available to date, the addition of oxaliplatin to neoadjuvant chemoRT is not recommended at this time.

Another randomized multicenter phase III trial looked at the addition of oxaliplatin during concurrent capecitabine chemoRT in the adjuvant setting for pathologic stage II/III disease.<sup>281</sup> Interim analysis showed no significant difference in 3-year DFS, OS, local recurrences, or distant metastases, with an increase in grade 3/4 acute toxicity in the CapeOx-RT group.

**Addition of targeted agents:** The randomized phase II EXPERT-C trial assessed complete response rate with the addition of cetuximab to radiation treatment in 165 patients.<sup>282</sup> Patients in the control arm received CapeOx followed by capecitabine/RT, then surgery followed by CapeOx. Patients randomized to the cetuximab arm received the same therapy with weekly cetuximab throughout all phases. A significant improvement in OS was seen in patients with *KRAS* exon 2/3 wild-type tumors treated with cetuximab (HR, 0.27; 95% CI, 0.07–0.99;  $P = .034$ ). However, the primary endpoint of complete response rate was not met, and other phase II trials have not shown a clear benefit to the addition



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of cetuximab in this setting.<sup>283,284</sup> Further evaluation of this regimen is warranted.

The randomized, multicenter, phase II SAKK 41/07 trial evaluated the addition of panitumumab to preoperative capecitabine-based chemoRT in patients with locally advanced, *KRAS* wild-type rectal cancer.<sup>285</sup> The primary endpoint was pathologic near-complete plus complete tumor response, which occurred in 53% (95% CI, 36%–69%) of patients in the panitumumab arm versus 32% (95% CI, 16%–52%) in the control arm. Patients receiving panitumumab experienced increased rates of grade 3 or greater toxicity.

A phase II study of 57 patients with resectable T3/T4 rectal cancer evaluated preoperative treatment with capecitabine, oxaliplatin, bevacizumab, and RT, followed by surgery 8 weeks later and adjuvant FOLFOX/bevacizumab.<sup>286</sup> The 5-year OS rate was 80%, and the 5-year relapse-free survival rate was 81%. However, the primary endpoint of pathologic complete response was not met, significant toxicities were observed, and compliance with adjuvant therapy was low.

Additional phase II trials assessing the effects of adding irinotecan or bevacizumab to neoadjuvant or adjuvant regimens have begun.<sup>287-289</sup>

However, at this time the panel does not endorse the use of bevacizumab, cetuximab, panitumumab, irinotecan, or oxaliplatin with concurrent radiotherapy for rectal cancer.

### *Induction Chemotherapy*

Several small trials have tested the utility of a course of neoadjuvant chemotherapy preceding chemoRT and resection.<sup>290-295</sup> In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CapeOx either before chemoRT or after surgery.<sup>292,296</sup> Similar pathologic complete response rates were seen, and induction chemotherapy

appeared to be less toxic and better tolerated. Another phase II trial randomized patients to chemoRT and surgery with or without FOLFOX induction therapy.<sup>294</sup> There were no differences between the clinical outcomes, but the group receiving induction therapy experienced higher toxicity. The phase II AVACROSS study assessed the safety and efficacy of adding bevacizumab to induction therapy with CapeOx prior to capecitabine/bevacizumab-chemoRT and surgery.<sup>295</sup> The regimen was well tolerated with a pathologic complete response rate of 36%.

Possible benefits of using chemotherapy first include the early prevention or eradication of micrometastases, higher rates of pathologic complete response, minimizing the time patients need an ileostomy, facilitating resection, and improving the tolerance and completion rates of chemotherapy. This approach was added to the 2015 version of these guidelines as an acceptable option.

### *Preoperative Chemotherapy Without Chemoradiation*

A small single-center phase II pilot trial treated patients with stage II or III rectal cancer with induction FOLFOX/bevacizumab chemotherapy followed by chemoRT only in those with stable or progressive disease and resection in all patients.<sup>297</sup> All 32 of the participants had an R0 resection, and the 4-year DFS was 84% (95% CI, 67%–94%). The ongoing N1048/C81001/Z6092 PROSPECT trial by The Alliance for Clinical Trials in Oncology is also asking whether chemotherapy alone is effective in treating stage II or III high rectal cancer in patients with at least 20% tumor regression following neoadjuvant treatment (clinicaltrials.gov NCT01515787).

The phase III FOWARC trial, discussed above, compared neoadjuvant therapy with and without radiation (without additional therapy for those with stable or progressive disease) and found that neoadjuvant FOLFOX without radiation gave lower rates of pathologic complete



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response than regimens that included radiation (6.6% vs. 14.0% for 5-FU-RT and 27.5% for FOLFOX-RT).<sup>280</sup> Rates of downstaging were similar to the 5-FU-RT (35.5% vs. 37.1% for 5-FU-RT and 56.4% for FOLFOX-RT).

A 2015 systematic review identified 1 randomized phase III trial, 6 single-arm phase II trials, and 1 retrospective case series study that addressed the effectiveness of neoadjuvant chemotherapy (without chemoRT) and surgery in patients with locally advanced rectal cancer.<sup>298</sup> The ranges of R0 resection and pathological complete response rates were 90% to 100% and 4% to 33%, respectively.

This approach could spare patients the morbidities associated with radiation, but the panel considered it investigational at this time.

### *Technical Aspects of Radiation Therapy*

With respect to administration of RT, multiple RT fields should include the tumor or tumor bed with a 2- to 5-cm margin, presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures; inclusion of the inguinal nodes for tumors invading into the distal anal canal can also be considered. Recommended doses of radiation are typically 45 to 50 Gy in 25 to 28 fractions to the pelvis using 3 or 4 fields. Positioning and other techniques to minimize radiation to the small bowel are encouraged. The Radiation Therapy Oncology Group (RTOG) has established normal pelvic contouring atlases for females and males (available online at <http://www.rtog.org/CoreLab/ContouringAtlases.aspx>).<sup>299</sup> Intensity-modulated RT (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations such as re-irradiation of previously treated recurrent disease or unique anatomical situations.

Coordination of preoperative therapy, surgery, and adjuvant chemotherapy is important. Although longer intervals from completion of chemoRT to surgery have been shown to be associated with an increase in pathologic complete response rates,<sup>300-305</sup> it is unclear whether such longer intervals are associated with clinical benefit. Results of one National Cancer Data Base analysis suggest that an interval of >8 weeks was associated with increased odds of pathologic complete response,<sup>306</sup> whereas other similar analyses concluded that an interval >56 or 60 days (8–8.5 weeks) is associated with higher rates of positive margins, lower rates of sphincter preservation, and/or shorter survival.<sup>307,308</sup>

The GRECCAR6 phase III, multicenter, randomized, open-label, parallel-group controlled trial randomized patients with stage II/III rectal cancer treated with chemoRT to a 7-week or an 11-week interval before surgery.<sup>309</sup> The pathologic complete response rate was not different between the groups (15.0% vs. 17.4%;  $P = .60$ ), but the morbidity (44.5% vs. 32%;  $P = .04$ ), medical complications (32.8% vs. 19.2%;  $P = .01$ ), and rate of complete mesorectal resection (78.7% vs. 90%;  $P = .02$ ) were worse in the 11-week group. The rate of anastomotic leaks and the mean length of hospital stay were similar between the groups.

Based on these data, the panel recommends an interval of 5 to 12 weeks following completion of full-dose 5½-week chemoRT prior to surgical resection for patients treated with preoperative chemoRT in order to allow patient recuperation from chemoRT-associated toxicities.

### *Short-course Radiation*

Several European studies have looked at the efficacy of a shorter course of preoperative radiation (25 Gy over 5 days), not combined with chemotherapy, for the treatment of rectal cancer. The results of the Swedish Rectal Cancer Trial evaluating the use of short-course RT



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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>310</sup> However, a follow-up study published in 2005 showed that the patients with short-course preoperative RT had increased relative risk for postoperative hospitalization due to bowel obstructions and other gastrointestinal complications.<sup>311</sup> A number of other studies also investigating the effectiveness of preoperative short-course RT in patients with rectal cancer staged as T1-3 have demonstrated that OS was not significantly affected despite improvements in local control of disease.<sup>166,312,313</sup> A more recent multicenter, randomized study of 1350 patients with rectal cancer compared 1) short-course preoperative RT and no postoperative treatment with 2) no preoperative RT and a postoperative approach that included chemoRT in selected patients (ie, those with a positive CRM following resection) and no RT in patients without evidence of residual disease following surgery.<sup>314</sup> Results indicated that patients in the preoperative RT arm had significantly lower local recurrence rates and a 6% absolute improvement in 3-year DFS ( $P = .03$ ), although no difference in OS was observed between the arms of the study.<sup>314,315</sup>

Long-term (12-year) follow-up of one of the short-course radiation trials (the Dutch TME trial<sup>312</sup>) was reported.<sup>316</sup> The analysis showed that 10-year survival was significantly improved in patients with stage III disease with a negative circumferential margin in the radiotherapy plus surgery group compared to the group that received surgery alone (50% vs. 40%;  $P = .032$ ).<sup>316</sup> However, this long follow-up showed that secondary malignancies and other non-rectal cancer causes of death were more frequent in the radiotherapy group than in the control group (14% vs. 9% for secondary malignancies), negating any survival advantage in the node-negative subpopulation.

A few studies have compared short-course RT to long-course chemoRT. One randomized study of 312 patients in Poland directly compared preoperative short-course radiation and more conventional preoperative long-course chemoRT and found no differences in local recurrence or survival.<sup>317</sup> Similarly, an Australian/New Zealand trial (Trans-Tasman Radiation Oncology Group [TROG] trial 01.04) that randomized 326 patients to short-course radiation or long-course chemoRT found no differences in local recurrence and OS rates.<sup>318</sup> In addition, rates of late toxicity, distant recurrence, and relapse-free survival were not significantly different between the arms. Patients in the long-course arm were more likely to experience serious adverse events (eg, radiation dermatitis rates, 0% vs. 5.6%;  $P = .003$ ), whereas patients in the short-course arm were more likely to have a permanent stoma (38.0% vs. 29.8%;  $P = .13$ ).<sup>319</sup> Finally, a trial compared short-course RT with long-course chemoRT with delayed surgery in both groups.<sup>320</sup> Although the long-course arm experienced greater tumor downsizing and downstaging compared with short-course treatment, no differences were seen in the R0 resection rates or postoperative morbidity.

A 2014 systematic review identified 16 studies (randomized controlled trials, phase II trials, and retrospective studies) that addressed the interval between short-course radiation and resection of rectal cancer.<sup>321</sup> Lower rates of severe acute post-radiation toxicity but higher rates of minor postoperative complications were seen in the immediate-surgery group (1- to 2-week interval) compared with the delayed surgery group (5- to 13-week interval). The pCR rates were significantly higher in the delayed-surgery group, with no differences in sphincter preservation and R0 resection rates.

Overall, it appears that short-course RT gives effective local control and the same OS as more conventional RT schedules, and therefore is





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considered as an appropriate option for patients with T3N0 or T1-3N1-2 rectal cancer. Short-course RT is not recommended for T4 disease. A multidisciplinary evaluation, including a discussion of the need for down-staging and the possibility of long-term toxicity, is recommended when considering short-course RT.

### *Response to Neoadjuvant Treatment*

Fifty percent to 60% of patients are down-staged following neoadjuvant therapy, with about 20% of patients showing a pathologic complete response.<sup>322-328</sup> Recent studies have suggested that the response to neoadjuvant treatment correlates with long-term outcomes in patients with rectal cancer. In the MERCURY prospective cohort trial, 111 patients were assessed by MRI and pathologic staging.<sup>329</sup> On multivariate analysis, MRI-assessed tumor regression grade was significantly associated with OS and DFS. Patients with poor tumor regression grade had 5-year survival rates of 27% versus 72% for patients with good tumor regression grade ( $P = .001$ ), and DFS rates were 31% versus 64% ( $P = .007$ ). Similarly, in the CAO/ARO/AIO-94 trial, patients with pathologic complete regression had 10-year cumulative incidence of distant metastasis and DFS of 10.5% and 89.5%, respectively, while those with poor regression had corresponding incidences of 39.6% and 63%.<sup>330</sup> A recent retrospective review of 725 patients with rectal cancer found similar results.<sup>326</sup> In this study, pathologically determined response to neoadjuvant treatment correlated with long-term outcomes. Five-year recurrence-free survival rates were 90.5%, 78.7%, and 58.5% for patients with complete, intermediate, and poor responses, respectively ( $P < .001$ ). Distant metastases and local recurrences also correlated with the level of response.

In addition to its prognostic value, there is some initial evidence of predictive value to neoadjuvant treatment response. Subgroup analysis

of the EORTC 22921 trial showed that patients down-staged to ypT0-2 were more likely to benefit from adjuvant chemotherapy than patients with ypT3-4 staging.<sup>322</sup> Similar results were seen from another retrospective review.<sup>331</sup> Although no prospective data to predict the benefit of adjuvant therapy in patients with tumor downstaging or a pathologic complete response exist, the panel believes that such patients should be strongly considered for adjuvant chemotherapy.

### *Wait-and-See Nonoperative Approach for Clinical Complete Responders*

As preoperative treatment and imaging modalities have improved, some have suggested that patients with a clinical complete response to chemoRT may be able to be spared the morbidities of surgery. In 2004, Habr-Gama et al<sup>332</sup> retrospectively compared the outcomes of 71 patients who were observed without surgery following complete clinical response (27% of patients) to the outcome of 22 patients (8%) who had incomplete clinical responses but complete pathologic responses post-TME. The OS and DFS rates at 5 years were 100% and 92%, respectively, in the nonoperative group compared to 88% and 83%, respectively, in the resected group. However, other studies did not achieve as impressive results, and many clinicians were skeptical of the approach.<sup>333</sup>

A more recent prospective study included a more thorough assessment of treatment response and used very strict criteria to select 21 of 192 patients (11%) with clinical complete responses who were then observed with careful follow-up and compared to 20 patients with a complete pathologic response after resection.<sup>334</sup> Only 1 patient in the nonoperative group developed a local recurrence after a mean follow-up of 25 months; that patient underwent successful surgery. No statistical differences in long-term outcomes were seen between the groups. The cumulative probabilities for 2-year DFS and OS were 89% (95% CI,



43%–98%) and 100%, respectively, in the wait-and-see group and 93% (95% CI, 59%–99%) and 91% (95% CI, 59%–99%), respectively, in the resected group. Short-term functional outcomes, however, were better in the wait-and-see group, with better bowel function scores, less incontinence, and 10 patients avoiding permanent colostomy.

Other non-randomized, prospective studies have added to the growing evidence that the nonoperative approach may warrant further study.<sup>335–</sup>

<sup>338</sup> For example, one study showed that 49% of patients experienced a complete clinical response after 5-FU-based chemoRT, and found that strict surveillance in these patients, with resection of recurrences when possible, resulted in a 5-year recurrence-free survival of 69%, which rose to 94% after resections were performed.<sup>336</sup>

Despite these impressive results, many still believe that longer follow-up, larger sample sizes, and additional careful observational studies are needed before patients with a clinical complete response are routinely managed by a wait-and-see approach.<sup>339</sup> Furthermore, recent studies have found that neither FDG-PET, nor MRI, nor CT can accurately determine a pathologic complete response, complicating the selection of appropriate patients for a nonoperative approach.<sup>185–193,340</sup> In addition, lymph node metastases are still seen in a subset of patients with pathologic complete response.<sup>341</sup> Overall, the panel does not support this approach in the routine management of localized rectal cancer.

### *Adjuvant Chemotherapy*

Adjuvant chemotherapy is recommended for all patients with stage II/III rectal cancer following neoadjuvant chemoRT and surgery if they did not receive neoadjuvant chemotherapy regardless of the surgical pathology results, although few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well defined.<sup>342,343</sup> The addition of 5-FU adjuvant chemotherapy to

preoperative chemoRT provided no benefit to the rate of local recurrence in the EORTC Radiotherapy Group Trial 22921.<sup>268</sup> However, this study did show an improvement in DFS (HR, 0.87; 95% CI, 0.72–1.04;  $P = .13$ ) of patients receiving adjuvant chemotherapy (+/- RT) following preoperative RT (+/- 5-FU–based chemotherapy).<sup>268</sup> Long-term results of the 22921 trial confirmed that adjuvant 5-FU chemotherapy did not improve OS, and the difference in DFS was less pronounced than following the previous analysis (HR, 0.91; 95% CI, 0.77–1.08;  $P = .29$ ).<sup>344</sup> Limitations of this trial include the fact that only 43% of participants received the full course of adjuvant chemotherapy. Other trials have failed to show an improvement in OS or DFS with adjuvant therapy with a fluoropyrimidine alone in this setting.<sup>345,346</sup>

Other trials have investigated the use of more modern agents in the adjuvant setting. The phase III ECOG E3201 trial was designed to investigate the effect of adding either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) to 5-FU/LV-based adjuvant chemotherapy administered to patients with stage II/III rectal cancer after either preoperative or postoperative chemoRT. This study was replaced with an alternative trial with bevacizumab, but results from an initial 165 patients indicate that adjuvant FOLFOX can be safely used in this patient population.<sup>347</sup> The open-label phase II ADORE trial randomized 321 patients with resected rectal cancer and neoadjuvant therapy to adjuvant 5-FU/LV or FOLFOX.<sup>348</sup> The FOLFOX arm had higher 3-year DFS, at 71.6% versus 62.9% (HR, 0.66; 95% CI, 0.43–0.99;  $P = .047$ ). The CAO/ARO/AIO-04 trial found an improvement in 3-year DFS when oxaliplatin was added to 5-FU in both neoadjuvant and adjuvant treatment (75.9% vs. 71.2%;  $P = .03$ ).<sup>277</sup>

A recent study in which patients who received neoadjuvant chemoRT and experienced a pathologic complete response were observed without additional adjuvant chemotherapy found 5-year DFS and OS





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rates of 96% and 100%, respectively.<sup>349</sup> In addition, a meta-analysis of 4 randomized trials (1196 patients) concluded that adjuvant fluorouracil-based chemotherapy (5-FU/LV, capecitabine, or CapeOx) after preoperative therapy and surgery did not improve OS, DFS, or the rate of distant recurrences in patients with stage II or III rectal cancer.<sup>350</sup>

However, more recent trials that found a DFS benefit to the addition of adjuvant oxaliplatin-based adjuvant therapy were not included in this study, and other meta-analyses have come to the opposite conclusion.<sup>351,352</sup> The panel continues to support the use of adjuvant therapy in this setting.

A recent analysis of the NCCN Colorectal Cancer Database found that, of 2073 patients with stage II/III rectal cancer who received neoadjuvant chemoRT treatment, 203 patients (9.8%) did not receive any adjuvant chemotherapy as recommended by these guidelines.<sup>353</sup> Multivariate analysis found that complete pathologic response, infection, no closure of ileostomy/colostomy, age, poor performance status, and being on Medicaid or indigent were associated with not receiving adjuvant chemotherapy. Results from the SEER database indicated that even fewer patients in the general population are receiving adjuvant therapy (61.5%) in this setting.<sup>354</sup> Pathologic stage, age, and postoperative readmissions were associated with a decreased likelihood of receiving adjuvant treatment.

Although conclusive data on the use of adjuvant therapy in patients with stage II/III rectal cancer are lacking, the panel recommends use of FOLFOX or CapeOx as preferred options. 5-FU/leucovorin or capecitabine can also be used in this setting and might be especially appropriate in patients who responded to neoadjuvant treatment with 5-FU or capecitabine.

**Timing and Duration of Adjuvant Therapy:** A 2011 systematic review and meta-analysis of 10 studies involving more than 15,000 patients with colorectal cancer looked at the effect of timing of adjuvant therapy following resection.<sup>355</sup> Results of this analysis showed that each 4-week delay in chemotherapy results in a 14% decrease in OS, indicating that adjuvant therapy should be administered as soon as the patient is medically able. These results are consistent with other similar analyses.<sup>356</sup>

The optimal duration of adjuvant treatment in rectal cancer is still unclear.<sup>357,358</sup> In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.<sup>359</sup> The use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) is justified when preoperative chemoRT is administered.

### *Multigene Assays*

Several multigene assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer (see the NCCN Guidelines for Colon Cancer, available at [www.NCCN.org](http://www.NCCN.org), for a full discussion).<sup>360</sup>

Among the multigene assays used in colon cancer is the Oncotype DX colon cancer assay, which quantifies the expression of 7 recurrence-risk genes and 5 reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.<sup>361</sup> Clinical validation in patients with stage II and III colon cancer from QUASAR and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trials showed that recurrence scores are prognostic for recurrence, DFS, and OS in stage II and III colon cancer, but are not predictive of benefit to adjuvant therapy.<sup>362</sup> For the low, intermediate, and high recurrence risk



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groups, recurrence at 3 years was 12%, 18%, and 22%, respectively. Similar results were found in other prospectively designed studies.<sup>363,364</sup>

A recent prospectively designed validation study assessed this assay for predicting recurrence risk in patients with stage II and III rectal cancer.<sup>365</sup> For patients who underwent surgery without neoadjuvant therapy in the Dutch Total Mesorectal Excision (TME) trial, recurrence score was predictive of recurrence, distant recurrence, and rectal-cancer-specific survival. In patients with stage II rectal cancer, recurrence at 5 years was 11%, 27%, and 43% for the low, intermediate, and high recurrence risk groups, respectively.

The panel believes the information from this test can further inform the risk of recurrence over other risk factors, but they question the value added. Furthermore, there is no evidence of predictive value in terms of the potential benefit of chemotherapy in patients with colon or rectal cancer with any of the available multigene assays. The panel believes that there are insufficient data to recommend the use of multigene assays to determine adjuvant therapy for patients with colorectal cancer.

### *Leucovorin Shortage*

A leucovorin shortage recently existed in the United States. No specific data guide management under these circumstances, and all proposed strategies are empiric. The panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m<sup>2</sup> of levo-leucovorin is equivalent to 400 mg/m<sup>2</sup> of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin

gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.<sup>366</sup> Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m<sup>2</sup>) or low-dose (20 mg/m<sup>2</sup>) leucovorin.<sup>367</sup> Also, the Mayo Clinic and NCCTG determined that there was no therapeutic difference between the use of high- (200 mg/m<sup>2</sup>) or low- (20 mg/m<sup>2</sup>) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.<sup>368</sup> Finally, if none of the above options is available, treatment without leucovorin would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

### ***Recommendations for Patients with T1 and T2 Lesions***

Node-negative T1 lesions are treated with transabdominal resection or transanal excision, as appropriate (see section on *Surgical Approaches*, above). If pathology review after local excision reveals no high-risk features or if a transabdominal resection was performed, then no additional treatment is required. If, however, pathology review after local excision reveals a poorly differentiated histology, positive margins, invasion into the lower third of the submucosa (sm3 level), or LVI or if the tumor is restaged to T2, additional treatment is required. The initial options are transabdominal re-resection or chemoRT. For resected patients with positive nodes or pT3-4 disease, chemotherapy and chemo RT “sandwich regimen” (as described below) should be given. For patients treated with transanal excision and then chemoRT, observation can be considered if a complete response is seen. Alternatively, the patient can undergo a transabdominal resection with optional adjuvant chemotherapy or chemotherapy can be given without resection.



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Node-negative T2 lesions are treated with transabdominal resection, since local recurrence rates of 11% to 45% have been observed for T2 lesions following local excision alone.<sup>168,369,370</sup> Following transabdominal resection, patients with tumors staged as pT1-2, N0, M0 require no further treatment. If pathology review reveals pT3-4, N0, M0 or node-positive disease, a “sandwich regimen,” consisting of: 1) an optional first round of adjuvant chemotherapy with 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin;<sup>371</sup> followed by 2) concurrent 5-FU/RT (infusional [preferred] or bolus infusion along with LV) or capecitabine/RT (preferred); followed by 3) 5-FU with or without LV or FOLFOX or capecitabine with or without oxaliplatin, is one option. Alternatively, these patients can be observed or can receive chemotherapy without radiation. Patients with pathologic findings of N1 disease should receive a “sandwich regimen” of chemotherapy and chemoRT.

The panel recommends perioperative therapy for a total duration of approximately 6 months.

### **Recommendations for Patients with T3-4 Lesions, Nodal Involvement, Locally Unresectable Disease, or Who Are Medically Inoperable**

Patients clinically staged as having resectable T3-4, N0 T any, N1-2 lesions, and/or who have locally unresectable disease or are medically inoperable have 3 options for the sequence of treatment: 1) chemotherapy with long-course RT, then resection if possible, followed by chemotherapy; 2) short-course RT (not recommended for T4 disease), then resection if possible, followed by chemotherapy; or 3) chemotherapy, then chemoRT, then resection if possible. Infusional 5-FU/RT and capecitabine/RT are the preferred chemoRT options (category 1 for both) regardless of the sequence. An alternative chemoRT regimen is bolus 5-FU/LV/RT. The preferred chemotherapy regimens when given before surgery are FOLFOX or CapeOx, with 5-

FU/leucovorin and capecitabine as additional options. In the postoperative setting, adjuvant FOLFOX (preferred), CapeOx (preferred), 5-FU/leucovorin, or capecitabine should be given.

Resection should be considered following preoperative therapy unless there is a clear contraindication. The panel advises that a poor clinical response does not necessarily imply unresectability, and surgical exploration is usually appropriate. Transabdominal resection should be performed 5 to 12 weeks following completion of neoadjuvant therapy. The panel recommends that the duration of perioperative chemotherapy, including chemotherapy and chemoRT, be approximately 6 months. When resection is contraindicated following primary treatment, patients should be treated with a systemic regimen for advanced disease (see discussion of *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer, available at [www.NCCN.org](http://www.NCCN.org)). FOLFOXIRI is not recommended in this setting.

For unresectable cancers, doses higher than 54 Gy may be required; the dose of radiation to the small bowel should be limited to 45 Gy. For patients with T4 tumors or recurrent cancers or if margins are very close or positive, intraoperative RT (IORT),<sup>372-376</sup> which involves direct exposure of tumors to RT during surgery while removing normal structures from the field of treatment, may be considered as an additional boost to facilitate resection. If IORT is not available, 10 to 20 Gy and/or brachytherapy to a limited volume can be considered.

### **Principles of the Management of Metastatic Disease**

Approximately 50% to 60% of patients diagnosed with colorectal cancer will develop colorectal metastases,<sup>377-379</sup> and 80% to 90% of these patients have unresectable metastatic liver disease.<sup>378,380-383</sup> Metastatic disease most frequently develops metachronously after treatment for



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locoregional colorectal cancer, with the liver as the most common site of involvement.<sup>384</sup> However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.<sup>383,385</sup> Some evidence indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In a retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement ( $P = .008$ ) and more bilobar metastases ( $P = .016$ ) than patients diagnosed with metachronous liver metastases.<sup>386</sup>

It has been estimated that more than half of patients who die of colorectal cancer have liver metastases at autopsy, with metastatic liver disease as the cause of death in most patients.<sup>387</sup> Reviews of autopsy reports of patients who died from colorectal cancer showed that the liver was the only site of metastatic disease in one-third of patients.<sup>382</sup>

Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.<sup>378,388</sup> Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than 3 tumors, and a disease-free interval of fewer than 12 months, have been associated with a poor prognosis in patients with colorectal cancer.<sup>385,389-393</sup>

Other groups, including ESMO, have established guidelines for the treatment of metastatic colorectal cancer.<sup>394</sup> The NCCN recommendations are discussed below.

### Surgical Management of Colorectal Metastases

Studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for a substantial number of these patients.<sup>378,395</sup>

Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,<sup>390,393</sup> and a recent meta-analysis reported a median 5-year survival of 38%.<sup>396</sup> In addition, retrospective analyses and meta-analyses have shown that patients with solitary liver metastases have a 5-year OS rate as high as 71% following resection.<sup>397-399</sup> Therefore, decisions relating to patient suitability, or potential suitability, and subsequent selection for metastatic colorectal surgery are critical junctures in the management of metastatic colorectal liver disease<sup>400</sup> (discussed further in *Determining Resectability*).

Colorectal metastatic disease sometimes occurs in the lung.<sup>377</sup> Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.<sup>177,401,402</sup> Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases.<sup>402-407</sup>

Evidence supporting resection of extrahepatic metastases in patients with metastatic colorectal cancer is limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower than in patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.<sup>408,409</sup> However, a recent international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent resection of extrahepatic and hepatic disease remained disease-free at a median follow-up of 26 months, suggesting that concurrent resection may be of significant benefit in well-selected patients (ie, those with a smaller total number of metastases).<sup>407</sup> A recent systematic review concluded





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similarly that carefully selected patients might benefit from this approach.<sup>410</sup>

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken. However, in a retrospective analysis, 5-year survival was shown to decrease with each subsequent curative-intent surgery, and the presence of extrahepatic disease at the time of surgery was independently associated with a poor prognosis.<sup>411-414</sup> In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year overall and PFS rates were reported to be 73% and 22%, respectively.<sup>411</sup> A recent meta-analysis of 27 studies including >7200 patients found that those with longer disease-free intervals; those whose recurrences were solitary, smaller, or unilobular; and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.<sup>415</sup> Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.<sup>402,416,417</sup>

Patients with a resectable primary rectal tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Recommendations for Treatment of Resectable Synchronous Metastases*. For patients presenting with unresectable metastases and an intact primary that is not acutely obstructed, palliative resection of the primary is rarely indicated, and systemic chemotherapy is the preferred initial maneuver (discussed in more detail below in *Recommendations for Treatment of Unresectable Synchronous Metastases*).<sup>418</sup>

### Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. If resection is not feasible, image-guided ablation<sup>419-</sup>

<sup>421</sup> or stereotactic body radiation therapy (SBRT; also called stereotactic ablative radiotherapy [SABR])<sup>381,422,423</sup> are reasonable options, as discussed in subsequent paragraphs. Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins<sup>420</sup> or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that cannot be resected or ablated arterially, other locally directed treatment options may be offered.<sup>424-426</sup>

A meta-analysis of 90 studies concluded that hepatic arterial infusion (HAI), radioembolization, and transcatheter arterial chemoembolization (TACE) have similar efficacy in patients with unresectable colorectal metastases in the liver.<sup>427</sup> Local therapies are described in more detail below. The role of non-extirpative local therapies in the treatment of colorectal metastases remains controversial.

### Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, HAI) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAI and intravenous 5-FU with or without leucovorin was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.<sup>382,428</sup> The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcome in the group receiving HAI at later follow-up periods.<sup>382,429</sup> Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAI therapy has been compared with systemic chemotherapy, although most have not shown a survival benefit of HAI therapy.<sup>382</sup> Results of some studies also suggest that HAI



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may be useful in the conversion of patients from an unresectable to a resectable status.<sup>430,431</sup>

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAI.<sup>395</sup> Limitations on the use of HAI therapy include the potential for biliary toxicity<sup>382</sup> and the requirement of specific technical expertise. Panel consensus is that HAI therapy should be considered selectively, and only at institutions with extensive experience in both the surgical and medical oncologic aspects of the procedure.

### **Arterially Directed Embolic Therapy**

TACE involves hepatic artery catheterization to cause vessel occlusion with locally delivered chemotherapy.<sup>425</sup> A recent randomized trial using HAI to deliver irinotecan-loaded drug-eluting beads (DEBIRI) reported an OS benefit (22 months vs. 15 months;  $P = .031$ ).<sup>432</sup> A 2013 meta-analysis identified 5 observational studies and 1 randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.<sup>433</sup> A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.<sup>434</sup> DEBIRI resulted in an improvement in the primary outcome measure of response rate (78% vs. 54% at 2 months;  $P = .02$ ).

Doxorubicin-eluting beads have also been studied; the strongest data supporting their effectiveness come from several phase II trials in hepatocellular carcinoma.<sup>435-440</sup> A recent systematic review concluded that data are not strong enough to recommend TACE for the treatment of colorectal liver metastases except as part of a clinical trial.<sup>441</sup>

The panel believes that arterially directed catheter therapy and, in particular, yttrium 90 microsphere selective internal radiation (see *Radioembolization*, below) is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

### **Liver- or Lung-Directed Radiation**

Local radiation therapies include arterial radioembolization with microspheres<sup>442-452</sup> and conformal (stereotactic) external beam RT (EBRT).<sup>453</sup>

EBRT to the metastatic site can be considered in highly selected cases in which the patient has a limited number of liver or lung metastases or the patient is symptomatic or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include three-dimensional conformal radiotherapy, SBRT,<sup>381,422,423,454,455</sup> and IMRT, which uses computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.<sup>456-459</sup>

### **Radioembolization**

A prospective, randomized, phase III trial of 44 patients showed that radioembolization combined with chemotherapy can lengthen time to progression in patients with liver-limited metastatic colorectal cancer following progression on initial therapy (2.1 vs. 4.5 months;  $P = .03$ ).<sup>460</sup> The effect on the primary endpoint of time to liver progression was more pronounced (2.1 vs. 5.5 months;  $P = .003$ ). Treatment of liver metastases with yttrium-90 glass radioembolization in a prospective, multicenter, phase II study resulted in a median PFS of 2.9 months for patients with colorectal primaries who were refractory to standard treatment.<sup>461</sup> In the refractory setting, a CEA level  $\geq 90$  and LVI at the time of primary resection were negative prognostic factors for OS.<sup>451</sup>





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Several large case series have been reported for yttrium-90 radioembolization in patients with refractory unresectable colorectal liver metastases, and the technique appears to be safe with some clinical benefit.<sup>444,462,463</sup>

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX+/- bevacizumab vs. FOLFOX+/- bevacizumab) have been published.<sup>464</sup> The trial assessed the safety and efficacy of yttrium-90 radioembolization as first-line therapy in 530 patients with colorectal liver metastases. Although the primary endpoint was not met, with PFS in the FOLFOX +/- bevacizumab arm at 10.2 months versus 10.7 months in the FOLFOX/Y-90 arm (HR, 0.93; 95% CI, 0.77–1.12;  $P = .43$ ), a prolonged liver PFS was demonstrated for the study arm (20.5 months for the FOLFOX/Y90 arm vs. 12.6 months for the chemotherapy only arm; HR, 0.69; 95% CI, 0.55–0.90;  $P = .002$ ).

Whereas very little data show any impact on patient survival and the data supporting its efficacy are limited, toxicity with radioembolization is relatively low.<sup>464-467</sup> Consensus amongst panel members is that arterially directed catheter therapy and, in particular, yttrium 90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

### **Tumor Ablation**

Although resection is the standard approach for the local treatment of resectable metastatic disease, patients with liver or lung oligometastases can be considered for tumor ablation therapy.<sup>468</sup> Ablative techniques include radiofrequency ablation (RFA),<sup>420,469</sup> microwave ablation, cryoablation, percutaneous ethanol injection, and electro-coagulation. Evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and those with recurrent

disease after hepatectomy with small liver metastases that can be treated with clear margins is growing.<sup>420,469-472</sup> Data on ablative techniques other than RFA are extremely limited.<sup>473-479</sup>

A small number of retrospective studies have compared RFA and resection in the treatment of liver or lung metastases.<sup>398,479-482</sup> Most of these studies have shown RFA to be inferior to resection in terms of rates of local recurrence and 5-year OS.<sup>468,483</sup> Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, technological limitations of RFA, or a combination of these factors is currently unclear.<sup>481</sup> A 2010 ASCO clinical evidence review determined that RFA has not been well-studied in the setting of colorectal cancer liver metastases, with no randomized controlled trials having been reported.<sup>479</sup> The ASCO panel concluded that a compelling need exists for more research in this area. A 2012 Cochrane Database systematic review came to similar conclusions, as have separate meta-analyses.<sup>475,478,484</sup>

Recently, a trial was reported in which 119 patients were randomized to receive systemic treatment or systemic treatment plus RFA with or without resection.<sup>485</sup> No difference in OS was seen, but PFS was improved at 3 years in the RFA group (27.6% vs. 10.6%; HR, 0.63; 95% CI, 0.42–0.95;  $P = .025$ ). Similarly 2 recent studies and a position paper by a panel of experts on ablation indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins.<sup>419-421</sup>

Resection or ablation (either alone or in combination with resection) should be reserved for patients with metastatic disease that is completely amenable to local therapy with adequate margins. Use of surgery, ablation, or the combination, with the goal of less-than-



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complete resection/ablation of all known sites of disease, is not recommended.

### Peritoneal Carcinomatosis

Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis.<sup>91</sup> Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.<sup>91</sup> The goal of treatment for most abdominal/peritoneal metastases is palliative, rather than curative, and primarily consists of systemic therapy (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer) with palliative surgery or stenting if needed for obstruction or impending obstruction.<sup>486-488</sup> If an R0 resection can be achieved, however, surgical resection of isolated peritoneal disease may be considered at experienced centers. The panel cautions that the use of bevacizumab in patients with colon or rectal stents is associated with a possible increased risk of bowel perforation.<sup>489,490</sup>

### Cytoreductive Debulking with Heated Intraperitoneal Chemotherapy

Several surgical series and retrospective analyses have addressed the role of cytoreductive surgery (ie, peritoneal stripping surgery) and perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.<sup>491-499</sup> In the only randomized controlled trial of this approach, Verwaal et al<sup>500</sup> randomized 105 patients to receive standard therapy (5-FU/LV with or without palliative surgery) or undergo aggressive cytoreductive surgery and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients. OS was 12.6 months in the standard arm and 22.3 months in the HIPEC arm ( $P = .032$ ). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this

treatment as seen by follow-up results.<sup>501</sup> Importantly, this trial was performed without oxaliplatin, irinotecan, or molecularly targeted agents. Some experts have argued that the OS difference seen might have been much smaller if these agents had been used (ie, the control group would have had better outcomes).<sup>502</sup>

Other criticisms of the Verwaal trial have been published.<sup>502</sup> One important point is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group that has seen greater benefit with the cytoreductive surgery/HIPEC approach.<sup>492,503-505</sup> A retrospective, multicenter, cohort study reported overall median survival times of 30 and 77 months for patients with peritoneal carcinomatosis of colorectal origin and appendiceal origin, respectively, treated with HIPEC or with cytoreductive surgery and early postoperative intraperitoneal chemotherapy.<sup>504</sup> The median OS time for patients with pseudomyxoma peritonei, which arises from mucinous appendiceal carcinomas, was not reached at the time of publication. A recent retrospective international registry study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with pseudomyxoma peritonei from mucinous appendiceal carcinomas treated with cytoreductive surgery and HIPEC.<sup>506</sup> HIPEC was not shown to be associated with improvements in OS in this study, whereas completeness of cytoreduction was. Thus, for patients with pseudomyxoma peritonei, optimal treatment is still unclear.<sup>507</sup>

The individual components of this approach have not been well-studied. In fact, studies in rats have suggested that the hyperthermia component of the treatment is irrelevant.<sup>508</sup> Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.<sup>493</sup> In addition, a randomized trial compared systemic 5-FU/oxaliplatin to cytoreductive surgery and intraperitoneal 5-FU without heat.<sup>509</sup> Although terminated prematurely because of poor accrual, analysis suggested



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that the cytoreductive surgery plus IPEC approach may have been superior to the systemic therapy approach (2-year OS, 54% vs. 38%;  $P = .04$ ) for patients with resectable colorectal peritoneal metastases.

In addition, significant morbidity and mortality are associated with this procedure. A 2006 meta-analysis of 2 randomized controlled trials and 12 other studies reported morbidity rates ranging from 23% to 44% and mortality rates ranging from 0% to 12%.<sup>499</sup> Furthermore, recurrences after the procedure are very common.<sup>510</sup> Whereas the risks are reportedly decreasing with time (ie, recent studies report 1%–5% mortality rates at centers of excellence<sup>496,502</sup>), the benefits of the approach have not been definitively shown, and HIPEC remains very controversial.<sup>511-514</sup>

The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. The panel recognizes the need for randomized clinical trials that will address the risks and benefits associated with each of these modalities.

### Determining Resectability

The consensus of the panel is that patients diagnosed with potentially resectable metastatic colorectal cancer should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (ie, with an experienced hepatic surgeon in cases involving liver metastases) to assess resectability status. The criteria for determining patient suitability for resection of metastatic disease are the likelihood of achieving complete resection of all evident disease with negative surgical margins and maintaining adequate liver reserve.<sup>515-518</sup> When the remnant liver is insufficient in size based on cross-sectional imaging volumetrics, preoperative portal vein embolization of the involved liver

can be done to expand the future liver remnant.<sup>519</sup> It should be noted that size alone is rarely a contraindication to resection of a tumor. Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease.<sup>520</sup> Resection should not be undertaken unless complete removal of all known tumor is realistically possible (R0 resection), because incomplete resection or debulking (R1/R2 resection) has not been shown to be beneficial.<sup>379,515</sup>

The role of PET/CT in determining resectability of patients with metastatic colorectal cancer is discussed in *Recommendations for Treatment of Metachronous Metastases*, below.

### Conversion to Resectability

The majority of patients diagnosed with metastatic colorectal disease have unresectable disease. However, for those with liver-limited unresectable disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished, preoperative chemotherapy is being increasingly considered in highly selected cases in an attempt to downsize colorectal metastases and convert them to a resectable status. Patients presenting with large numbers of metastatic sites within the liver or lung are unlikely to achieve an R0 resection simply on the basis of a favorable response to chemotherapy, as the probability of complete eradication of a metastatic deposit by chemotherapy alone is low. These patients should be regarded as having unresectable disease not amenable to conversion therapy. In some highly selected cases, however, patients with significant response to conversion chemotherapy can be converted from unresectable to resectable status.<sup>468</sup>

Any active metastatic systemic regimen can be used in an attempt to convert a patient's unresectable status to a resectable status, because



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the goal is not specifically to eradicate micrometastatic disease, but rather to obtain the optimal size regression of the visible metastases. An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steatohepatitis and sinusoidal liver injury, respectively.<sup>521-525</sup> To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed below.

In the study of Pozzo et al, it was reported that chemotherapy with irinotecan combined with 5-FU/LV enabled a significant portion (32.5%) of the patients with initially unresectable liver metastases to undergo liver resection.<sup>517</sup> The median time to progression was 14.3 months, with all of these patients alive at a median follow-up of 19 months. In a phase II study conducted by the NCCTG,<sup>380</sup> 42 patients with unresectable liver metastases were treated with FOLFOX. Twenty-five patients (60%) had tumor reduction and 17 patients (40%; 68% of the responders) were able to undergo resection after a median period of 6 months of chemotherapy. In another study, 1104 patients with initially unresectable colorectal liver disease were treated with chemotherapy, which included oxaliplatin in the majority of cases, and 138 patients (12.5%) classified as “good responders” underwent secondary hepatic resection.<sup>389</sup> The 5-year DFS rate for these 138 patients was 22%. In addition, results from a retrospective analysis of 795 previously untreated patients with metastatic colorectal cancer enrolled in the Intergroup N9741 randomized phase III trial evaluating the efficacy of mostly oxaliplatin-containing chemotherapy regimens indicated that 24 patients (3.3%; 2 of the 24 had lung metastases) were able to undergo curative resection after treatment.<sup>526</sup> The median OS time in this group was 42.4 months.

In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI (infusional 5-FU, LV, irinotecan) in 2 randomized clinical trials in patients with unresectable disease.<sup>527,528</sup> In both studies, FOLFOXIRI led to an increase in R0 secondary resection rates: 6% versus 15%,  $P = .033$  in the Gruppo Oncologico Nord Ovest (GONO) trial<sup>527</sup>; and 4% versus 10%,  $P = .08$  in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.<sup>528</sup> In a follow-up study of the GONO trial, the 5-year survival rate was higher in the group receiving FOLFOXIRI (15% vs. 8%), with a median OS of 23.4 vs. 16.7 months ( $P = .026$ ).<sup>529</sup>

More recent favorable results of randomized clinical trials evaluating FOLFIRI or FOLFOX for the purpose of conversion of unresectable disease to resectable disease in combination with anti-epidermal growth factor receptor (EGFR) inhibitors have been reported.<sup>530</sup> For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.<sup>530</sup> Retrospective analysis showed that, in both treatment arms combined, resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* exon 2 ( $P < .0001$ ) with the addition of cetuximab. Another recent randomized controlled trial compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable colorectal cancer metastatic to the liver.<sup>531</sup> The primary endpoint was the rate of conversion to resectability based on evaluation by a multidisciplinary team. After evaluation, 20 of 70 patients (29%) in the cetuximab arm and 9 of 68 patients (13%) in the control arm were determined to be eligible for curative-intent hepatic resection. R0 resection rates were 25.7% in the cetuximab arm and 7.4% in the control arm ( $P < .01$ ). In addition, surgery improved the median survival time compared to unresected participants in both arms, with longer survival in patients receiving cetuximab (46.4 vs. 25.7 months;  $P = .007$ ).





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for the cetuximab arm and 36.0 vs. 19.6 months;  $P = .016$  for the control arm). A recent meta-analysis of 4 randomized controlled trials concluded that the addition of cetuximab or panitumumab to chemotherapy significantly increased the response rate, the R0 resection rate (from 11%–18%; RR, 1.59;  $P = .04$ ), and PFS, but not OS in patients with wild-type *KRAS* exon 2-containing tumors.<sup>532</sup>

The role of bevacizumab in the patient with unresectable, metastatic colorectal cancer, whose disease is felt to be potentially convertible to resectability with a reduction in tumor size, has also been studied. Data seem to suggest that bevacizumab modestly improves the response rate to irinotecan-based regimens.<sup>533</sup> As such, when an irinotecan-based regimen is selected for an attempt to convert unresectable disease to resectability, the use of bevacizumab would seem to be an appropriate consideration. On the other hand, a 1400-patient, randomized, double-blind, placebo-controlled trial of CapeOx or FOLFOX with or without bevacizumab showed no benefit in terms of response rate or tumor regression for the addition of bevacizumab, as measured by both investigators and an independent radiology review committee.<sup>534</sup> Therefore, arguments for use of bevacizumab with oxaliplatin-based therapy in this “convert to resectability” setting are not compelling. However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When initial chemotherapy is planned for patients with unresectable disease that is felt to be potentially convertible to resectability, the panel recommends that a surgical re-evaluation be planned approximately 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical re-evaluation approximately every 2 months thereafter.<sup>525,535-537</sup> Reported risks associated with chemotherapy include the potential for development of

liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.<sup>521</sup> To limit the development of hepatotoxicity, it is therefore recommended that surgery should be performed as soon as possible after the patient becomes resectable.

### Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

The panel recommends consideration of administration of a course of an active systemic therapy regimen for metastatic disease, for a total perioperative treatment time of approximately 6 months, for most patients undergoing liver or lung resection, to increase the likelihood that residual microscopic disease will be eradicated (category 2B for the use of biologic agents in the perioperative metastatic setting). A recent meta-analysis identified 3 randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.<sup>538</sup> The pooled analysis showed a benefit of chemotherapy in PFS (pooled HR, 0.75; CI, 0.62–0.91;  $P = .003$ ) and DFS (pooled HR, 0.71; CI, 0.58–0.88;  $P = .001$ ), but not in OS (pooled HR, 0.74; CI, 0.53–1.05;  $P = .088$ ). Another meta-analysis published in 2015 combined data on 1896 patients from 10 studies and also found that perioperative chemotherapy improved DFS (HR, 0.81; 95% CI, 0.72–0.91;  $P = .0007$ ) but not OS (HR, 0.88; 95% CI, 0.77–1.01;  $P = .07$ ) in patients with resectable colorectal liver metastases.<sup>539</sup> Additional recent meta-analyses have also failed to observe an OS benefit with the addition of adjuvant chemotherapy in resectable metastatic colorectal cancer.<sup>540,541</sup>

The choice of chemotherapy regimen in the preoperative setting is dependent on a number of factors, including the chemotherapy history of the patient, whether disease is synchronous or metachronous, and the response rates and safety/toxicity issues associated with the



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regimens, as outlined in the guidelines. Biologics are not recommended in the perioperative metastatic setting, with the exception of initial therapy in unresectable patients who may be converted to a resectable state.

Although the benefits of perioperative chemotherapy for patients with liver metastases have not yet been fully validated in randomized clinical trials, a recent EORTC phase III study (EORTC 40983) evaluating use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with initially resectable liver metastases demonstrated absolute improvements in 3-year PFS of 8.1% ( $P = .041$ ) and 9.2% ( $P = .025$ ) for all eligible patients and all resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.<sup>542</sup> The partial response rate after preoperative FOLFOX was 40%, and operative mortality was <1% in both treatment groups. However, no difference in OS was seen between the groups, perhaps because second-line therapy was given to 77% of the patients in the surgery only arm and to 59% of the patients in the chemotherapy arm.<sup>543</sup>

The optimal sequencing of chemotherapy remains unclear. Patients with initially resectable disease may undergo liver resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) chemotherapy can be used.<sup>540,544</sup>

Potential advantages of the preoperative chemotherapy approach include earlier treatment of micrometastatic disease; determination of responsiveness to chemotherapy, which can be prognostic and help plan postoperative therapy; and avoidance of local therapy in those who progress early. Potential disadvantages include missing the “window of opportunity” for resection because of the possibility of disease

progression or achievement of a complete response, thereby making it difficult to identify areas for resection.<sup>382,545,546</sup> Importantly, results from a study of patients with colorectal cancer receiving preoperative chemotherapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.<sup>546,547</sup> It is therefore essential that during treatment with preoperative chemotherapy, frequent evaluations are undertaken and close communication is maintained between medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.<sup>521</sup>

Other reported risks associated with the preoperative chemotherapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.<sup>521-525</sup> To reduce the development of hepatotoxicity, the neoadjuvant period is usually limited to 2 to 3 months, and patients should be carefully monitored by a multidisciplinary team.

It is important to note that some of the treatment approaches for patients diagnosed with rectal cancer and resectable synchronous lung or liver metastases differ relative to those for patients diagnosed with similarly staged colon cancer. In particular, initial treatment options for synchronous resectable rectal cancer include preoperative chemoRT directed toward treatment of the primary cancer; a 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, while a disadvantage is that preoperative pelvic RT





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may decrease tolerance to systemic bevacizumab-containing adjuvant regimens, thereby limiting subsequent treatment of systemic disease. Data to guide decisions regarding optimal treatment approaches in this population of patients are very limited.

Based largely on extrapolation from stage III disease and limited randomized data for stage IV disease, the panel recommends the use of postoperative adjuvant chemotherapy in patients who have undergone liver or lung resection and who have received preoperative chemoRT. Postoperative chemoRT is recommended for patients with synchronous metastases who have not received prior chemoRT and who are at higher risk for pelvic recurrence following staged or synchronous resection of metastases and rectal lesion (ie, patients with disease staged as pT3-4, Any N, M1 or Any T, N1-2, M1).

### ***Perioperative Bevacizumab for Resectable Metastatic Disease***

The efficacy of bevacizumab in combination with FOLFOX and FOLFIRI in the treatment of unresectable metastatic disease (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer) has led to study of its use in combination with these regimens in the preoperative setting. However, the safety of administering bevacizumab pre- or postoperatively in combination with 5-FU-based regimens has not been adequately evaluated. A retrospective evaluation of data from 2 randomized clinical trials of 1132 patients receiving chemotherapy with or without bevacizumab as initial therapy for metastatic colorectal cancer indicated that the incidence of wound healing complications was increased for the group of patients undergoing a major surgical procedure while receiving a bevacizumab-containing regimen when compared to the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively;  $P = .28$ ).<sup>548</sup> However, when chemotherapy plus bevacizumab or chemotherapy alone was administered prior to surgery,

the incidence of wound healing complications in either group of patients was low (1.3% vs. 0.5%;  $P = .63$ ).

A recent meta-analysis of randomized controlled trials demonstrated that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than chemotherapy alone (RR, 1.33; 95% CI, 1.02–1.73;  $P = .04$ ); hemorrhage (23.5%), neutropenia (12.2%), and gastrointestinal perforation (7.1%) were the most common causes of fatality.<sup>549</sup> Venous thromboembolisms, however, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.<sup>550</sup>

The panel recommends against the use of bevacizumab as neoadjuvant treatment of patients with resectable metastatic rectal cancer. For patients who receive bevacizumab for unresectable disease and are converted to a resectable state, the panel recommends at least a 6-week interval (which corresponds to 2 half-lives of the drug<sup>551</sup>) between the last dose of bevacizumab and surgery.

### ***Perioperative Cetuximab and Panitumumab for Resectable Metastatic Disease***

The New EPOC trial, which was stopped early because it met protocol-defined futility criteria, found a lack of benefit to cetuximab with chemotherapy in the perioperative metastatic setting (>85% received FOLFOX or CapeOx; patients with prior oxaliplatin received FOLFIRI).<sup>552</sup> In fact, with less than half of expected events observed, PFS was significantly reduced in the cetuximab arm (14.8 vs. 24.2 months; HR 1.50; 95% CI, 1.00–2.25;  $P < .048$ ). The panel thus recommends against panitumumab and cetuximab in the neoadjuvant setting. The panel also points out cetuximab and panitumumab should be used with caution in patients with unresectable disease that could potentially be converted to a resectable status.



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### Systemic Therapy for Advanced or Metastatic Disease

The current management of disseminated metastatic colorectal cancer involves various active drugs, either in combination or as single agents: 5-FU/LV, capecitabine, irinotecan, oxaliplatin, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, ramucirumab, regorafenib, trifluridine-tipiracil, pembrolizumab, and nivolumab. The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, the mutational profile of the tumor, and the differing efficacy and toxicity profiles of the constituent drugs. Although the specific chemotherapy regimens listed in the guidelines are designated according to whether they pertain to initial therapy or therapy after first, second, or third progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete. For example, if oxaliplatin is administered as a part of an initial treatment regimen but is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the remainder of the treatment regimen would still be considered initial therapy.

Principles to consider at the start of therapy include preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive, and plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices after first progression of disease should be based partly on the prior therapies received (ie, exposing the patient to a range of cytotoxic agents). Furthermore, an evaluation of the efficacy and safety of these regimens for an individual patient must take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, and the potential for surgical cure and the performance status of the patient.

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 *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Colon Cancer for a detailed discussion of the various options for systemic treatment (available at [www.NCCN.org](http://www.NCCN.org)). The roles of predictive markers for treatment selection in the advanced and metastatic disease setting are discussed below.

#### **Predictive Markers for Cetuximab and Panitumumab** **Primary Tumor Sidedness**

A growing body of data has shown that the location of the primary tumor can be both prognostic and predictive of response to EGFR inhibitors in metastatic colorectal cancer.<sup>553-560</sup> For example, outcomes of 75 patients with metastatic colorectal cancer treated with cetuximab, panitumumab, or cetuximab/irinotecan in first-line or subsequent lines of therapy at 3 Italian centers were analyzed based on sidedness of the primary tumor.<sup>554</sup> No responses were seen in the patients with right-sided primary tumors compared with a response rate of 41% in those with left-sided primaries ( $P = .003$ ). The median PFS was 2.3 and 6.6 months in patients with right-sided and left-sided tumors, respectively (HR, 3.97; 95% CI, 2.09–7.53;  $P < .0001$ ).

The strongest evidence for the predictive value of primary tumor sidedness and response to EGFR inhibitors is in the first-line treatment of patients in the phase III CALGB/SWOG 80405 trial.<sup>560,561</sup> The study showed that patients with all *RAS* wild-type, right-sided primary tumors (cecum to hepatic flexure) had longer OS if treated with bevacizumab than if treated with cetuximab in first line (HR, 1.36; 95% CI, 0.93–1.99;  $P = .10$ ), whereas patients with all *RAS* wild-type, left-sided primary tumors (splenic flexure to rectum) had longer OS if treated with cetuximab than if treated with bevacizumab (HR, 0.77; 95% CI, 0.59–



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0.99;  $P = 0.04$ ).<sup>561</sup> OS was prolonged with cetuximab versus bevacizumab in the left-sided primary group (39.3 months vs. 32.6 months), but was shortened in the right-sided primary group (13.6 months vs. 29.2 months).

These and other data suggest that cetuximab and panitumumab confer little if any benefit to patients with metastatic colorectal cancer if the primary tumor originated on the right side.<sup>553,554,556,557</sup> The panel believes that primary tumor sidedness is a surrogate for the non-random distribution of molecular subtypes across the colon and that the ongoing analysis of tumor specimens from the study will enable a better understanding of the biologic explanation of the observed difference in response to EGFR inhibitors. Until that time, only patients whose primary tumors originated on the left side of the colon (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease. Evidence also suggests that sidedness is predictive of response to EGFR inhibitors in subsequent lines of therapy,<sup>553,554,557</sup> but the panel awaits more definitive studies. Until such data are available, all patients with *RAS* wild-type tumors can be considered for panitumumab or cetuximab in subsequent lines of therapy if neither was previously given.

### *KRAS, NRAS, and BRAF Status*

EGFR has been shown to be overexpressed in 49% to 82% of colorectal tumors.<sup>562-565</sup> EGFR testing of colorectal tumor cells has no proven predictive value in determining likelihood of response to either cetuximab or panitumumab. Data from the BOND-1 study indicated that the intensity of immunohistochemical staining of EGFR in colorectal tumor cells did not correlate with the response rate to cetuximab.<sup>566</sup> A similar conclusion was drawn with respect to panitumumab.<sup>567</sup> Therefore, routine EGFR testing is not recommended, and no patient

should be considered for or excluded from cetuximab or panitumumab therapy based on EGFR test results.

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways, but EGFR status as assessed using immunohistochemistry is not predictive of treatment efficacy.<sup>566,568</sup> Furthermore, cetuximab and panitumumab are only effective in approximately 10% to 20% of patients with colorectal cancer.<sup>566,568,569</sup> The *RAS*/*RAF*/*MAPK* pathway is downstream of EGFR; mutations in components of this pathway are being studied in search of predictive markers for efficacy of these therapies.

A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of response to cetuximab or panitumumab therapy.<sup>570-579</sup> More recent evidence shows that mutations in *KRAS* outside of exon 2 and mutations in *NRAS* are also predictive for a lack of benefit to cetuximab and panitumumab (see *NRAS and Other KRAS Mutations, below*).<sup>580,581</sup> The panel therefore strongly recommends *KRAS*/*NRAS* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer. Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. It is implied throughout the guidelines that NCCN recommendations involving cetuximab or panitumumab relate only to patients with disease characterized by *KRAS*/*NRAS* wild-type genes. ASCO released a Provisional Clinical Opinion Update on extended *RAS* testing in patients with metastatic colorectal cancer that is consistent with the NCCN panel's recommendations.<sup>582</sup>



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The panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer for *RAS* (*KRAS* exon 2 and non-exon 2; *NRAS*) and *BRAF* at diagnosis of stage IV disease. The recommendation for *KRAS/NRAS* testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *KRAS/NRAS* status is appropriate 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/NRAS* mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the management of stage I, II, or III disease, *KRAS/NRAS* genotyping of colorectal cancers at these earlier stages is not recommended.

*KRAS* mutations are early events in colorectal cancer formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.<sup>583,584</sup> For this reason, *KRAS/NRAS* genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *KRAS/NRAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable.

The panel recommends that *KRAS*, *NRAS*, and *BRAF* 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>585</sup> No specific testing methodology is recommended.<sup>586</sup>

***KRAS* Exon 2 Mutations:** 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>570,587</sup> A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to

cetuximab or panitumumab therapy,<sup>570-579</sup> and 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>588,589</sup> Results are mixed as far as the prognostic value of *KRAS* mutations. In the Alliance N0147 trial, patients with *KRAS* exon 2 mutations experienced a shorter DFS than patients without such mutations.<sup>590</sup> At this time, however, the test is not recommended for prognostic reasons.

A retrospective study from De Roock et al<sup>591</sup> raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive of non-response to EGFR inhibition. Another retrospective study showed similar results.<sup>592</sup> Furthermore, a more recent retrospective analysis of 3 randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were unlikely to respond to panitumumab.<sup>593</sup> Results from a prospective phase II single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory metastatic colorectal cancer whose tumors contained *KRAS* G13D mutations.<sup>594</sup> The primary endpoint of 4-month progression-free rate was not met (25%), and no responses were seen. Preliminary results of the AGITG phase II ICECREAM trial also failed to see a benefit of cetuximab monotherapy in patients with *KRAS* G13D mutations.<sup>595</sup> However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. The panel believes that patients with any known *KRAS* mutation, including G13D, should not be treated with cetuximab or panitumumab.

***NRAS* and Other *KRAS* Mutations:** In the AGITG MAX study, 10% of patients with wild-type *KRAS* exon 2 had mutations in *KRAS* exons 3 or 4 or in *NRAS* exons 2, 3, and 4.<sup>596</sup> In the PRIME trial, 17% of 641 patients without *KRAS* exon 2 mutations were found to have mutations





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in exons 3 and 4 of *KRAS* or mutations in exons 2, 3, and 4 of *NRAS*. A predefined retrospective subset analysis of data from PRIME revealed that PFS (HR, 1.31; 95% CI, 1.07–1.60;  $P = .008$ ) and OS (HR, 1.21; 95% CI, 1.01–1.45;  $P = .04$ ) were decreased in patients with any *KRAS* or *NRAS* mutation who received panitumumab plus FOLFOX compared to those who received FOLFOX alone.<sup>580</sup> These results show that panitumumab does not benefit patients with *KRAS* or *NRAS* mutations and may even have a detrimental effect in these patients.

Updated analysis of the FIRE-3 trial was recently published.<sup>597</sup> When all *RAS* (*KRAS*/*NRAS*) mutations were considered, PFS was significantly worse in patients with *RAS*-mutant tumors receiving FOLFIRI plus cetuximab than patients with *RAS*-mutant tumors receiving FOLFIRI plus bevacizumab (6.1 months vs. 12.2 months;  $P = .004$ ). On the other hand, patients with *KRAS*/*NRAS* wild-type tumors showed no difference in PFS between the regimens (10.4 months vs. 10.2 months;  $P = .54$ ). This result indicates that cetuximab likely has a detrimental effect in patients with *KRAS* or *NRAS* mutations.

The FDA indication for panitumumab was updated to state that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* mutation-positive disease in combination with oxaliplatin-based chemotherapy.<sup>588</sup> The NCCN Colon/Rectal Cancer Panel believes that non-exon 2 *KRAS* mutation status and *NRAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *KRAS* mutation (exon 2 or non-exon 2) or *NRAS* mutation should not be treated with either cetuximab or panitumumab.

***BRAF* V600E Mutations:** Although mutations of *KRAS*/*NRAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *KRAS*/*NRAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *KRAS*/*NRAS* as

possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of colorectal cancers are characterized by a specific mutation in the *BRAF* gene (V600E).<sup>598,599</sup> *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.<sup>598,600</sup> Activation of the protein product of the non-mutated *BRAF* gene occurs downstream of the activated *KRAS* protein in the EGFR pathway. The mutated *BRAF* protein product is believed to be constitutively active,<sup>601-603</sup> thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

Limited data from unplanned retrospective subset analyses of patients with metastatic colorectal cancer treated in the first-line setting suggest that although a *BRAF* V600E mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy.<sup>604,605</sup> On the other hand, results from the randomized phase III Medical Research Council (MRC) COIN trial suggest that cetuximab may have no effect or even a detrimental effect in patients with *BRAF*-mutated tumors treated with CapeOx or FOLFOX in the first-line setting.<sup>600</sup>

In subsequent lines of therapy, retrospective evidence suggests that mutated *BRAF* is a marker of resistance to anti-EGFR therapy in the non-first-line setting of metastatic disease.<sup>606-608</sup> A retrospective study of 773 primary tumor samples from patients with chemotherapy-refractory disease showed that *BRAF* mutations conferred a significantly lower response rate to cetuximab (2/24; 8.3%) compared with tumors with wild-type *BRAF* (124/326; 38.0%;  $P = .0012$ ).<sup>609</sup> Furthermore, data from the multicenter randomized controlled PICCOLO trial are consistent with this conclusion, with a suggestion of harm seen for the addition of panitumumab to irinotecan in the non-first-line setting in the small subset of patients with *BRAF* mutations.<sup>610</sup>





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A meta-analysis published in 2015 identified 9 phase III trials and 1 phase II trial that compared cetuximab or panitumumab with standard therapy or best supportive care including 463 patients with metastatic colorectal tumors with *BRAF* mutations (first-line, second-line, or refractory settings).<sup>611</sup> The addition of an EGFR inhibitor did not improve PFS (HR, 0.88; 95% CI, 0.67–1.14;  $P = .33$ ), OS (HR, 0.91; 95% CI, 0.62–1.34;  $P = .63$ ), or overall response rate (ORR) (RR, 1.31; 95% CI, 0.83–2.08,  $P = .25$ ) compared with control arms. Similarly, another meta-analysis identified 7 randomized controlled trials and found that cetuximab and panitumumab did not improve PFS (HR, 0.86; 95% CI, 0.61–1.21) or OS (HR, 0.97; 95% CI, 0.67–1.41) in patients with *BRAF* mutations.<sup>612</sup>

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.<sup>587,600,605,613-616</sup> A recent prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the *BRAF* mutation is prognostic for OS in patients with low levels of MSI (MSI-L) or stable microsatellites (MSS) (HR, 2.2; 95% CI, 1.4–3.4;  $P = .0003$ ).<sup>587</sup> Moreover, an updated analysis of the CRYSTAL trial showed that patients with metastatic colorectal tumors carrying a *BRAF* mutation have a worse prognosis than those with the wild-type gene.<sup>605</sup> Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (CI, 0.33–0.73;  $P = .001$ ).<sup>614</sup> The OS in patients with *BRAF* mutations in the COIN trial was 8.8 months, while those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 months and 20.1 months, respectively.<sup>600</sup> Results from a recent systematic review and meta-analysis of 21 studies, including 9885 patients, suggest that *BRAF* mutation may accompany specific high-risk clinicopathologic characteristics.<sup>617</sup> In particular, an association was observed between *BRAF* mutation and proximal tumor location

(OR, 5.22; 95% CI, 3.80–7.17;  $P < .001$ ), T4 tumors (OR, 1.76; 95% CI, 1.16–2.66;  $P = .007$ ), and poor differentiation (OR, 3.82, 95% CI, 2.71–5.36;  $P < .001$ ).

Overall, the panel believes that evidence increasingly suggests that *BRAF* V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely. The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis<sup>618</sup>) at diagnosis of stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by PCR amplification and direct DNA sequence analysis. Allele-specific PCR is another acceptable method for detecting this mutation.

### *HER2* Overexpression

HER2 is a member of the same family of signaling kinase receptors as EGFR and has been successfully targeted in breast cancer in both the advanced and adjuvant settings. HER2 is rarely overexpressed in colorectal cancer (approximately 3% overall), but the prevalence is higher in *RAS/BRAF*–wild type tumors (reported at 5%–14%).<sup>619,620</sup>

Specific molecular diagnostic methods have been proposed for HER2 testing in colorectal cancer,<sup>621</sup> and various therapeutic approaches are being tested in patients with tumors that have HER2 overexpression (eg, trastuzumab plus lapatinib, trastuzumab plus pertuzumab).<sup>620,622</sup> These approaches are currently considered investigational, and enrollment in a clinical trial is encouraged.

Evidence does not support a prognostic role of HER2 overexpression.<sup>623</sup> However, initial results indicate HER2 overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.<sup>619,624</sup> For example, in a cohort of 97 patients with *RAS/BRAF*–wild type metastatic colorectal cancer, median PFS on first-line therapy without an EGFR



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inhibitor was similar regardless of HER2 status.<sup>619</sup> However, in second-line therapy with an EGFR inhibitor, the PFS was significantly shorter in those with HER2 amplification compared with those without HER2 amplification (2.9 months vs. 8.1 months; HR, 5.0;  $P < .0001$ ). Larger confirmatory studies are needed, and the panel does not recommend HER2 testing for prognostication or treatment planning at this time.

### ***Predictive Marker for Pembrolizumab and Nivolumab: MSI Status***

The percentage of stage IV colorectal tumors characterized as MSI-H (mismatch repair-deficient; dMMR) ranges from 3.5% to 5.0% in clinical trials and was 6.5% in the Nurses' Health Study and Health Professionals Follow-up Study.<sup>625-627</sup> dMMR tumors contain thousands of mutations, which can encode mutant proteins with the potential to be recognized and targeted by the immune system. However, programmed death-ligands PD-L1 and PD-L2 on tumor cells can suppress the immune response by binding to programmed death receptor-1 (PD-1) on T-effector cells. This system evolved to protect the host from an unchecked immune response. Many tumors upregulate PD-L1 and thus evade the immune system.<sup>628</sup> It has therefore been hypothesized that dMMR tumors may be sensitive to PD-1 inhibitors.

Pembrolizumab is a humanized, IgG4 monoclonal antibody that binds to PD-1 with high affinity, preventing its interaction with PD-L1 and PD-L2 and thus allowing immune recognition and response.<sup>629</sup> Pembrolizumab is FDA-approved for the treatment of patients with unresectable or metastatic melanoma following disease progression on other standard therapies and has shown activity against non-small cell lung cancer.<sup>629,630</sup>

A recent phase II study evaluated the activity of pembrolizumab in 11 patients with dMMR colorectal cancer, 21 patients with MMR-proficient colorectal cancer, and 9 patients with dMMR non-colorectal

carcinomas.<sup>631</sup> All patients had progressive metastatic disease; the patients in the colorectal arms had progressed through 2 to 4 previous therapies. The primary endpoints were the immune-related objective response rate and the 20-week immune-related PFS rate. The immune-related objective response rates were 40% (95% CI, 12%–74%) in the dMMR colorectal cancer group, 0% (95% CI, 0%–20%) in the MMR-proficient colorectal cancer group, and 71% (95% CI, 29%–96%) in the dMMR non-colorectal group. The 20-week immune-related PFS rates were 78% (95% CI, 40–97), 11% (95% CI, 1–35), and 67% (95% CI, 22–96), respectively. These results indicate that MSI is a predictive marker for the effectiveness of pembrolizumab across tumor types. Furthermore, the median PFS and OS were not reached in the arm with dMMR colorectal cancer and were 2.2 and 5.0 months, respectively, in the MMR-proficient colorectal cancer group (HR for disease progression or death, 0.10;  $P < .001$ ).

Nivolumab is another humanized IgG4 PD-1 blocking antibody, with FDA indications in melanoma and non-small cell lung cancer.<sup>632</sup>

Nivolumab was studied with or without ipilimumab in patients with metastatic colorectal cancer in a phase II trial.<sup>633</sup> The median PFS was 5.3 months (95% CI, 1.4–not estimable) in the MMR-deficient patients who received nivolumab monotherapy, not reached in the MMR-deficient patients who received nivolumab plus ipilimumab, and 1.4 months (95% CI, 1.2–1.9) in the pooled MMR-proficient group.

Based on these data, the panel recommends pembrolizumab or nivolumab as treatment options in patients with metastatic MMR-deficient colorectal cancer in second- or third-line therapy. Patients progressing on either of these drugs should not be offered the other. Additional clinical trials are ongoing to confirm the benefit of these drugs in this setting.



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Although PD-1 immune checkpoint inhibitors are generally well tolerated, serious adverse reactions—many immune-mediated—occur in as many as 21% to 41% of patients.<sup>631,633,634</sup> The most common immune-mediated side effects are to the skin, liver, kidneys, gastrointestinal tract, lungs, and endocrine systems.<sup>635-637</sup> Pneumonitis, occurring in approximately 3% to 7% of patients on pembrolizumab or nivolumab, is one of the most serious side effects of PD-1 inhibitors.<sup>635,638-640</sup>

### Recommendations for Treatment of Resectable Synchronous Metastases

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

When patients present with colorectal cancer and synchronous liver metastases, resection of the primary tumor and liver can be done in a simultaneous or staged approach following neoadjuvant treatment (options discussed below).<sup>641-648</sup> Historically, in the staged approach, the primary tumor was usually resected first. However, the approach of liver resection before resection of the primary tumor is now well-accepted. In addition, emerging data suggest that chemotherapy, followed by resection of liver metastases before resection of the primary tumor, might be an effective approach in some patients, although more studies are needed.<sup>649-651</sup> In addition, neoadjuvant short-course radiation of T1-T3 primary rectal tumors is an option in this setting.<sup>652</sup> Locally ablative procedures can be considered instead of or in addition to resection in cases of liver or lung oligometastases (see *Local Therapies for Metastases*, above), but resection is preferred.

There are several acceptable sequences of therapy in the setting of resectable synchronous disease as outlined in the guidelines. As in other settings, the total perioperative therapy should not exceed 6 months.

In the 2014 version of these guidelines, the panel removed the option of surgery as the initial treatment because it believes that the majority of patients should receive preoperative therapy. Upfront systemic treatment has the goal of early eradication of micrometastases, while the goal of consolidating chemoRT is local control of disease prior to surgery/local therapy. For patients receiving neoadjuvant therapy, surgery/local therapy should be performed 5 to 12 weeks following completion of treatment. The panel acknowledges that some patients may not be candidates for chemotherapy or radiation; clinical judgment should be used in such cases.

### Recommendations for Treatment of Unresectable Synchronous Metastases

Patients with unresectable metastases or who are medically inoperable are treated according to whether they are symptomatic or asymptomatic. Symptomatic patients are treated with chemotherapy alone, combined modality therapy with 5-FU/RT or capecitabine/RT, short-course radiation (not recommended for T4 tumors), resection of the involved rectal segment, diverting colostomy, or stenting. Primary treatment should be followed by an active systemic therapy regimen for advanced or metastatic disease.

For patients with asymptomatic liver or lung disease that is deemed to be unresectable, the panel recommends systemic therapy for advanced or metastatic disease to attempt to render these patients candidates for resection (see *Determining Resectability* and *Conversion to Resectability*, above). Chemotherapy regimens with high response rates



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should be considered for patients with potentially convertible disease.<sup>653</sup> These patients should be re-evaluated for resection after 2 months of chemotherapy and every 2 months thereafter while undergoing such therapy.

Results from a recent study suggest that there may be some benefit in both OS and PFS from resection of the primary in the setting of unresectable colorectal metastases.<sup>654</sup> Other retrospective analyses have also shown a potential benefit.<sup>655,656</sup> However, the prospective, multicenter, phase II NSABP C-10 trial showed that patients with an asymptomatic primary colon tumor and unresectable metastatic disease who received mFOLFOX6 with bevacizumab experienced an acceptable level of morbidity without upfront resection of the primary tumor.<sup>657</sup> The median OS was 19.9 months. Notably, symptomatic improvement in the primary is often seen with first-line systemic chemotherapy even within the first 1 to 2 weeks. Furthermore, complications from the primary lesion are uncommon in these circumstances,<sup>418</sup> and its removal delays initiation of systemic chemotherapy. In fact, a recent systematic review concluded that resection of the primary does not reduce complications and does not improve OS.<sup>658</sup> However, a different systematic review concluded that, while data are not strong, resection of the primary tumor may provide a survival benefit.<sup>659</sup> Another systematic review and meta-analysis identified 5 studies that compared open to laparoscopic palliative colectomies in this setting.<sup>660</sup> The laparoscopic approach resulted in shorter lengths of hospital stays ( $P < .001$ ), fewer postoperative complications ( $P = 0.01$ ), and lower estimated blood loss ( $P < .01$ ).

Overall, the panel believes that the risks of surgery outweigh the possible benefits of this approach. Routine palliative resection of a synchronous primary lesion should therefore only be considered if the

patient has an unequivocal imminent risk of obstruction or acute significant bleeding.<sup>418</sup>

An intact primary tumor 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 *Systemic Therapy for Advanced or Metastatic Disease* in the Discussion section of the NCCN Guidelines for Colon Cancer, available at [www.NCCN.org](http://www.NCCN.org)).

### Recommendations for Treatment of Metachronous Metastases

On documentation of metachronous, potentially resectable, metastatic disease with dedicated contrast-enhanced CT or MRI, characterization of the disease extent using PET/CT scan should be considered in select cases if a surgical cure of M1 disease is feasible. PET/CT is used at this juncture to promptly characterize the extent of metastatic disease, and to identify possible sites of extrahepatic disease that could preclude surgery.<sup>661,662</sup> A recent randomized clinical trial of patients with resectable metachronous metastases also assessed the role of PET/CT in the workup of potential curable disease.<sup>663</sup> While there was no impact of PET/CT on survival, surgical management was changed in 8% of patients after PET/CT. For example, resection was not undertaken for 2.7% of patients because additional metastatic disease was identified (bone, peritoneum/omentum, abdominal nodes). In addition, 1.5% of patients had more extensive hepatic resections and 3.4% had additional organ surgery. An additional 8.4% of patients in the PET/CT arm had false-positive results, many of which were investigated with biopsies or additional imaging. A meta-analysis of 18 studies including 1059 patients with hepatic colorectal metastases found that PET or PET/CT results changed management in 24% of patients.<sup>664</sup>





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As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) of *KRAS/NRAS* genotype should be performed to define whether anti-EGFR agents can be considered among the potential options. Although *BRAF* genotyping can be considered for patients with tumors characterized by the wild-type *KRAS/NRAS* genes, this testing is currently optional and is not a necessary part of deciding whether to use anti-EGFR agents (see *Perioperative Cetuximab and Panitumumab for Resectable Metastatic Disease: The Role of KRAS, NRAS, and BRAF Status*, above). Close communication between members of the multidisciplinary treatment team is recommended, including upfront evaluation by a surgeon experienced in the resection of hepatobiliary and lung metastases.

The management of metachronous metastatic disease is distinguished from that of synchronous disease through also including an evaluation of the chemotherapy history of the patient and through the absence of transabdominal resection. Patients with resectable disease are classified according to whether they have undergone previous chemotherapy. For patients who have resectable metastatic disease, treatment is resection with 6 months of perioperative chemotherapy (pre- or postoperative or a combination of both), with choice of regimens based on previous therapy. Locally ablative procedures can be considered instead of or in addition to resection in cases of liver oligometastases (see *Local Therapies for Metastases*, above), but resection is preferred. For patients without a history of chemotherapy use, FOLFOX or CapeOx are preferred, with FLOX, capecitabine, and 5-FU/LV as additional category 2B options. There are also cases when perioperative chemotherapy is not recommended in resectable metachronous disease. In particular, patients with a history of previous chemotherapy and upfront resection can be observed or may be given an active regimen for advanced disease, and the same is true for

patients whose tumors grew on therapy before resection (category 2B for the use of biologic agents in these settings). Observation is preferred if oxaliplatin-based therapy was previously administered. In addition, observation is an appropriate option for patients whose tumors grew through neoadjuvant treatment.

Patients determined to have unresectable disease through cross-sectional imaging scan (including those considered potentially convertible) should receive an active systemic therapy regimen based on prior chemotherapy history (see *Therapy after Progression* in the Discussion section of the NCCN Guidelines for Colon Cancer, available at [www.NCCN.org](http://www.NCCN.org)). In the case of liver metastases only, HAI therapy with or without systemic 5-FU/LV (category 2B) is an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Patients receiving palliative chemotherapy should be monitored with CT or MRI scans approximately every 2 to 3 months.

### Endpoints for Advanced Colorectal Cancer Clinical Trials

In the past few years, there has been much debate over what endpoints are most appropriate for clinical trials in advanced colorectal cancer.<sup>665</sup> Quality of life is an outcome that is rarely measured but is of unquestioned clinical relevance.<sup>666</sup> While OS is also of clear clinical relevance, it is often not used because large numbers of patients and long follow-up periods are required.<sup>666</sup> PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.<sup>666-668</sup> GROUP Español Multidisciplinar en Cancer Digestivo (GEMCAD) recently proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.<sup>669</sup>





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A recent study, in which individual patient data from 3 randomized controlled trials were pooled, tested endpoints that take into account subsequent lines of therapy: duration of disease control, which is the sum of PFS times of each active treatment; and time to failure of strategy, which includes intervals between treatment courses and ends when the planned lines of treatment end (because of death, progression, or administration of a new agent).<sup>667</sup> The authors found a better correlation between these endpoints and OS than between PFS and OS. Another alternative endpoint, time to tumor growth, has also been suggested to predict OS.<sup>670,671</sup> Further evaluation of these and other surrogate endpoints is warranted.

### Post-Treatment Surveillance

After curative-intent surgery and adjuvant chemotherapy, if administered, 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 identify new metachronous neoplasms at a preinvasive stage. An analysis of data from 20,898 patients enrolled in 18 large, adjuvant colon cancer, randomized trials showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor,<sup>672</sup> and a recent study found that 95% of recurrences occurred in the first 5 years.<sup>673</sup>

The approach to monitoring and surveillance of patients with rectal cancer is similar to that described for colon cancer.

### Surveillance for Locoregional Disease

Advantages of more intensive follow-up of patients after treatment of stage II and/or stage III disease have been demonstrated prospectively in several older studies<sup>674-676</sup> and in multiple meta-analyses of randomized controlled trials designed to compare low-intensity and

high-intensity programs of surveillance.<sup>677-680</sup> In the final analysis of Intergroup trial 0114 comparing bolus 5-FU to bolus 5-FU/LV in patients with surgically resectable rectal cancer, local recurrence rates continued to rise after 5 years.<sup>254</sup> Further, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year relative survival rate of 15.6%), thereby providing support for more intensive post-treatment follow-up in these patients.<sup>681</sup>

Results from a recent randomized controlled trial of 1202 patients with resected stage I to III disease showed that intensive surveillance imaging or CEA screening resulted in an increased rate of curative-intent surgical treatment compared with a minimum follow-up group that only received testing if symptoms occurred, but no advantage was seen in the CEA and CT combination arm (2.3% in the minimum follow-up group, 6.7% in the CEA group, 8% in the CT group, and 6.6% in the CEA plus CT group).<sup>682</sup> In this study, no mortality benefit to regular monitoring with CEA, CT, or both was observed compared with minimum follow-up (death rate, 18.2% vs. 15.9%; difference, 2.3%; 95% CI, -2.6%–7.1%). The authors concluded that any strategy of surveillance is unlikely to provide a large survival advantage over a symptom-based approach.<sup>682</sup>

The CEAwatch trial compared usual follow-up care to CEA measurements every two months, with imaging performed if CEA increases were seen twice, in 3223 patients at 11 hospitals treated for non-metastatic colorectal cancer in the Netherlands.<sup>683</sup> The intensive CEA surveillance protocol resulted in the detection of more total recurrences and recurrences that could be treated with curative intent than usual follow-up, and the time to detection of recurrent disease was shorter. Another randomized trial of 1228 patients found that more intensive surveillance led to earlier detection of recurrences than a less



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intensive program (less frequent colonoscopy and liver ultrasound and the absence of an annual chest x-ray) but did not affect OS.<sup>684</sup>

The randomized phase III PRODIGE 13 trial will compare 5-year OS after intensive radiological monitoring (abdominal ultrasound, chest/abdomen/pelvis CT, and CEA) with a lower intensity program (abdominal ultrasound and chest x-ray) in patients with resected stage II or III colon or rectal tumors.<sup>685</sup>

Clearly, controversies remain regarding selection of optimal strategies for following patients after potentially curative colorectal cancer surgery, and the panel's recommendations are based mainly on consensus. The panel endorses surveillance as a means to identify patients who are potentially curable of metastatic disease with surgical resection.

The following panel recommendations for post-treatment surveillance pertain to patients with stage I through stage III disease who have undergone successful treatment (ie, no known residual disease): history and physical examination every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years; and a CEA test (also see *Managing an Increasing CEA Level*, below) is recommended at baseline and every 3 to 6 months for 2 years,<sup>686</sup> then every 6 months for a total of 5 years for patients with stage III disease and those with stage II disease if the clinician determines that the patient is a potential candidate for aggressive curative surgery.<sup>677,686,687</sup>

Colonoscopy is recommended at approximately 1 year following resection (or at approximately 3 to 6 months post-resection if not performed preoperatively due to an obstructing lesion). Repeat colonoscopy is typically recommended at 3 years, and then every 5 years thereafter, unless follow-up colonoscopy indicates advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia), in which

case colonoscopy should be repeated in 1 year.<sup>688</sup> More frequent colonoscopies may be indicated in patients who present with colorectal cancer before age 50.<sup>688</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>689</sup> particularly in the first 2 years following resection. The 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>688</sup>

Proctoscopy with EUS or MRI is recommended to evaluate the rectal anastomosis for local recurrence only in patients treated with transanal excision. Proctoscopy is not recommended for other patients, because isolated local recurrences are rarely found in these patients and are rarely curable. In fact, in a single-center study of 112 patients who had TME for rectal cancer, only one local recurrence occurred, and it was not identified by rectal surveillance but by CEA and symptoms.<sup>690</sup> In these 112 patients, 20 anoscopies, 44 proctoscopies, and 495 flexible sigmoidoscopies were performed.

Chest, abdominal, and pelvic CT scans are recommended every 3 to 6 months for 2 years and then every 6 to 12 months for up to 5 years.<sup>677,691</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. A recent analysis of patients with resected or ablated colorectal liver metastases found that the frequency of surveillance imaging did not correlate with time to second procedure or median survival duration.<sup>692</sup> Those scanned once per year survived a median of 54 months versus 43 months for those scanned 3 to 4 times per year (P



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= .08), suggesting that annual scans may be sufficient in this population.

Routine CEA monitoring and CT scanning are not recommended beyond 5 years. In addition, use of PET/CT to monitor for disease recurrence is not recommended.<sup>691,693</sup> The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore is not of ideal quality for routine surveillance.

The ASCO Clinical Practice Guidelines Committee recently endorsed the Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer, from Cancer Care Ontario (CCO).<sup>694,695</sup> These guidelines differ only slightly from the surveillance recommendations in these NCCN Guidelines for Rectal Cancer. While ASCO/CCO recommend abdominal and chest CT annually for 3 years, the NCCN Panel recommends semi-annual to annual scans for 5 years (category 2B for more frequent than annual scanning). The panel bases its recommendation on the fact that approximately 10% of disease recurrences occur after 3 years.<sup>673,696</sup> The American Society of Colon and Rectal Surgeons also released surveillance guidelines, which are also very similar to NCCN surveillance recommendations.<sup>697</sup> One exception is the inclusion of intensive surveillance for patients with resected stage I colon or rectal cancer if the provider deems the patient to be at increased risk for recurrence.

### Surveillance for Metastatic Disease

Patients who had resection of metastatic colorectal cancer can undergo subsequent curative-intent resection of recurrent disease (*see Surgical Management of Colorectal Metastases*, above). A retrospective analysis of 952 patients who underwent resection at Memorial Sloan Kettering Cancer Center showed that 27% of patients with recurrent disease underwent curative-intent resection and that 25% of those patients (6%

of recurrences; 4% of the initial population) were free of disease for ≥36 months.<sup>698</sup>

Panel recommendations for surveillance of patients with stage IV rectal cancer with NED after curative-intent surgery and perioperative treatment are similar to those listed for patients treated for locoregional rectal cancer. One difference is that the frequency of chest, abdominal, and pelvic CT scan for the first 2 years is every 3 to 6 months (category 2B for frequency <6 months), whereas it is every 6 to 12 months for patients treated for locoregional disease.

### Managing an Increasing CEA Level

Managing patients with an elevated CEA level after resection should include colonoscopy; chest, abdominal, and pelvic CT scans; physical examination; and consideration of a PET/CT scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans are recommended every 3 months until either disease is identified or CEA level stabilizes or declines.

In a recent retrospective chart review at Memorial Sloan Kettering Cancer Center, approximately half of elevations in CEA levels after R0 resection of locoregional colorectal cancer were false positives, with most being single high readings or repeat readings in the range of 5 to 15 ng/mL.<sup>699</sup> In this study, false-positive results >15 ng/mL were rare, and all results >35 ng/mL represented true-positives. Following a systematic review and meta-analysis, the pooled sensitivity and specificity of CEA at a cut-off of 10 ng/mL were calculated at 68% (95% CI, 53%–79%) and 97% (95% CI, 90%–99%), respectively.<sup>700,701</sup> In the first 2 years post-resection, a CEA cut-off of 10 ng/mL is estimated to detect 20 recurrences, miss 10 recurrences, and result in 29 false positives.



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Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (ie, some panel members favored use of PET/CT in this scenario whereas others noted that the likelihood of PET/CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). A recent systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.<sup>702</sup> The pooled estimates of sensitivity and specificity for the detection of tumor recurrence were 94.1% (95% CI, 89.4–97.1%) and 77.2% (95% CI, 66.4–85.9), respectively. 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>703</sup> nor do they recommend use of anti-CEA-radiolabeled scintigraphy.

### Treatment of Locally Recurrent Disease

Locally recurrent rectal cancer is characterized by isolated pelvic/anastomotic recurrence of disease. In a single-center study, Yu et al reported low rates of 5-year local recurrence (ie, 5-year locoregional control rate of 91%) for patients with rectal cancer treated with surgery and either RT or chemoRT, and 49% of recurrences occurred in the low pelvic and presacral regions with an additional 14% occurring in the mid and high pelvis.<sup>704</sup> Patients with disease recurrence at the anastomotic site are more likely to be cured following re-resection than those with an isolated pelvic recurrence.<sup>705,706</sup>

Potentially resectable isolated pelvic/anastomotic recurrence is optimally managed with resection followed by adjuvant chemoRT or with preoperative RT and concurrent chemotherapy. IORT or brachytherapy should be considered with resection if it can be safely delivered.<sup>374,707-709</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 infusion concurrent with RT enabled the majority of patients (77%) to undergo re-resection with curative intent.<sup>706</sup> Studies of patients who previously received pelvic radiotherapy show that re-irradiation can be effective, with acceptable rates of toxicity.<sup>710-712</sup> In one such study of 48 patients with recurrent rectal cancer and a history of pelvic radiation, the 3-year rate of grade 3 to 4 late toxicity was 35%, and 36% of treated patients were able to undergo surgery following radiation.<sup>710</sup> IMRT can be used in this setting of re-irradiation.

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

### Survivorship

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.<sup>713</sup> The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to the patient. The care plan should include an overall summary of treatments received, including surgeries, radiation treatments, and chemotherapy. The possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment should be described. Finally, surveillance and health behavior recommendations should be part of the care plan.

Disease preventive measures, such as immunizations; early disease detection through periodic screening for second primary cancers (eg, breast, cervical, or prostate cancers); and routine good medical care and monitoring are recommended (see the NCCN Guidelines for Survivorship, available at [www.NCCN.org](http://www.NCCN.org)). Additional health monitoring





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should be performed as indicated under the care of a primary care physician. Survivors are encouraged to maintain a therapeutic relationship with a primary care physician throughout their lifetime.<sup>714</sup>

Other recommendations include monitoring for late sequelae of rectal cancer or of the treatment of rectal cancer, such as chronic diarrhea or incontinence (eg, patients with stoma).<sup>715-720</sup> Urogenital dysfunction following resection and/or pelvic irradiation is common.<sup>715,721-723</sup> Patients should be screened for sexual dysfunction, erectile dysfunction, dyspareunia, vaginal dryness, and urinary incontinence, frequency, and urgency. Referral to a gynecologist or urologist can be considered for persistent symptoms. Other long-term problems common to colorectal cancer survivors include oxaliplatin-induced peripheral neuropathy, fatigue, insomnia, cognitive dysfunction, and emotional or social distress.<sup>724-729</sup> Specific management interventions to address side effects of colorectal cancer have been described,<sup>730</sup> and a survivorship care plan for patients with colorectal cancer has recently been published.<sup>731</sup>

The NCCN Guidelines for Survivorship, available at [www.NCCN.org](http://www.NCCN.org), provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in specialty cancer survivor clinics and primary care practices. The NCCN Guidelines for Survivorship include many topics with potential relevance to survivors of colorectal cancer, including Anxiety, Depression, and Distress; Cognitive Dysfunction; Fatigue; Pain; Sexual Dysfunction; Healthy Lifestyles; and Immunizations. Concerns related to employment, insurance, and disability are also discussed. The ACS has also established guidelines for the care of survivors of colorectal cancer, including surveillance for recurrence, screening for subsequent primary

malignancies, the management of physical and psychosocial effects of cancer and its treatment, and promotion of healthy lifestyles.<sup>714</sup>

### Healthy Lifestyles for Survivors of Colorectal Cancer

Evidence indicates that certain lifestyle characteristics, such as smoking cessation, maintaining a healthy BMI, engaging in regular exercise, and making certain dietary choices are associated with improved outcomes and quality of life after treatment for colorectal cancer. In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, DFS was found to be directly related to how much exercise these patients received.<sup>732</sup> In addition, a recent study of a large cohort of men treated for stage I through III colorectal cancer showed an association between increased physical activity and lower rates of colorectal cancer-specific mortality and overall mortality.<sup>733</sup> More recent data support the conclusion that physical activity improves outcomes. In a cohort of over 2000 survivors of non-metastatic colorectal cancer, those who spent more time in recreational activity had a lower mortality than those who spent more leisure time sitting.<sup>734</sup> In addition, recent evidence suggests that both pre- and post-diagnosis physical activity decreases colorectal cancer mortality. Women enrolled in the Women's Health Initiative study who subsequently developed colorectal cancer had lower colorectal cancer-specific mortality (HR, 0.68; 95% CI, 0.41–1.13) and all-cause mortality (HR, 0.63; 95% CI, 0.42–0.96) if they reported high levels of physical activity.<sup>735</sup> Similar results were seen in other studies and in recent meta-analyses of prospective studies.<sup>736-739</sup>

A retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI of 35 kg/m<sup>2</sup> or greater had an increased risk of disease recurrence and death.<sup>740</sup> Recent analyses confirm the increased risk for recurrence





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and death in obese patients.<sup>741</sup> Data from the ACCENT database also found that pre-diagnosis BMI has a prognostic impact on outcomes in patients with stage II/III colorectal cancer undergoing adjuvant therapy.<sup>742</sup> However, a recent analysis of participants in the Cancer Prevention Study-II Nutrition Cohort who subsequently developed non-metastatic colorectal cancer found that pre-diagnosis obesity but not post-diagnosis obesity was associated with higher all-cause and colorectal cancer-specific mortality.<sup>743</sup> A meta-analysis of prospective cohort studies found that pre-diagnosis obesity was associated with increased colorectal cancer-specific and all-cause mortality.<sup>744</sup> Other analyses confirm the increased risk for recurrence and death in obese patients.<sup>741,745-748</sup>

In contrast, pooled data from first-line clinical trials in the ARCAD database indicate that a low BMI may be associated with an increased risk of progression and death in the metastatic setting, whereas a high BMI may not be.<sup>749</sup> In addition, results of one retrospective observational study of a cohort of 3408 patients with resected stage I to III colorectal cancer suggest that the relationship between mortality and BMI might be U shaped, with the lowest mortality for those with BMI 28 kg/m<sup>2</sup>.<sup>750</sup> However, several possible explanations for this so-called “obesity paradox” have been suggested.<sup>751</sup> Overall the panel believes that survivors of colorectal cancer should be encouraged to achieve and maintain a healthy body weight (see the NCCN Guidelines for Survivorship at [www.NCCN.org](http://www.NCCN.org)).

A diet consisting of more fruits, vegetables, poultry, and fish, less red meat, 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>752</sup> There is also some evidence that higher postdiagnosis intake of total milk and calcium may be associated with a lower risk of death in patients with stage I, II, or III

colorectal cancer.<sup>76</sup> Recent analysis of the CALGB 89803 trial found that higher dietary glycemic load was also associated with an increased risk of recurrence and mortality in patients with stage III disease.<sup>753</sup> Another analysis of the data from CALGB 89803 found an association between high intake of sugar-sweetened beverages and an increased risk of recurrence and death in patients with stage III colon cancer.<sup>754</sup> The link between red and processed meats and mortality in survivors of non-metastatic colorectal cancer has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intake had a higher risk of colorectal cancer-specific mortality than those with low intake (RR, 1.79; 95% CI, 1.11–2.89).<sup>69</sup>

A discussion of lifestyle characteristics that may be associated with a decreased risk of colorectal cancer recurrence, such as those recommended by the American Cancer Society (ACS),<sup>755</sup> 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. In addition, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of colorectal cancer, suggesting that survivors may be open to health behavior change.<sup>756</sup>

Therefore, survivors of colorectal cancer should be encouraged to maintain a healthy body weight throughout life; adopt a physically active lifestyle (at least 30 minutes of moderate intensity activity on most days of the week); consume a healthy diet with emphasis on plant sources; limit alcohol consumption; and quit smoking.<sup>757</sup> Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy), and diet recommendations may be modified based on the severity of bowel dysfunction.<sup>758</sup>



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### Secondary Chemoprevention for Colorectal Cancer Survivors

Limited data suggest a link between post-colorectal-cancer-diagnosis statin use and increased survival.<sup>89,759,760</sup> A meta-analysis that included 4 studies found that post-diagnosis statin use increased OS (HR, 0.76; 95% CI, 0.68–0.85;  $P < .001$ ) and cancer-specific survival (HR, 0.70; 95% CI, 0.60–0.81;  $P < .001$ ).<sup>759</sup>

Abundant data show that low-dose aspirin therapy after a diagnosis of colorectal cancer decreases the risk of recurrence and death.<sup>761-767</sup> For example, a population-based, observational, retrospective cohort study of 23,162 patients with colorectal cancer in Norway found that post-diagnosis aspirin use was associated with improved colorectal cancer-specific survival (HR, 0.85; 95% CI, 0.79–0.92) and OS (HR, 0.95; 95% CI, 0.90–1.01).<sup>761</sup> Some evidence suggests that tumor mutations in *PIK3CA* may be predictive for response to aspirin, although the data are somewhat inconsistent and other predictive markers have also been suggested.<sup>763,768-772</sup>

Based on these data, the panel believes that survivors of colorectal cancer can consider taking low-dose aspirin to reduce their risk of recurrence and death. Importantly, aspirin may increase the risk of gastrointestinal bleeding and hemorrhagic stroke, and these risks should be discussed with colorectal cancer survivors.<sup>773</sup>

### Summary

The NCCN Rectal Cancer Panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology is necessary for treating patients with rectal cancer. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes when possible. Patients with very-early-

stage tumors that are node-negative by endorectal ultrasound or endorectal or pelvic MRI and who meet carefully defined criteria can be managed with a transanal excision. A transabdominal resection is appropriate for all other rectal lesions. Perioperative chemoRT and chemotherapy are preferred for the majority of patients with suspected or proven T3-4 disease and/or regional node involvement.

The recommended post-treatment surveillance program for patients following treatment for rectal cancer includes serial CEA determinations, as well as periodic chest, abdominal, and pelvic CT scans, and periodic evaluation by colonoscopy. Patients with recurrent localized disease should be considered for resection with chemotherapy and radiation. If resection is not possible, then chemotherapy is given with or without radiation.

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) can be achieved. Perioperative chemotherapy and chemoRT are used in the synchronous setting, and perioperative chemotherapy is used in the metachronous setting.

Recommendations for patients with disseminated, unresectable metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at the start of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression and plans for adjusting therapy for patients who experience certain toxicities. Recommended initial therapy options for advanced or metastatic disease depend on whether or not the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CapeOX, and FOLFOXIRI. Addition of a biologic agent (ie, bevacizumab, cetuximab, panitumumab) is listed as an option



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in combination with some of these regimens, depending on available data. Systemic therapy options for patients with progressive disease are dependent on the choice of initial therapy. The panel endorses the concept that treating patients in a clinical trial has priority over standard treatment regimens.



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