



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Rectal Cancer

Version 2.2019 — May 15, 2019

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[NCCN Guidelines Panel Disclosures](#)

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¶ Internal medicine	¶ Surgery/Surgical oncology
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[NCCN Rectal Cancer Panel Members](#) [Summary of the Guidelines Updates](#)

Clinical Presentations and Primary Treatment:

- [Pedunculated Polyp or Sessile Polyp with Invasive Cancer \(REC-1\)](#)
- [Rectal Cancer Appropriate for Resection \(REC-2\)](#)
 - ▶ [Treatment after Transanal Local Excision of T1, N0 \(REC-3\)](#)
 - ▶ [Treatment after Transabdominal Resection of T1-2, N0 \(REC-4\)](#)
 - ▶ [T3, N Any with Clear Circumferential Margin \(CRM\) \(by MRI\); T1-2, N1-2 \(REC-5\)](#)
 - ▶ [T3, N Any with Involved CRM \(by MRI\); T4, N Any \(REC-6\)](#)
- [Locally Unresectable or Medically Inoperable \(REC-6\)](#)
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[Surveillance \(REC-11\)](#)

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[Staging \(ST-1\)](#)

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/clinicians.aspx](#).

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 2.2019 of the NCCN Guidelines for Colon Cancer from Version 1.2019 include:****Systemic Therapy for Advanced or Metastatic Disease (COL-D)****[REC-F \(2 of 13\)](#)**

- The following regimens added as treatment options in subsequent therapy:
 - ▶ Trastuzumab + pertuzumab (HER2-amplified and RAS WT) (category 2B)
 - ▶ Trastuzumab + lapatinib (HER2-amplified and RAS WT) (category 2B) (also applies to REC-F 3 of 13, 4 of 13, 5 of 13, 6 of 13)
- Footnote p added: If no previous treatment with HER2 inhibitor.

[REC-F \(11 of 13\)](#)

- Dosing schedules and references added for the following regimens:
 - ▶ Trastuzumab + pertuzumab (HER2-amplified and RAS WT)
Trastuzumab 8mg/kg IV loading dose on Day 1 of Cycle 1, then 6mg/kg IV every 21 days
Pertuzumab 840mg IV loading dose on Day 1 of Cycle 1, then 420mg IV every 21 days
 - ▶ Trastuzumab + lapatinib (HER2-amplified and RAS WT)
Trastuzumab 4mg/kg IV loading dose on Day 1 of Cycle 1, then 2mg/kg IV weekly
Lapatinib 1000mg PO daily

Updates in Version 1.2019 of the NCCN Guidelines for Rectal Cancer from Version 3.2018 include:**[General](#)**

- **BRAF** WT added as an indication for treatment, where **KRAS** and **NRAS** WT are noted.

[REC-1](#)

- Fragmented specimen or margin cannot be assessed or unfavorable histologic features
 - ▶ The following workup added: Consider rigid proctoscopy; Chest CT and abdominal CT or MRI; CBC, chemistry profile, CEA; Pelvic MRI with contrast; Endorectal ultrasound (if MRI is contraindicated or consider for superficial lesions); Enterostomal therapist as indicated for preoperative marking of site, teaching; PET/CT scan is not indicated.

[REC-2](#)

- Rectal cancer appropriate for resection (non-metastatic)
 - ▶ Bullet 7 modified: Pelvic MRI with *or without* contrast
 - ▶ Bullet 8 modified: Endorectal ultrasound (~~only~~ if MRI is contraindicated [e.g. pacemaker]) *or consider for superficial lesions*)
 - ▶ The following added to the workup:
 - ◇ Multidisciplinary team evaluation
 - ◇ Consider fertility risk discussion/counseling in appropriate patients.

[REC-3](#)

- pT1, NX with high-risk features or pT2, NX
 - ▶ Chemo/RT
 - ◇ Clarification added to Transabdominal resection: (if evidence of disease)

[REC-5](#)

- The following treatment option added:
 - ▶ Short-course RT followed by 12–16 weeks of chemotherapy
 - ◇ FOLFOX (preferred) or CAPEOX (preferred) or 5-FU/leucovorin or capecitabine
- Footnote t modified with addition of this sentence: Short-course RT is not recommended for low-lying tumors, <5 cm from anal verge. (also applies to REC-6)

[REC-7](#)

- Bullet 4 modified: Pelvic MRI with *or without* contrast
- Footnote y added: Testing should include the neurotrophic receptor tyrosine kinase (**NTRK**) gene fusion. (also applies to REC-12)

[REC-8](#)

- Footnote z modified: If obstructing lesion, consider diversion *or resection* (see REC-10).



Updates in Version 1.2019 of the NCCN Guidelines for Rectal Cancer from Version 3.2018 include:

REC-9

- Unresectable synchronous liver and/or lung metastases
The following regimen added as a treatment option: FOLFOXIRI ± panitumumab or cetuximab (category 2B for FOLFOXIRI combination) (KRAS/NRAS/BRAF WT gene)

REC-11

- The clarification “after surgery” added after colonoscopy.

REC-B 4 of 7

- Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry
 - ▶ Bullet 1 modified: Examination of the sentinel lymph nodes (*sentinel or routine*) allows an-by intense histologic and/or immunohistochemical investigation helps to detect the presence of metastatic disease. The detection of single cells by IHC or by multiple H&E levels and/or clumps of tumor cells <0.2 mm are considered isolated tumor cells (pN0) Studies in the literature have been reported using multiple hematoxylin and eosin (H&E) sections and/or immunohistochemistry (IHC) to detect cytokeratin-positive cells. The significance of detection of single cells by IHC alone is controversial. 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. The 8th edition of the AJCC Cancer Staging Manual and Handbook defines clumps of tumor cells notes that micrometastases have been defined as clusters of 10 to 20 tumor cells or clumps of tumor ≥0.2 mm in diameter or clusters of 10-20 tumor cells as micrometastasis and recommends that these micrometastases be considered as standard positive lymph nodes (pN+).

REC-B 4 of 7

- Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry
 - ▶ Bullet 2 modified: At the present time the use of sentinel lymph nodes and detection of cancer isolated tumor cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions. 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 some of these studies, *what is presently defined as* isolated tumor cells were considered to be micrometastases.

REC-B 5 of 7

- KRAS, NRAS, and BRAF Mutation Testing
 - ▶ Bullet 1 modified: All patients with metastatic colorectal cancer should have tumor tissue genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of a next-generation sequencing (NGS) Panel.
- Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing
 - ▶ Bullet 2 modified: The presence of a BRAF V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome in the vast majority of cases. However, approximately 1% of cancers with BRAF V600E mutations (and loss of MLH-1) are Lynch syndrome. Caution should be exercised in excluding cases with strong family history from germline screening in the case of BRAF V600E mutations.
 - ▶ Bullet 6 is new: Immunohistochemistry (IHC) refers to staining tumor tissue for protein expression of the four mismatch repair MMR genes known to be mutated in Lynch syndrome LS (MLH1, MSH2, MSH6, and PMS2.) A normal IHC test implies that all four MMR proteins are normally expressed (retained). Loss (absence) of expression of one or more of the four DNA MMR proteins is often reported as abnormal or positive IHC. When IHC is reported as positive, caution should be taken to ensure that positive refers to absence of mismatch expression and not presence of expression. NOTE: Normal is the presence of positive protein staining (retained) and abnormal is negative or loss of staining of protein. Loss of protein expression by IHC in any one of the MMR genes guides further genetic testing (mutation detection to the genes where the protein expression is not observed). Abnormal MLH1 IHC should be followed by tumor testing for BRAF V600E mutation. The presence of BRAF V600E mutation is consistent with sporadic cancer. However, approximately 1% of Lynch syndrome patients with loss of MLH-1 can express BRAF V600E mutation.



Updates in Version 1.2019 of the NCCN Guidelines for Rectal Cancer from Version 3.2018 include:

REC-C 1 of 3

- **Transanal Local Excision**
 - ▶ **Bullet 2 modified:** When the lesion can be adequately identified *in localized to the rectum, local excision of more proximal lesions may be technically feasible using advanced techniques, such as transanal endoscopic-microscopic surgery (TEM) or transanal minimally invasive surgery (TAMIS) may be technically feasible for more proximal lesions.*
- **Transabdominal Resection; Management principles modified:**
 - ▶ **Bullet 1 modified:** The treating surgeon should assess *the distal margin before initiating treatment by digital rectal examination ± perform a rigid or flexible proctoscopy, particularly for non-palpable lesions before initiating treatment.*
 - ▶ **Bullet 2 modified:** Remove primary tumor with adequate *circumferential and distal margins.*
 - ▶ **Bullet 4 modified:** ~~Restore organ integrity, if possible.~~ *Sphincter preservation and restoration of organ integrity should be achieved without compromise of oncologic resection and consideration of anticipated patient functional outcome and quality of life.*
 - ▶ **Bullet 5 modified:** Surgery should be 5–12 weeks following full-dose 5.5-week neoadjuvant chemoradiation. *For short-course neoadjuvant radiation therapy, surgery can be considered at 3–7 days or 4–8 weeks.*

REC-C 1 of 3

- **Transabdominal Resection; Total mesorectal excision modified:**
 - ▶ **Bullet added:** Total mesorectal excision is a standard component of radical rectal cancer surgery. TME reduces the positive radial margin and local recurrence rates.
 - ▶ **Bullet removed:** Reduces positive radial margin rate.
- **Transabdominal Resection; Lymph node dissection modified:**
 - ▶ **Bullet 1 modified:** ~~Biopsy or remove~~ *Clinically suspicious nodes beyond the field of resection should be biopsied and/or removed, if possible. Extensive resection of M1 lymph nodes is not indicated.*
 - ▶ **Bullet 2 modified:** Extended *lymph node* resection is not indicated in the absence of clinically suspected nodes.
 - ▶ **Bullet 5, diamond 3 modified:** It is not *generally* indicated for acute bowel obstruction or perforation from cancer.

REC-E

- **Treatment Information**
 - ▶ **Bullet 2 modified:** IMRT/SBRT 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, or patients with localized oligometastases.
 - ▶ **Target Volumes; Sub-bullet 1 modified**
 - ◊ Radiation therapy fields should include the tumor or tumor bed, with a 2–5 cm margin, *the mesorectum*, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.
 - ▶ **Target Volumes; Sub-bullet 2 modified**
 - ▶ **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~~ *is encouraged.*

REC-F 2 of 12

- The following regimens added as treatment options in subsequent therapy:
 - ▶ Dabrafenib + trametinib + (cetuximab or panitumumab) (*BRAF V600E mutation positive*)
 - ▶ Encorafenib + binimetinib + (cetuximab or panitumumab) (*BRAF V600E mutation positive*) (also applies to COL-D 3 of 12, 4 of 12, 5 of 12)
- Footnote a added: Larotrectinib is a treatment option for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.

REC-F 3 of 12

- The combination regimen FOLFOX + cetuximab or panitumumab added for *KRAS/NRAS/BRAF* WT tumors.

REC-F 6 of 12

- Footnote 8 added: If patients had therapy stopped for reasons other than progression (eg, cumulative toxicity, elective treatment break, patient preference), rechallenge is an option at time of progression.



Updates in Version 1.2019 of the NCCN Guidelines for Rectal Cancer from Version 3.2018 include:

[REC-F 9 of 12](#)

- Dosing schedules added for the following regimens:
 - ▶ Irinotecan + panitumumab (KRAS/NRAS/BRAF WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks
 - ▶ Irinotecan + ramucirumab
Ramucirumab 8 mg/kg IV over 60 minutes every 2 weeks
 - ▶ Nivolumab 480 mg IV every 4 weeks

[REC-F 10 of 12](#)

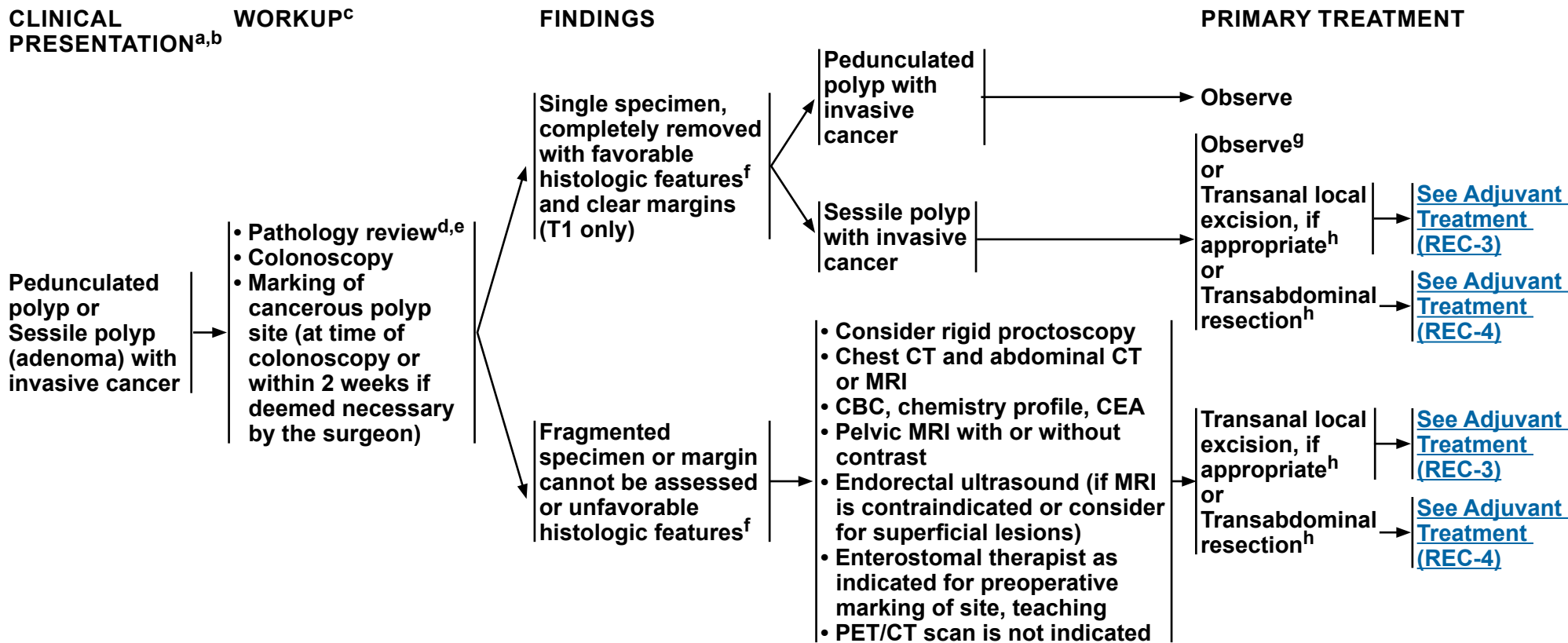
- Dosing schedules added for the following regimens:
 - ▶ Dabrafenib + trametinib + cetuximab
(*BRAF* V600E mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly
 - ▶ Dabrafenib + trametinib + panitumumab
(*BRAF* V600E mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Panitumumab 6 mg/kg IV every 14 days
 - ▶ Encorafenib + binimetinib + cetuximab
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO twice daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly
 - ▶ Encorafenib + binimetinib + panitumumab
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO twice daily
Panitumumab 6 mg/kg IV every 14 days
 - ▶ Larotrectinib
(*NTRK* gene fusion positive)
100 mg PO twice daily

[REC-F 12 of 12](#)

- The following references were added:
 - Atreya CE, Van Cutsem E, Bendell JC, et al. Phase 1/2 Study of the MEK Inhibitor Trametinib, BRAF Inhibitor Dabrafenib, and Anti-EGFR Antibody Panitumumab in Patients With BRAF V600E-Mutated Metastatic Colorectal Cancer J Clin Oncol 2015;33 (suppl; abstr 103).
 - Van Cutsem E, Cuyle P, Huijberts S, et al. BEACON CRC study safety lead-in: assessment of the BRAF inhibitor encorafenib + MEK inhibitor binimetinib + anti-epidermal growth factor receptor antibody cetuximab for BRAF V600E metastatic colorectal cancer. Ann Oncol 2018;29(suppl 5; abstr O-027).
 - Van Cutsem E, Cuyle P-J, Huijberts S, et al. BEACON CRC study safety lead-in (SLI) in patients with BRAF V600E metastatic colorectal cancer: efficacy and tumor markers. J Clin Oncol 2018;36(suppl; abstr 627).
 - Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378:731-739.

[REC-G 1 of 2](#)

- Management of Late/Long-Term Sequelae of Disease or Treatment
 - ▶ For oxaliplatin-induced neuropathy
 - ◊ Bullet added: Pregabalin or gabapentin are not recommended



^a 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](#).

^b For melanoma histology, see the [NCCN Guidelines for Cutaneous Melanoma](#).

^c [See Principles of Imaging \(REC-A\)](#).

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

^e 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.

^f [See Principles of Pathologic Review \(REC-B\)](#) - Endoscopically removed malignant polyp.

^g 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 \(REC-B\)](#) - Endoscopically removed malignant polyp.

^h [See Principles of Surgery \(REC-C\)](#).

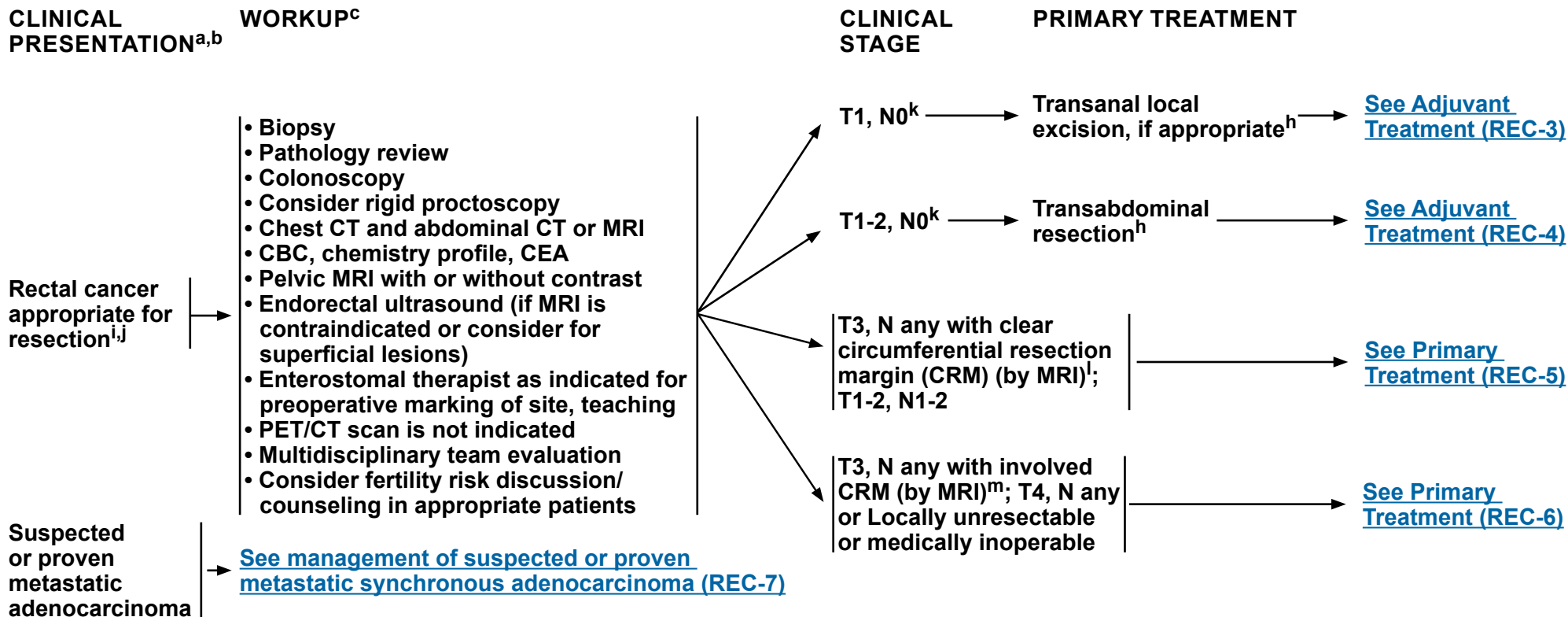
Note: All recommendations are category 2A unless otherwise indicated.

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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Rectal Cancer



^a 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](#).

^b For melanoma histology, see the [NCCN Guidelines for Cutaneous Melanoma](#).

^c See [Principles of Imaging \(REC-A\)](#).

^h See [Principles of Surgery \(REC-C\)](#).

ⁱ For tools to aid optimal assessment and management of older adults with cancer, see the [NCCN Guidelines for Older Adult Oncology](#).

^j The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.

^k T1-2, N0 should be based on assessment of pelvic MRI (preferred) or endorectal ultrasound.

^l CRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.

^m CRM measured at the closest distance of the tumor to the mesorectal fascia. Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.

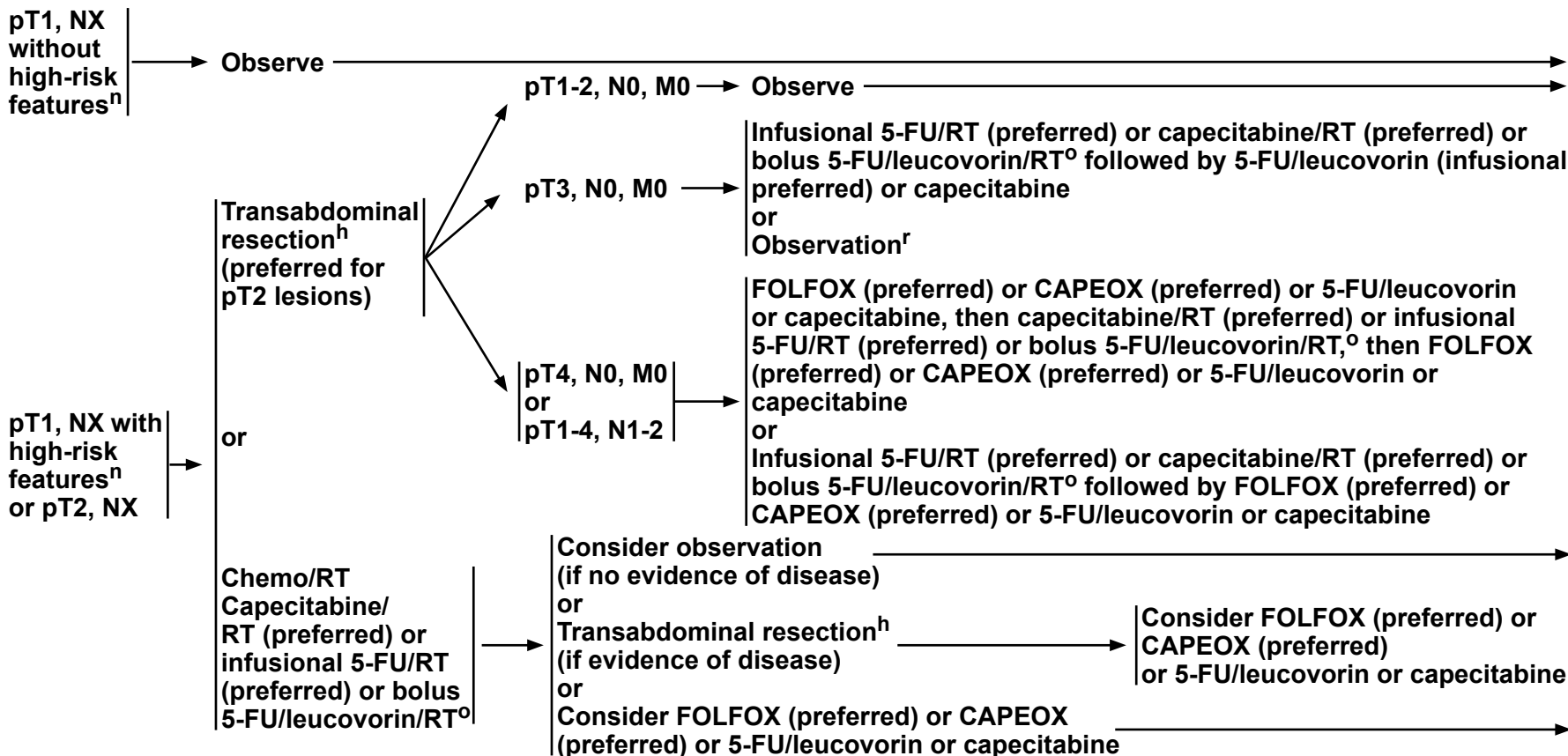
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PATHOLOGIC FINDINGS AFTER TRANSANAL LOCAL EXCISION FOR T1, N0

ADJUVANT TREATMENT^{c,p,q} (6 MO PERIOPERATIVE TREATMENT PREFERRED)^s



^c See Principles of Imaging (REC-A).

^h See Principles of Surgery (REC-C).

ⁿ High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion (submucosal invasion to the lower third of the submucosal level).

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

^p See Principles of Adjuvant Therapy (REC-D).

^q See Principles of Radiation Therapy (REC-E).

^r Observation following transabdominal resection can be considered in patients with pT3N0 rectal cancer if the tumor was well-differentiated or moderately well-differentiated carcinoma invading less than 2 mm into the mesorectum, without lymphatic or venous vessel involvement and was located in upper rectum. Willett CG, Badizadegan K, Ancukiewicz M, Shellito PC. Prognostic factors in stage T3N0 rectal cancer: do all patients require postoperative pelvic irradiation and chemotherapy? Dis Colon Rectum 1999;42:167-173.

^s A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years or older has not been proven.

[Surveillance \(See REC-11\)](#)

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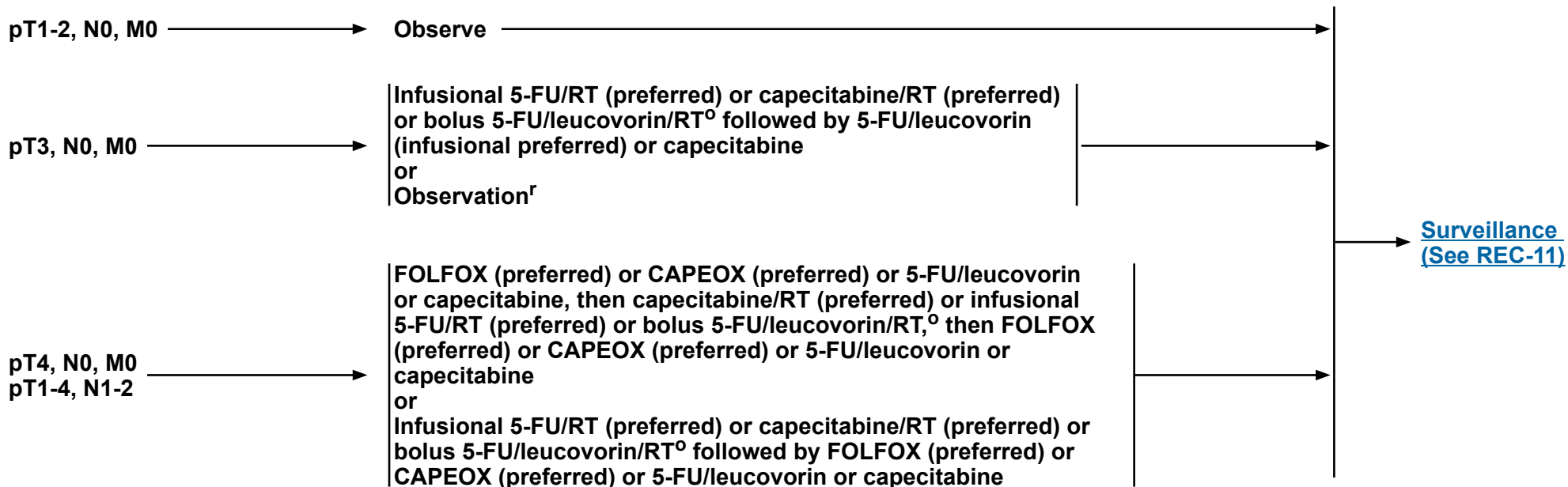


NCCN Guidelines Version 2.2019

Rectal Cancer

PATHOLOGIC FINDINGS AFTER TRANSABDOMINAL RESECTION FOR T1-2, N0

ADJUVANT TREATMENT^{c,p,q} (6 MO PERIOPERATIVE TREATMENT PREFERRED)^s



^c See Principles of Imaging (REC-A).

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

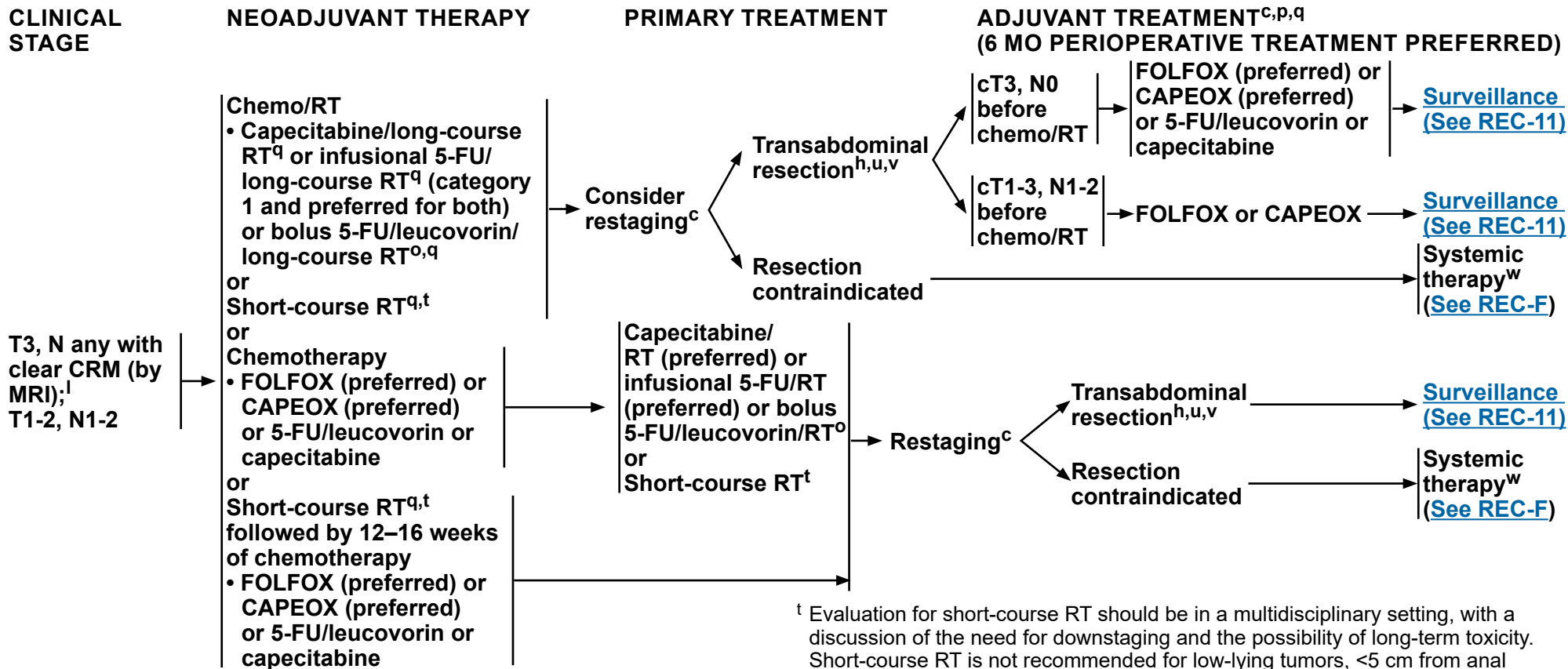
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^l CRM measured at the closest distance of the tumor to the mesorectal fascia.

Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.

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

^p See Principles of Adjuvant Therapy (REC-D).

^q See Principles of Radiation Therapy (REC-E).

^t Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity. Short-course RT is not recommended for low-lying tumors, <5 cm from anal verge.

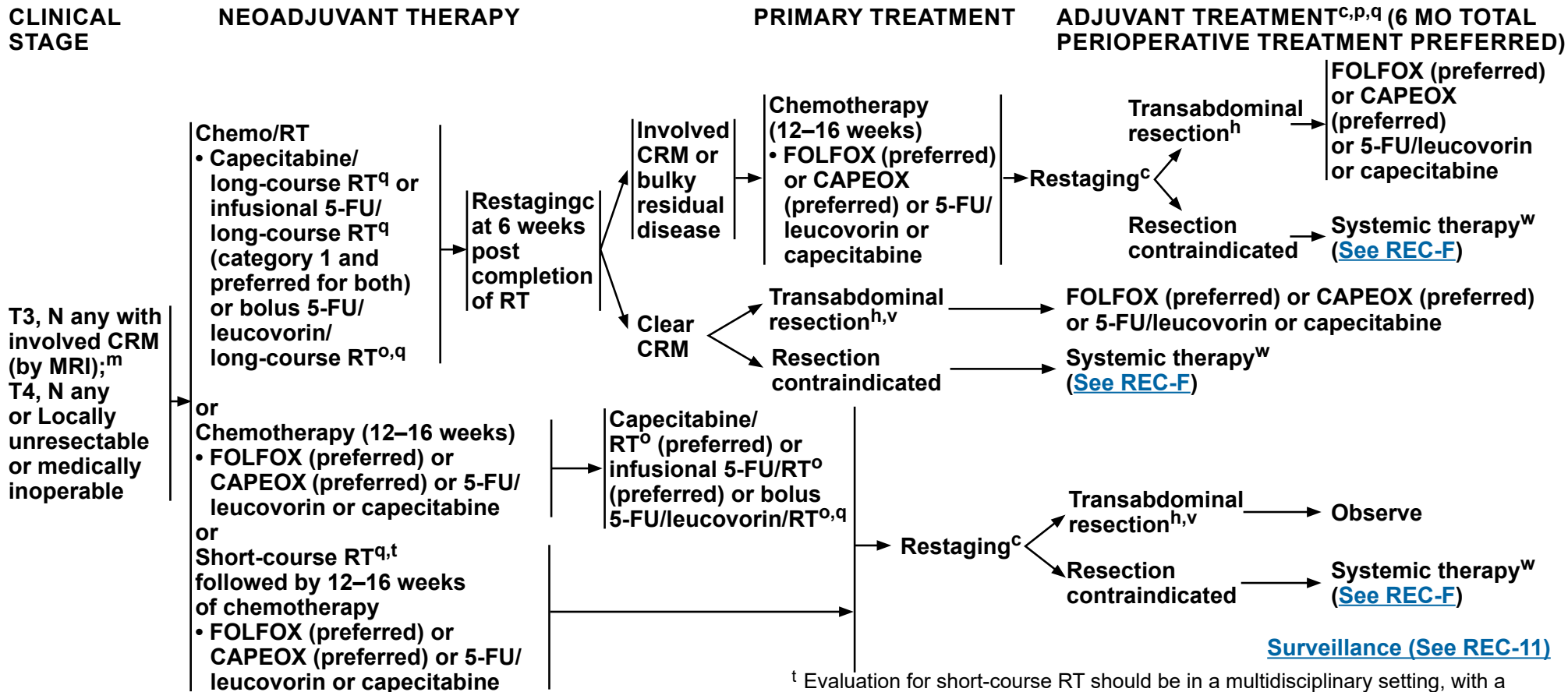
^u If patient treated with short-course RT, surgery should be within 1 week or delayed 6–8 weeks.

^v In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a “watch and wait,” nonoperative management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for non-operative management should involve a careful discussion with the patient of his/her risk tolerance.

^w FOLFOXIRI is not recommended in this setting.

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Surveillance (See REC-11)

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CLINICAL PRESENTATION

WORKUP^c

FINDINGS

Suspected or proven metastatic synchronous adenocarcinoma (T any, N any, M1)

- Colonoscopy
- Consider rigid proctoscopy
- Chest CT and abdominal CT or MRI
- Pelvic MRI with or without contrast
- CBC, chemistry profile
- CEA
- Determination of tumor gene status for *RAS* and *BRAF* (individually or as part of next-generation sequencing [NGS panel])^{x,y}
- Determination of tumor MMR or MSI status^x (if not previously done)
- Biopsy, if clinically indicated
- Consider PET/CT scan (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases
- Multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary and lung metastases

Synchronous liver only and/or lung only metastases

Resectable^h

[See Primary Treatment \(REC-8\)](#)

Unresectable^h or medically inoperable

[See Primary Treatment \(REC-9\)](#)

Synchronous abdominal/peritoneal metastases

[See Primary Treatment \(REC-10\)](#)

Synchronous unresectable metastases of other sites^z

Systemic therapy
([See REC-F](#))

^c See Principles of Imaging (REC-A).

^h See Principles of Surgery (REC-C).

^x See Principles of Pathologic Review (REC-B 5 of 7) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

^y Testing should include the neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion.

^z Consider resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

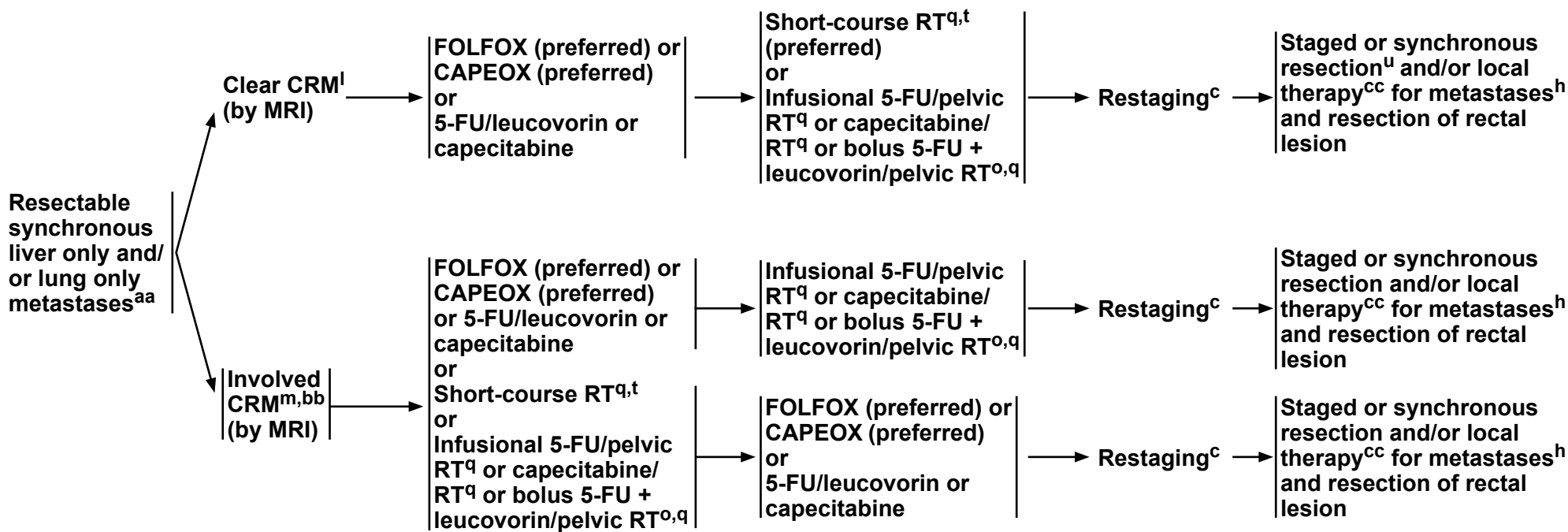
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FINDINGS

PRIMARY TREATMENT



^c See Principles of Imaging (REC-A).

^h See Principles of Surgery (REC-C).

^l CRM measured at the closest distance of the tumor to the mesorectal fascia.
Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane.

^m CRM measured at the closest distance of the tumor to the mesorectal fascia.
Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.

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

^q See Principles of Radiation Therapy (REC-E).

^t Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity. Short-course RT is not recommended for low-lying tumors, <5 cm from anal verge.

^u If patient treated with short-course RT, surgery should be within 1 week or delayed 6–8 weeks.

^{aa} If obstructing lesion, consider diversion or resection (see REC-10).

^{bb} There are limited data regarding available treatment options.

^{cc} 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-C and REC-E).

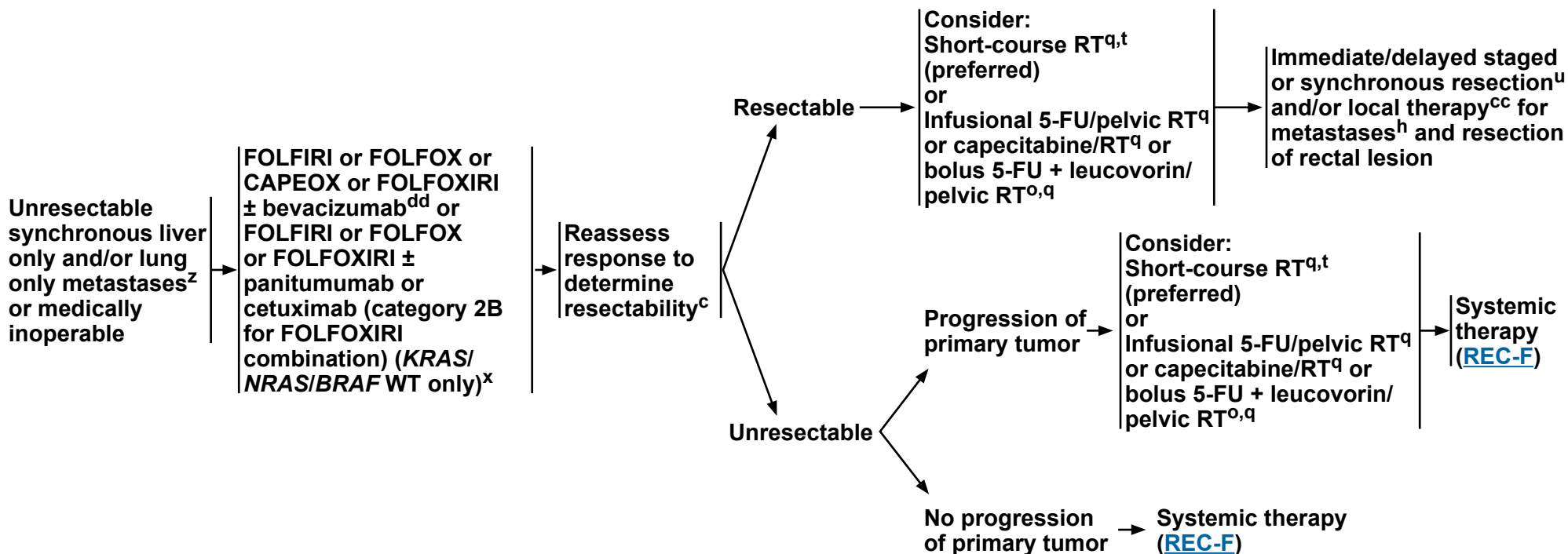
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FINDINGS

PRIMARY TREATMENT



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^h See Principles of Surgery (REC-C).

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

^q See Principles of Radiation Therapy (REC-E).

^t Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity. Short-course RT is not recommended for low-lying tumors, <5 cm from anal verge.

^u If patient treated with short-course RT, surgery should be within 1 week or delayed 6–8 weeks.

^x See Principles of Pathologic Review (REC-B 5 of 7) - KRAS, NRAS, and BRAF Mutation Testing.

^z If obstructing lesion, consider diversion or resection (see REC-10).

^{cc} 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-C and REC-E).

^{dd} There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery, and re-initiation of bevacizumab should be delayed at least 6–8 weeks postoperatively. 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.

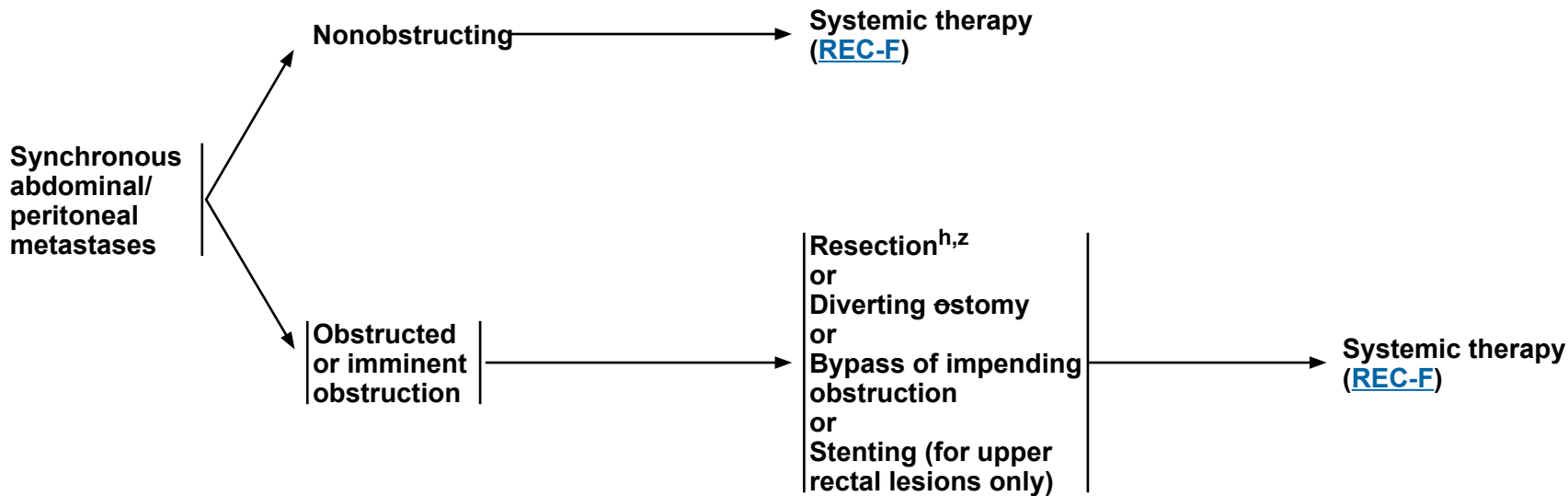
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FINDINGS

PRIMARY TREATMENT



^h See [Principles of Surgery \(REC-C\)](#).

^z Consider resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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SURVEILLANCE^c

Transanal local
excision only

- 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
- Colonoscopy^a at 1 y after surgery
 - If advanced adenoma, repeat in 1 y
 - If no advanced adenoma,^{ee} repeat in 3 y, then every 5 y^{ff}

Stage I with full
surgical staging

- Colonoscopy^a at 1 y after surgery
 - If advanced adenoma, repeat in 1 y
 - If no advanced adenoma,^{ee} repeat in 3 y, then every 5 y^{ff}

Stage II-IV

- History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA^{gg} every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdominal/pelvic CT
 - Stage II, III: every 6–12 mo (category 2B for frequency <12 mo) for a total of 5 y
 - Stage IV: 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^a in 1 y after surgery 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,^{ee} repeat in 3 y, then every 5 y^{ffe}
- PET/CT scan is not recommended
- See [Principles of Survivorship \(REC-G\)](#)

Serial CEA
elevation or
documented
recurrence

[See
Workup and
Treatment
\(REC-12\)](#)

^a 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](#).

^c See [Principles of Imaging \(REC-A\)](#).

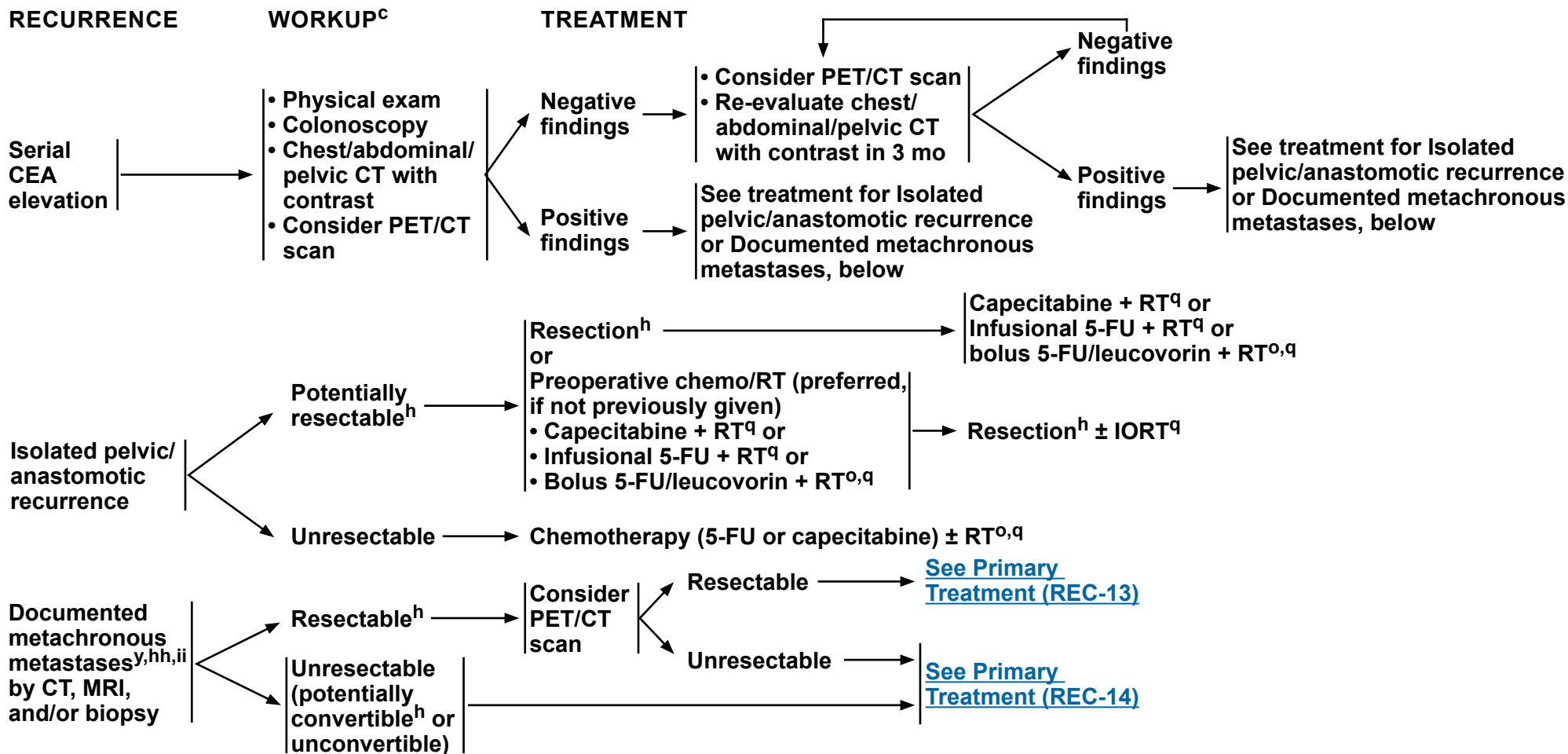
^{ee} Villous polyp, polyp >1 cm, or high-grade dysplasia.

^{ff} 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.

^{gg} If patient is a potential candidate for resection of isolated metastasis.

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^c See Principles of Imaging (REC-A).

^h See Principles of Surgery (REC-C).

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

^q See Principles of Radiation Therapy (REC-E).

^y Testing should include the neurotrophic receptor tyrosine kinase (*NTRK*) gene fusion.

^{hh} Determination of tumor gene status for RAS and BRAF (individually or as part of next-generation sequencing [NGS] panel). See Principles of Pathologic Review (REC-B 5 of 7) - KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

ⁱⁱ Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

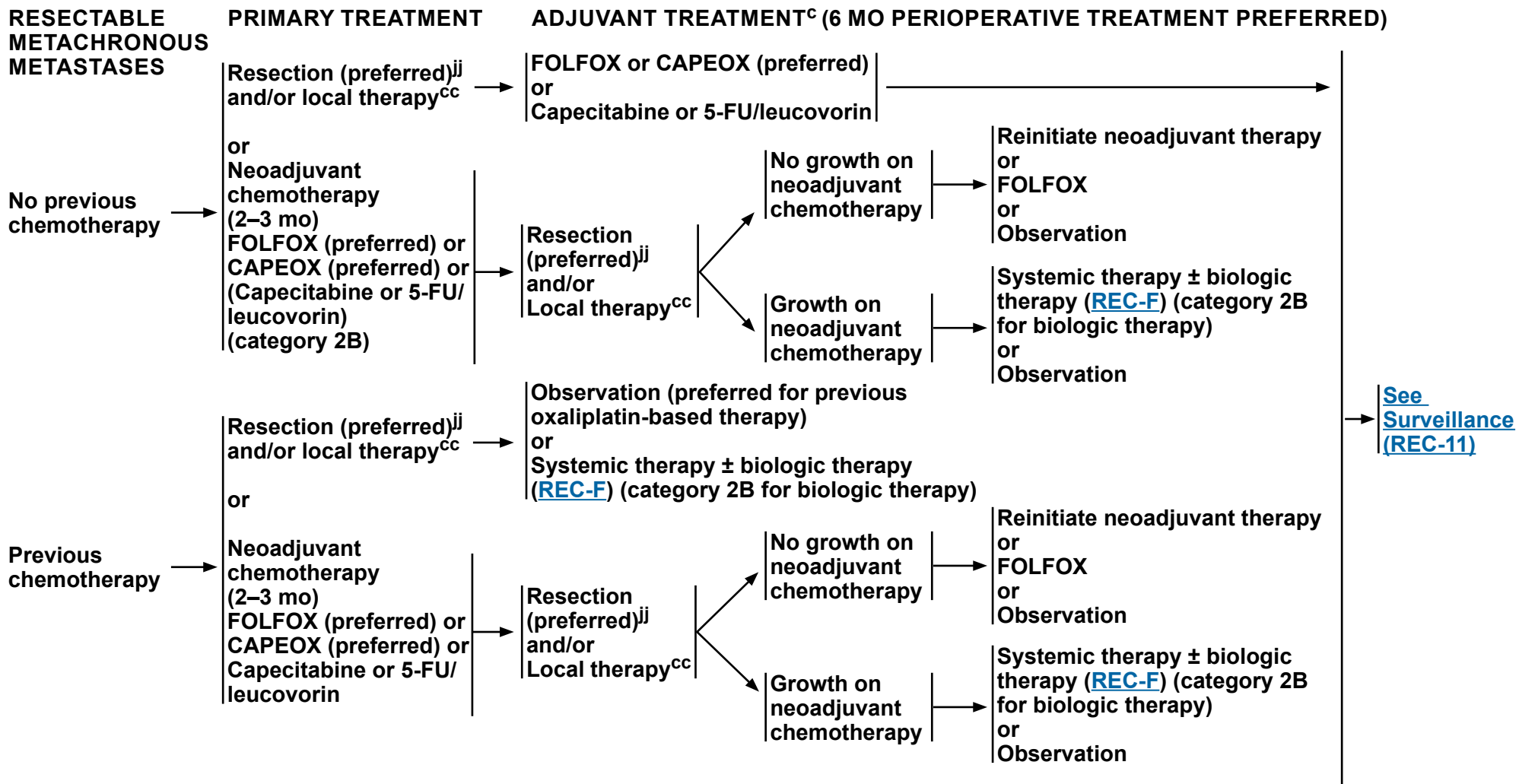
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NCCN Guidelines Version 2.2019

Rectal Cancer



^c See Principles of Imaging (REC-A).

^{cc} 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-C and REC-E).

^{jj} 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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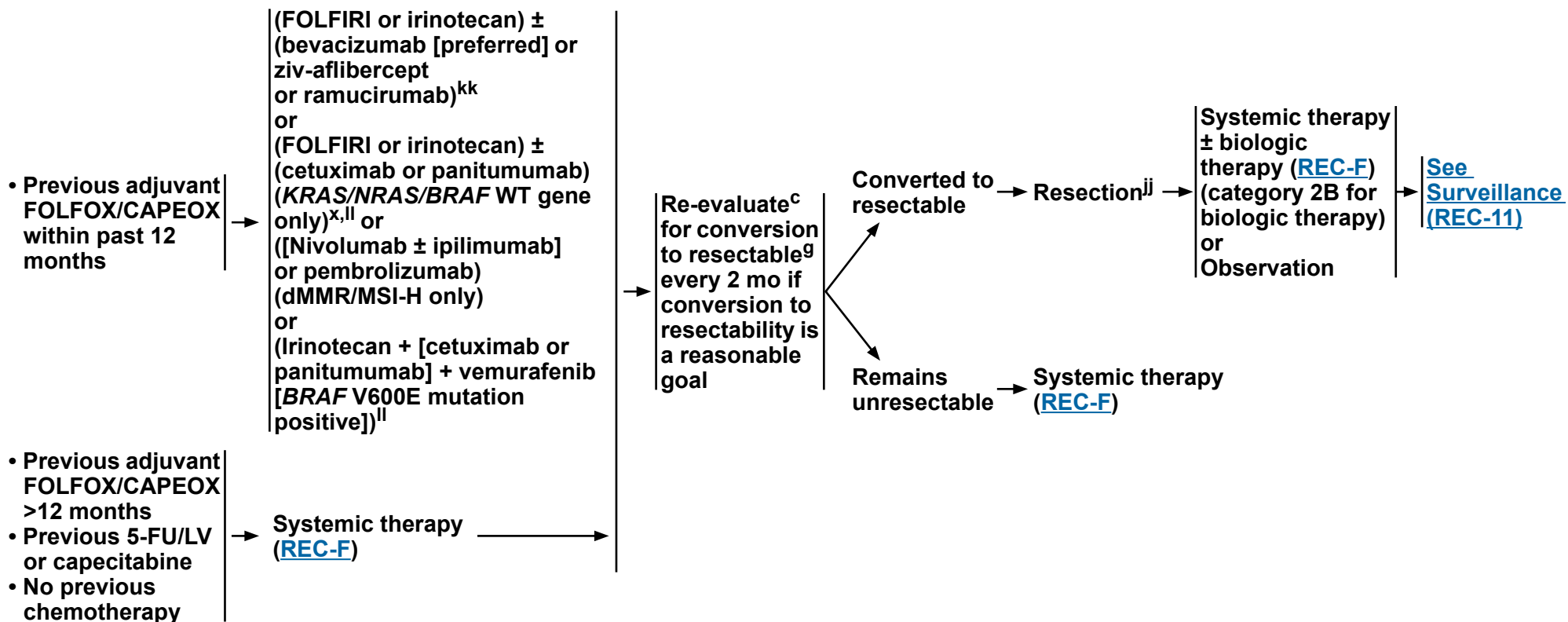
NCCN Guidelines Version 2.2019

Rectal Cancer

UNRESECTABLE METACHRONOUS METASTASES

PRIMARY TREATMENT

ADJUVANT TREATMENT^c (6 MO PERIOPERATIVE TREATMENT PREFERRED)



^c See Principles of Imaging ([REC-A](#)).

^g See Principles of Surgery ([REC-C](#)).

^x See Principles of Pathologic Review ([REC-B 5 of 7](#)) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.

^{jj} 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.

^{kk} Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

^{ll} *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor.

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PRINCIPLES OF IMAGING¹⁻³

Initial Workup/Staging

- Chest CT and abdominal CT or MRI
 - ▶ Evaluate local extent of tumor or infiltration into surrounding structures.
 - ▶ Assess for distant metastatic disease to lungs, thoracic and abdominal lymph nodes, liver, peritoneal cavity, and other organs.
 - ▶ CT performed with intravenous iodinated contrast and oral contrast material unless contraindicated.
 - ▶ Intravenous contrast is not required for the chest CT (but usually given if performed with abdominal CT scan).
 - ▶ If IV iodinated contrast material is contraindicated because of significant contrast allergy, then MR examination of the abdomen with IV gadolinium -ased contrast agent (GBCA) can be obtained instead. In patients with chronic renal failure (glomerular filtration rate [GFR] <30 mL/min) who are not on dialysis, IV iodinated contrast material is also contraindicated, and IV GBCA can be administered in select cases using gadofosveset trisodium, gadoxetate disodium, gadobenate dimeglumine, or gadoteridol.
 - ▶ If iodinated and gadolinium contrast are both contraindicated due to significant allergy or chronic renal failure without dialysis, then consider MR without IV contrast or consider PET/CT imaging.
- Pelvic MRI with or without contrast or endorectal ultrasound (only if MRI is contraindicated [eg, pacemaker]) (See Pelvic MRI Requirements ([REC-A 3 of 4](#)) and Reporting ([REC-A 4 of 4](#)))
 - ▶ Assess T and N stage of the primary rectal tumor.
 - ▶ Pelvic MRI or CT can be used for workup of synchronous metastatic disease.
 - ▶ Pelvic MRI can be performed with or without intravenous gadolinium contrast per institutional preferences.
 - ▶ Pelvic MRI may not be required for local staging if tumor is known to be definite T1 or if patient is not a candidate for primary tumor resection (widespread metastases, plan for permanent colonic diversion, etc).
 - ▶ The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.
- PET/CT is not routinely indicated.
 - ▶ PET/CT does not supplant a contrast-enhanced diagnostic CT or MR and should only be used to evaluate an equivocal finding on a contrast-enhanced CT or MR scan or in patients with strong contraindications to IV contrast administration.
 - ▶ Consider PET/CT (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases.
- If liver-directed therapy or surgery is contemplated, a hepatic MRI with intravenous routine extra-cellular or hepatobiliary GBCA is preferred over CT (and PET/CT) to assess exact number and distribution of metastatic foci for local treatment planning.

[Restaging and Follow up/Surveillance \(REC-A 2 of 4\)](#)

¹ Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 2010;257:674-84.

² van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. *Ann Surg Oncol* 2012;19:2805-2813.

³ ACR manual on contrast media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

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PRINCIPLES OF IMAGING¹⁻³

Restaging

- Chest CT and abdominal CT or MRI and pelvic MRI
 - ▶ Prior to surgery for restaging
 - ▶ Prior to adjuvant treatment to assess response to primary therapy or resection
 - ▶ During re-evaluation of conversion to resectable disease
- PET/CT is not indicated.

Follow up/Surveillance

- Stage I disease:
 - ▶ Imaging is not routinely indicated and should only be based on symptoms and clinical concern for recurrent/metastatic disease.
- Stage II & III disease:
 - ▶ Chest, abdominal, and pelvic CT every 6–12 months (category 2B for frequency <12 months) for a total of 5 years.
 - ▶ MRI or EUS of the rectum every 3–6 months for 2 years, then every 6 months for a total of 5 years (for patients with transanal local excision only).
 - ▶ PET/CT examination is not recommended.
- Stage IV disease:
 - ▶ Chest, abdominal, and pelvic CT every 3–6 months (category 2B for frequency <6 months) x 2 years, then every 6–12 months for a total of 5 years.
 - ▶ MRI or EUS of the rectum every 3–6 months for 2 years, then every 6 months for a total of 5 years (for patients with trans-anal excision only).
- PET/CT is not indicated.

¹ Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. *Radiology* 2010;257:674-84.

² van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. *Ann Surg Oncol* 2012;19:2805-2813.

³ ACR manual on contrast media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

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[Continued](#)

REC-A
2 OF 4

**PRINCIPLES OF IMAGING**
Pelvic MRI Requirements³**Patient Preparation**

Rectal distension with gel	Not a requirement. There is controversy on the effect of rectal distension on accurately assessing the distance of tumor to mesorectal fascia (MRF)
Use of spasmolytic agents	Not a requirement. Can help decrease bowel movement-related artifacts if needed

MRI Hardware Requirement

Magnet strength	Minimum requirement 1.5 T 1.0 T magnets produce limited signal and should be avoided when possible
Coil	External surface body coil adequate and preferred to endorectal coils

MRI Sequences

2D high-resolution T2-weighted	<ul style="list-style-type: none"> • Slice thickness 1–3 mm (no more than 4 mm). 3D T2-weighted sequences are not adequate substitute • Main sequences for T staging and detection of pathologic lymph nodes • Axial, sagittal, and coronal plane to assess extent and relationship to all surrounding structures • Axial and coronal slices should be angulated along the short (perpendicular) and long (parallel) axis of tumor for tumors in the middle and upper part of the rectum and along the anal canal for low rectal tumors
T1-weighted without contrast	Not a requirement for staging. May be helpful in assessing other pelvic organs and/or pathologies
Diffusion-weighted imaging (DWI)	Not a requirement for T staging or detection of pathologic lymph node. Helpful in assessing treatment response after neoadjuvant therapy (assessing the yT-stage)
T1-weighted with contrast	Not a requirement for staging*

*IV contrast can be administered (after completion of non-contrast scans) if DCE (dynamic contrast-enhanced) MRI and/or perfusion assessment is needed for tumor response evaluation, currently performed primarily in investigational setting.

³ACR manual on contrast media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

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Continued



PRINCIPLES OF IMAGING Pelvic MRI Reporting³

<p>At presentation (before neoadjuvant therapy)</p>	<ul style="list-style-type: none"> • Distance from the anal verge or anorectal junction to the lower aspect of the tumor • Tumor length • T-stage of primary mass • Tumor deposits within the mesorectum • Involvement of the mesorectal fascia and the smallest distance (mm) between the tumor and the MRF and its location^a • N-stage • Presence/absence of suspicious extramesorectal lymph nodes • Additional findings that can be provided in synoptic report: <ul style="list-style-type: none"> ▶ The circumferential location of the tumor ▶ In T3 tumor, the extent (mm) of extramural growth or depth of invasion ▶ Number of suspicious lymph nodes ▶ Presence/absence of extramural vascular invasion (EMVI) ▶ Morphologic pattern of tumor growth (eg, annular, polypoid, mucinous, ulcerated, perforated)
<p>After neoadjuvant therapy</p>	<ul style="list-style-type: none"> • Distance from the anal verge or anorectal junction to the lower aspect of the remaining tumor • Tumor length • Presence/absence of a residual tumor (high signal on T2-weighted images) • Presence/absence of fibrosis (low signal on T2-weighted images) • yT-stage and any remaining tumor deposits within the mesorectum • yN-stage and number of remaining suspicious lymph nodes • Presence of any remaining suspicious extramesorectal lymph nodes • Persistent involvement/regression from the MRF^a • The smallest distance (mm) between the remaining tumor and the mesorectal fascia and its location^a • Additional findings that can be provided in synoptic report: <ul style="list-style-type: none"> ▶ The circumferential location of the remaining tumor within the wall ▶ In the case of a yT3 tumor, the extent (mm) of extramural growth ▶ The morphologic pattern of tumor growth ▶ Presence/absence of EMVI (no clear consensus on reporting this finding)

^aCRM measured at the closest distance of the tumor to the mesorectal fascia. Clear CRM: Greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane. Involved CRM: within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.

³ACR manual on contrast media v10.3 https://www.acr.org/-/media/ACR/Files/Clinical-Resources/Contrast_Media.pdf. Accessed May 25, 2017.

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PRINCIPLES OF PATHOLOGIC REVIEW

Endoscopically Removed Malignant Polyps

- A malignant polyp is defined as one with cancer invading through the muscularis mucosae and into the submucosa (pT1). pTis is not considered 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.¹⁻⁴
- 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 histologic 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.³⁻⁷

Transanal Local Excision

- Favorable histopathologic features: <3 cm size, T1, grade I or II, no lymphatic or venous invasion, or negative margins.^{8,9}
- Unfavorable histopathologic features: >3 cm in size, >T1, with grade III, or lymphovascular invasion, positive margin, or sm3 depth of tumor invasion.⁸⁻¹⁰

Rectal Cancer Appropriate for Resection

- Histologic confirmation of primary malignant rectal neoplasm.
- The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.

[Pathologic Stage on REC-B 2 of 7](#)

[Lymph Node Evaluation on REC-B 3 of 7](#)

[Sentinel Lymph Node Evaluation on REC-B 4 of 7](#)

[KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B 5 of 7](#)

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[References](#)

**PRINCIPLES OF PATHOLOGIC REVIEW****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.¹¹⁻¹²
- ▶ CRM¹³⁻¹⁷
- ▶ Neoadjuvant treatment effect^{15,16,18,19}
- ▶ Lymphovascular invasion^{15,16,20}
- ▶ Perineural invasion (PNI)²¹⁻²³
- ▶ Tumor deposits²⁴⁻²⁵

• CRM - A positive CRM is defined as tumor ≤ 1 mm from the margin. This assessment includes both tumor within a lymph node as well as direct tumor extension. However, if CRM positivity is based solely on intranodal tumor, 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.¹³⁻¹⁷

• 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.^{15,16,18,19}

[Pathologic Stage continued on REC-B 3 of 7](#)**[Lymph Node Evaluation on REC-B 3 of 7](#)****[Endoscopically Removed Malignant Polyps, Transanal Local Exision, Rectal Cancer Appropriate for Resection on REC-B 1 of 7](#)****[Sentinel Lymph Node Evaluation on REC-B 4 of 7](#)****[KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B 5 of 7](#)**

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[References](#)

**PRINCIPLES OF PATHOLOGIC REVIEW****Pathologic Stage (continued)**

- **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.²¹⁻²³
- **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.

Lymph Node Evaluation

- The AJCC and CAP recommend examination of a minimum of 12 lymph nodes to accurately stage rectal cancer.^{11,12,26} 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 >30.²⁶⁻³⁴ Most of these studies have combined rectal and colon cancers and reflect those cases with surgery as the initial treatment. Two studies confined only to rectal cancer have reported 14 and >10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.^{30,33} The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade, and tumor site.²⁷ For stage II (pN0) colon cancer, if 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, $P < .001$).^{35,36} If 12 lymph nodes is considered the number needed to accurately stage stage II tumors, then only 20% of cases treated with neoadjuvant therapy had adequate lymph node sampling.³⁶ To date, the number of lymph nodes needed to accurately stage neoadjuvant-treated cases is unknown. However, it is not known what is the clinical significance of this in the neoadjuvant setting, as postoperative therapy is indicated in all patients who receive preoperative therapy regardless of the surgical pathology results.

[Endoscopically Removed Malignant Polyps, Transanal Local Excision, Rectal Cancer Appropriate for Resection on REC-B 1 of 7](#)

[Pathologic Stage on REC-B 2 of 7](#)

[Sentinel Lymph Node Evaluation on REC-B 4 of 7](#)

[KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B 5 of 7](#)

[References](#)

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PRINCIPLES OF PATHOLOGIC REVIEW

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry

- Examination of the lymph nodes (sentinel or routine) by intense histologic and/or immunohistochemical investigation helps to detect the presence of metastatic disease. The detection of single cells by IHC or by multiple H&E levels and/or clumps of tumor cells <0.2 mm are considered isolated tumor cells (pN0)³⁷ The 8th edition of the AJCC Cancer Staging Manual and Handbook³⁷ defines clumps of tumor cells ≥0.2 mm in diameter or clusters of 10-20 tumor cells as micrometastasis and recommends that these micrometastases be considered as standard positive lymph nodes (pN+).
- At the present time the use of sentinel lymph nodes and detection isolated tumor cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.³⁸⁻⁴⁵ 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 some of these studies, what is presently defined as isolated tumor cells were considered to be micrometastases.⁴¹⁻⁴⁵

Evaluation of Mesorectum (TME)

- The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).⁴⁶⁻⁴⁸

[Endoscopically Removed Malignant Polyps, Transanal Local Excision, Rectal Cancer Appropriate for Resection on REC-B 1 of 7](#)

[Lymph Node Evaluation on REC-B 3 of 7](#)

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[KRAS, NRAS, and BRAF Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B 5 of 7](#)

[References](#)

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 PATHOLOGIC REVIEW****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 individually or as part of a next-generation sequencing (NGS) panel. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.⁴⁹⁻⁵¹ *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely.⁵²⁻⁵⁴
- 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.⁵⁵

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 in the vast majority of cases. However, approximately 1% of cancers with *BRAF* V600E mutations (and loss of MLH-1) are Lynch syndrome. Caution should be exercised in excluding cases with strong family history from germline screening in the case of *BRAF* V600E mutations.⁵⁶
- Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.⁵⁷
- MMR or MSI testing should be performed only in CLIA-approved laboratories.
- Testing for MSI may be accomplished with a validated NGS panel, especially in patients with metastatic disease who require genotyping of *RAS* and *BRAF*.
- Immunohistochemistry (IHC) refers to staining tumor tissue for protein expression of the four mismatch repair MMR genes known to be mutated in Lynch syndrome LS (MLH1, MSH2, MSH6, and PMS2.) A normal IHC test implies that all four MMR proteins are normally expressed (retained). Loss (absence) of expression of one or more of the four DNA MMR proteins is often reported as abnormal or positive IHC. When IHC is reported as positive, caution should be taken to ensure that positive refers to absence of mismatch expression and not presence of expression. NOTE: Normal is the presence of positive protein staining (retained) and abnormal is negative or loss of staining of protein. Loss of protein expression by IHC in any one of the MMR genes guides further genetic testing (mutation detection to the genes where the protein expression is not observed). Abnormal MLH1 IHC should be followed by tumor testing for *BRAF* V600E mutation. The presence of *BRAF* V600E mutation is consistent with sporadic cancer. However, approximately 1% of Lynch syndrome patients with loss of MLH-1 can express *BRAF* V600E mutation.⁵⁶

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* IHC for MMR and DNA analysis for MSI are different assays measuring the same biological effect.

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**PRINCIPLES OF SURGERY****Transanal Local Excision**¹

- **Criteria**
 - ▶ <30% circumference of bowel
 - ▶ <3 cm in size
 - ▶ Margin clear (>3 mm)
 - ▶ Mobile, nonfixed
 - ▶ Within 8 cm of anal verge
 - ▶ T1 only
 - ▶ Endoscopically removed polyp with cancer or indeterminate pathology
 - ▶ No lymphovascular invasion or PNI
 - ▶ Well to moderately differentiated
 - ▶ No evidence of lymphadenopathy on pretreatment imaging
 - ▶ Full-thickness excision must be feasible
- When the lesion can be adequately localized to the rectum, local excision of more proximal lesions may be technically feasible using advanced techniques, such as transanal microscopic surgery or transanal minimally invasive surgery (TAMIS).

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

- **Management principles**
 - ▶ The treating surgeon should assess the distal margin before initiating treatment by digital rectal examination ± rigid or flexible endoscopy, particularly for non-palpable lesions.
 - ▶ Remove primary tumor with adequate circumferential and distal margins.
 - ▶ Treat draining lymphatics by total mesorectal excision.
 - ▶ Sphincter preservation and restoration of organ integrity should be achieved without compromise of oncologic resection and consideration of anticipated patient functional outcome and quality of life.
 - ▶ Surgery should be 5–12 weeks following full-dose 5.5-week neoadjuvant chemoradiation. For short-course neoadjuvant radiation therapy, surgery can be considered at 3–7 days or 4–8 weeks.

- **Total mesorectal excision (TME)**
 - ▶ TME is a standard component of radical rectal cancer surgery. TME reduces the positive radial margin and local recurrence rates.
 - ▶ 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,^{2,3} whereas other studies have shown that laparoscopy is associated with higher rates of circumferential margin positivity and incomplete TME.^{4,5} 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 generally indicated for acute bowel obstruction or perforation from cancer.
 - ◇ Thorough abdominal exploration is required.
- **Lymph node dissection**^{6,7}
 - ▶ Clinically suspicious nodes beyond the field of resection should be biopsied and/or removed, if possible. Extensive resection of M1 lymph nodes is not indicated.
 - ▶ Extended lymph node resection is not indicated in the absence of clinically suspected nodes.

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[References](#)

REC-C
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**PRINCIPLES OF SURGERY****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.⁸
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.^{9,10}
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.¹¹⁻¹³ 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.⁸ 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.¹⁴

Lung

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

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**PRINCIPLES OF ADJUVANT THERAPY**

Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy. A total of approximately 6 months of perioperative treatment is preferred.

Postoperative Adjuvant Chemotherapy:• **mFOLFOX 6^{1,2,3}**

Oxaliplatin 85 mg/m² IV, day 1,* leucovorin 400 mg/m² IV day 1,** 5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.

• **Simplified biweekly infusional 5-FU/LV (sLV5FU2)⁴**

Leucovorin 400 mg/m² IV day 1, followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 mo perioperative therapy.

• **Capecitabine⁵**

Capecitabine[#] 1000–1250 mg/m² twice daily days 1–14 every 3 weeks to a total of 6 months perioperative therapy.

• **CAPEOX^{6,7}**

Oxaliplatin 130 mg/m² day 1.* Capecitabine[#] 1000 mg/m² twice daily days 1–14 every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.

• **5-FU 500 mg/m² IV bolus weekly x 6 + leucovorin 500 mg/m² IV weekly x 6, each 8-week cycle. Repeat every 8 weeks to a total of 6 months perioperative therapy.⁸****Dosing Schedules for Concurrent Chemotherapy/RT:**• **XRT + continuous infusion 5-FU⁹**

5-FU 225 mg/m² over 24 hours 5 or 7 days/week during XRT

• **XRT + Capecitabine^{10,11}**

Capecitabine[#] 825 mg/m² twice daily 5 d/wk + XRT x 5 weeks

• **XRT + 5-FU/leucovorin^{12‡}**

5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during week 1 and 5 of XRT

* Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/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/m²/min. J Oncol Pract 2016;12:e548-553.

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

‡ 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/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

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.

References



PRINCIPLES OF ADJUVANT THERAPY - REFERENCES

- ¹ Andre T, Boni C, Mounedji-Boudiaf L, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. *N Engl J Med* 2004;350:2343-2351.
- ² 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.
- ³ 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.
- ⁴ 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.
- ⁵ 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.
- ⁶ 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.
- ⁷ 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.
- ⁸ 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.
- ⁹ 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.
- ¹⁰ 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.
- ¹¹ 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.
- ¹² 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.

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**PRINCIPLES OF RADIATION THERAPY****General Principles**

- Fluoropyrimidine-based chemotherapy should be delivered concurrently with radiation therapy.
- 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, intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT).

Treatment Information

- Image-guided radiation therapy (IGRT) with kilovoltage (kV) imaging and cone-beam CT imaging should be routinely used during the course of treatment with IMRT and SBRT.
- IMRT/SBRT 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, or patients with localized oligometastases.
- 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. 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.
- Target Volumes
 - ▶ Radiation therapy fields should include the tumor or tumor bed, with a 2- to 5-cm margin, the mesorectum, 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.
- RT Dosing
 - ▶ 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 week of completion of therapy or delayed 6–8 weeks can also be considered for patients with stage T3 rectal cancer.¹
 - ◊ For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.
 - ▶ If IORT is not available, 10–20 Gy external beam radiation therapy and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.

Supportive Care

- 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.

¹ 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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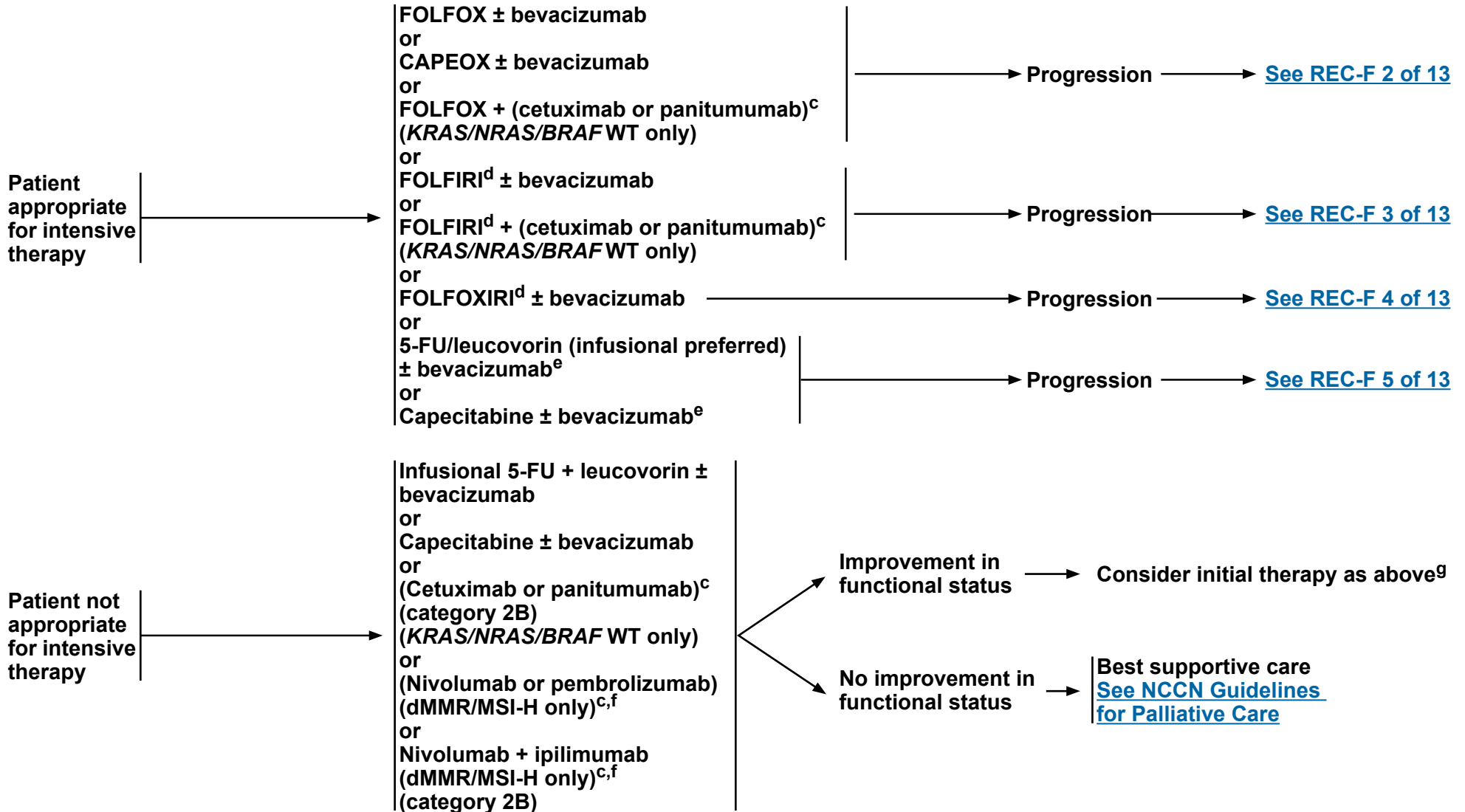


NCCN Guidelines Version 2.2019

Rectal Cancer

CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^a

INITIAL THERAPY^b

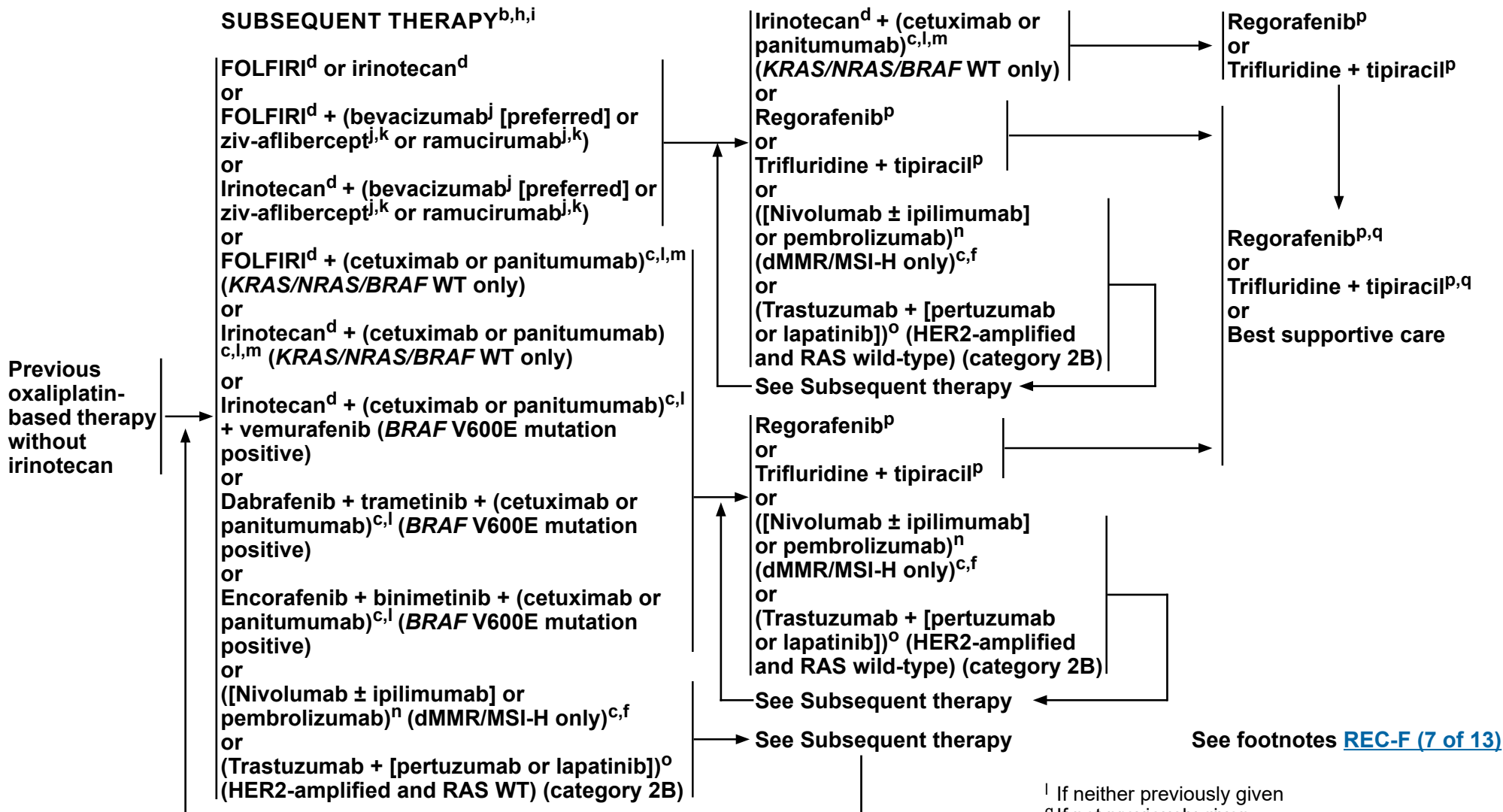


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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^a

SUBSEQUENT THERAPY^{b,h,i}



^l If neither previously given
^q If not previously given
ⁿ If no previous treatment with a checkpoint inhibitor
^o If no previous HER2 inhibitor.

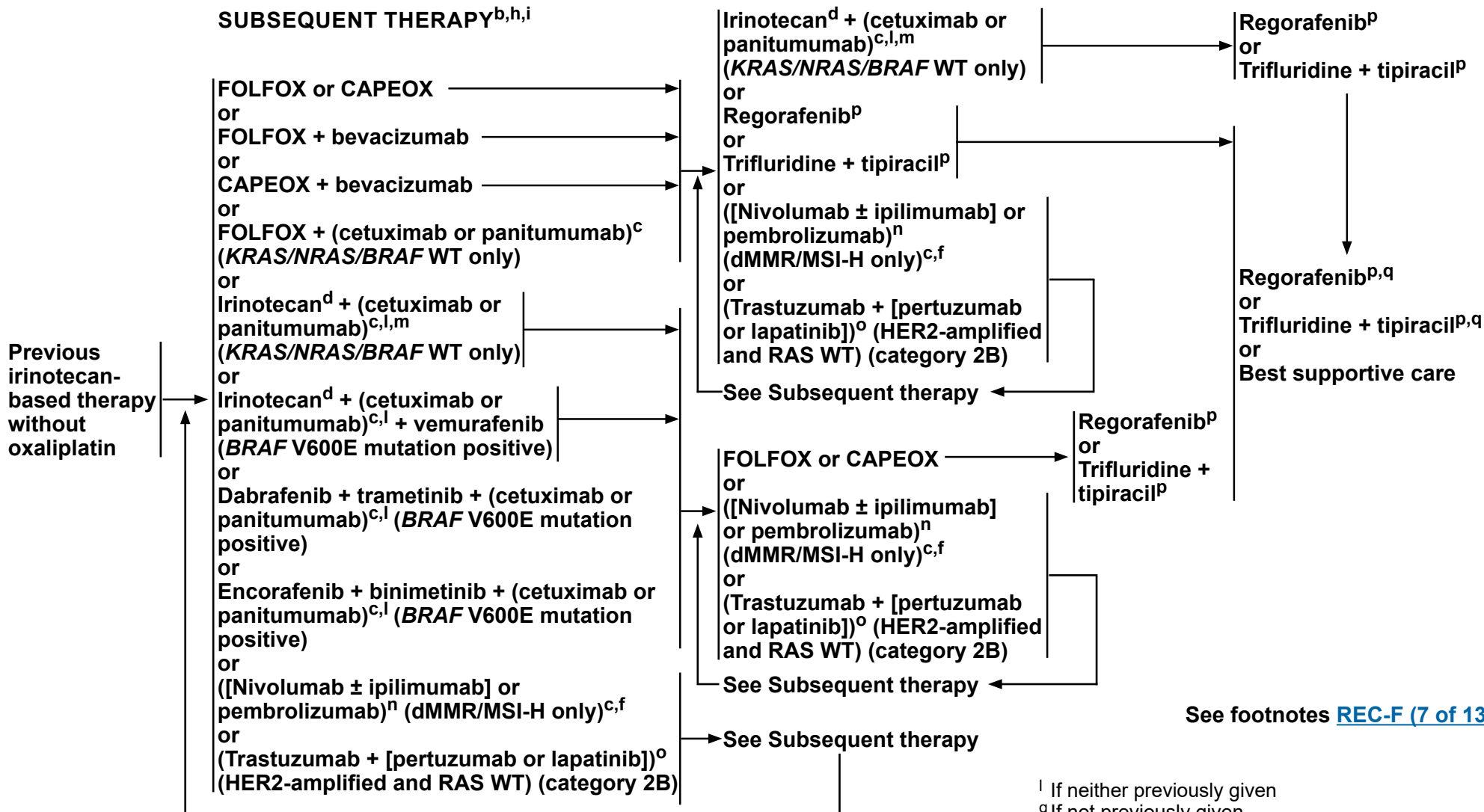
^h Larotrectinib is a treatment option for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^a

SUBSEQUENT THERAPY^{b,h,i}



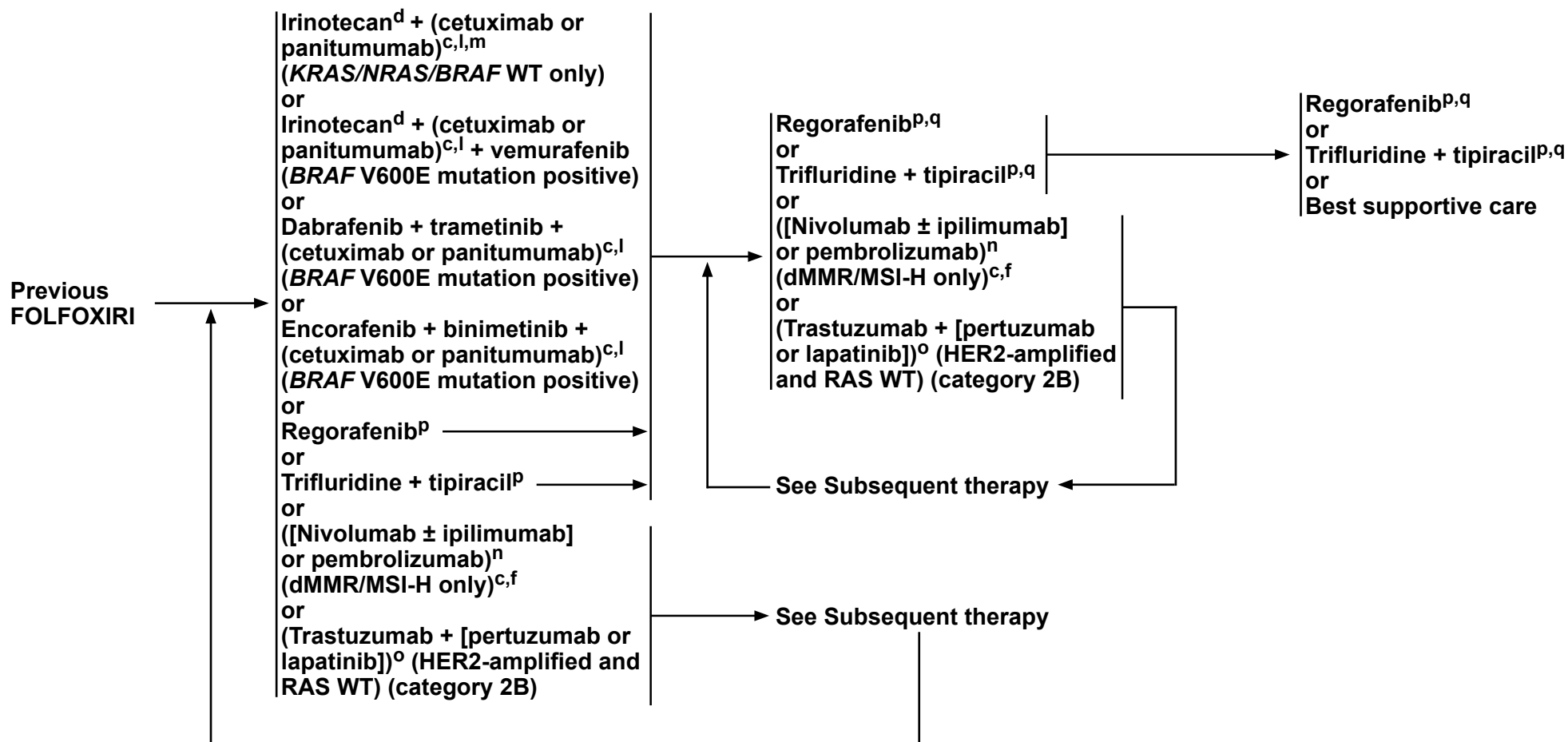
^l If neither previously given
^q If not previously given
ⁿ If no previous treatment with a checkpoint inhibitor
^o If no previous HER2 inhibitor.

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^a

SUBSEQUENT THERAPY^{b,h,i}



^h Larotrectinib is a treatment option for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.

^l If neither previously given

ⁿ If no previous treatment with a checkpoint inhibitor

^o If no previous *HER2* inhibitor.

^q If not previously given

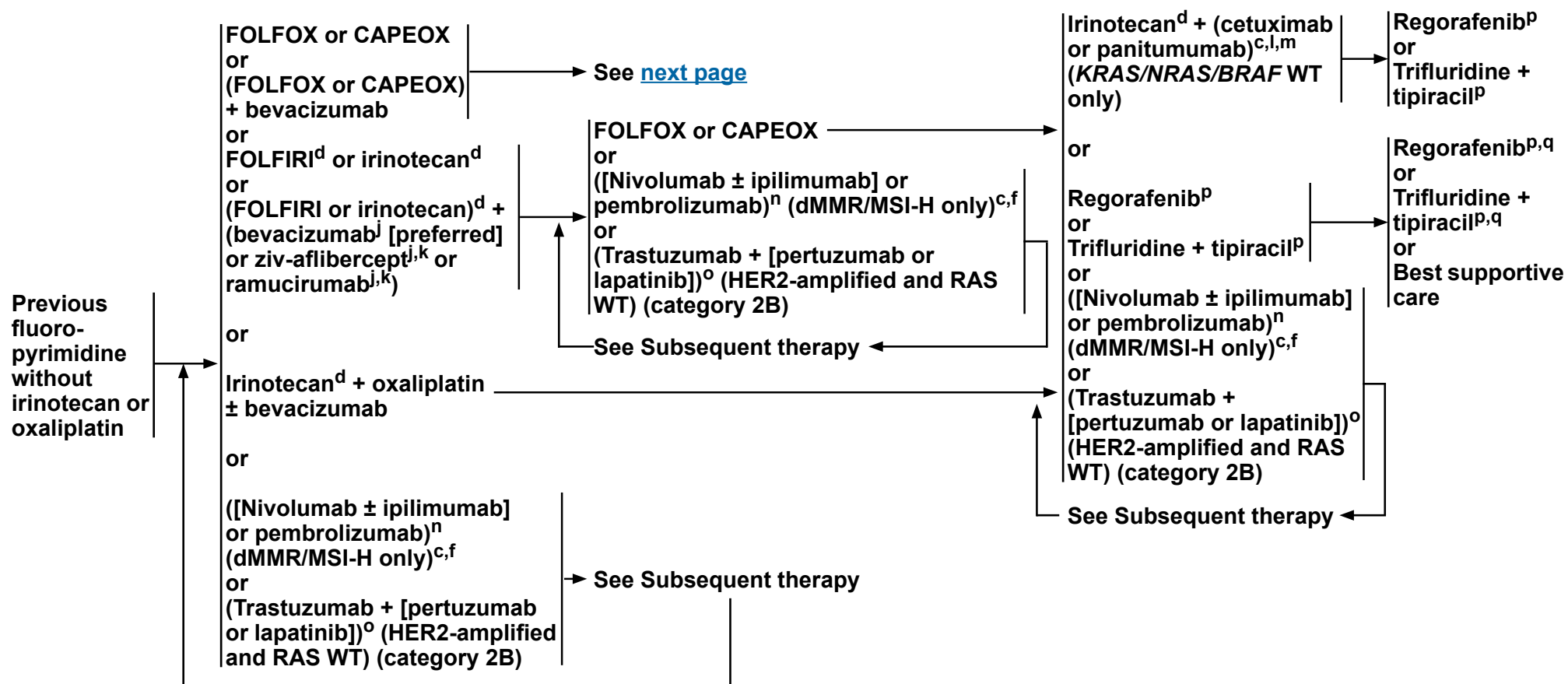
See footnotes [REC-F \(7 of 13\)](#)

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^a

SUBSEQUENT THERAPY^{b,h,i}



^h Larotrectinib is a treatment option for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.

^l If neither previously given

ⁿ If no previous treatment with a checkpoint inhibitor

^o If no previous HER2 inhibitor.

^q If not previously given

See footnotes [REC-F \(7 of 13\)](#)

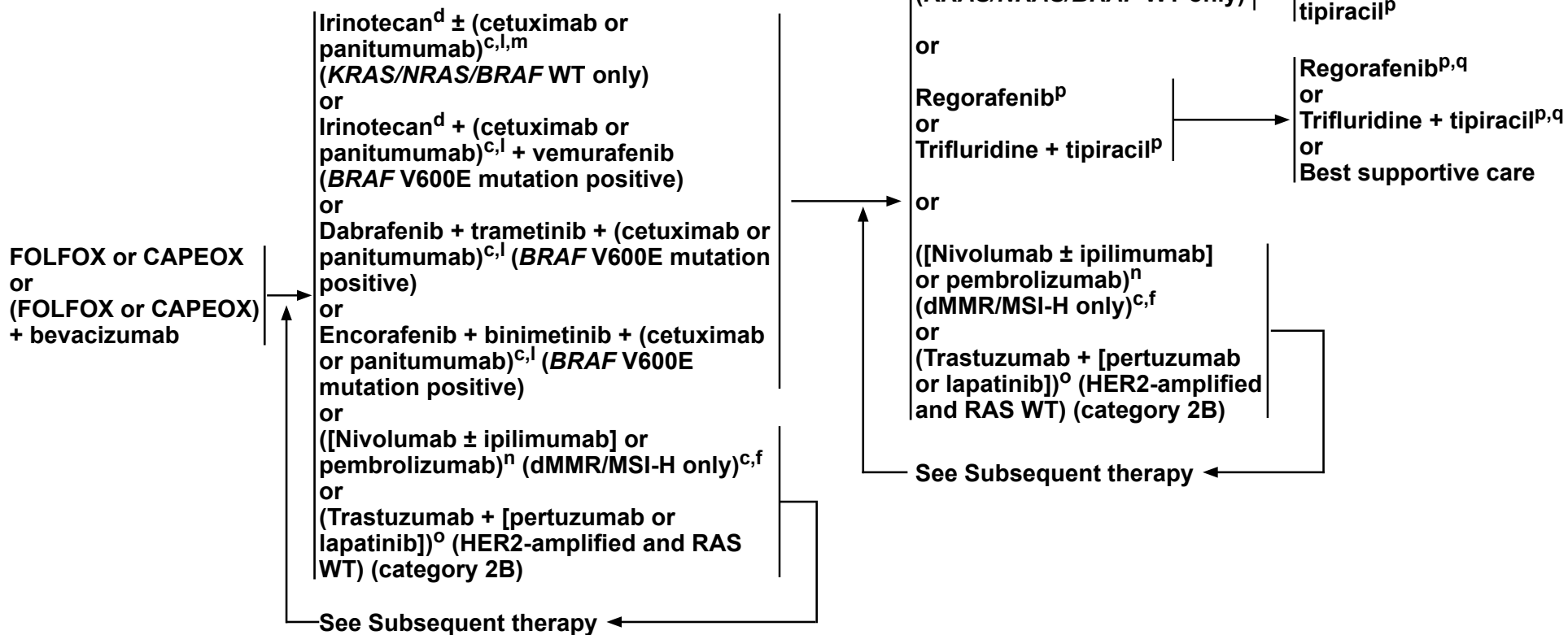
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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE^a

SUBSEQUENT THERAPY^{b,h,i}
following fluoropyrimidine
without irinotecan or oxaliplatin



^h Larotrectinib is a treatment option for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.

^l If neither previously given

ⁿ If no previous treatment with a checkpoint inhibitor

^o If no previous HER2 inhibitor.

^q If not previously given

See footnotes [REC-F \(7 of 13\)](#)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE FOOTNOTES

^a For chemotherapy references, [see Chemotherapy Regimens and References \(REF-F \[8 of 13\]\)](#).

^b 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. See [Principles of Imaging \(REC-A\)](#).

^c See [Principles of Pathologic Review \(REC-B 5 of 7\)](#).

^d 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.

^e A treatment option for patients not able to tolerate oxaliplatin or irinotecan.

^f These therapies are FDA approved for colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. However, a number of patients in the clinical trials had not received all three prior systemic therapies. Thirty-seven percent of patients received nivolumab monotherapy and 24% received ipilimumab/nivolumab combination therapy in first- or second-line, and 28% and 31% of patients had not received all three indicated prior therapies before treatment with nivolumab or ipilimumab/nivolumab, respectively.

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

^h Larotrectinib is a treatment option for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.

ⁱ If patients had therapy stopped for reasons other than progression (eg, cumulative toxicity, elective treatment break, patient preference), rechallenge is an option at time of progression.

^j Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

^k 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.

^l If neither previously given

^m Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.

ⁿ If no previous treatment with a checkpoint inhibitor

^o If no previous HER2 inhibitor.

^p Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.

^q If not previously given

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**SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS****mFOLFOX 6^{1,2,3¶}****Oxaliplatin 85 mg/m² IV day 1*****Leucovorin 400 mg/m² IV day 1******5-FU 400 mg/m² IV bolus on day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion****Repeat every 2 weeks****mFOLFOX7⁴****Oxaliplatin 85 mg/m² IV day 1*****Leucovorin 400 mg/m² IV day 1******5-FU 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion****Repeat every 2 weeks****FOLFOX + bevacizumab⁵****Bevacizumab 5 mg/kg IV, day 1****Repeat every 2 weeks****FOLFOX + panitumumab⁶ (KRAS/NRAS/BRAF WT only)****Panitumumab 6 mg/kg IV over 60 minutes, day 1****Repeat every 2 weeks****FOLFOX + cetuximab⁷ (KRAS/NRAS/BRAF WT only)****Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly****or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks****CAPEOX⁸****Oxaliplatin 130 mg/m² IV day 1*****Capecitabine 1000[‡] mg/m² twice daily PO for 14 days****Repeat every 3 weeks****CAPEOX + bevacizumab^{8¶}****Oxaliplatin 130 mg/m² IV day 1*****Capecitabine 1000[‡] mg/m² PO twice daily for 14 days****Bevacizumab 7.5 mg/kg IV day 1****Repeat every 3 weeks****FOLFIRI^{9,10}****Irinotecan 180 mg/m² IV over 30–90 minutes, day 1****Leucovorin** 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1****5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion****Repeat every 2 weeks****FOLFIRI + bevacizumab^{11,¶}****Bevacizumab 5 mg/kg IV, day 1****Repeat every 2 weeks**See References on [REC-F \(12 of 13\)](#)* Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/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/m²/min. J Oncol Pract 2016;12:e548-553.** Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².‡ The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.

¶ 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**

FOLFIRI + cetuximab (KRAS/NRAS/BRAF WT only)
Cetuximab 400 mg/m² IV over 2 hours first infusion,
then 250 mg/m² IV over 60 minutes weekly¹²
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks¹³

FOLFIRI + panitumumab¹⁴ (KRAS/NRAS/BRAF WT only)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept¹⁵
Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks
FOLFIRI + ramucirumab¹⁶
Ramucirumab 8 mg/kg over 60 minutes, day 1
Repeat every 2 weeks

FOLFOXIRI¹⁷
Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² IV day 1,*
Leucovorin 400 mg/m² day 1, fluorouracil 1600 mg/m²/d x 2 days**
(total 3200 mg/m² 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^{18†}
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

IROX¹⁹
Oxaliplatin 85 mg/m² IV,*
followed by irinotecan 200 mg/m² over 30–90 minutes every 3 weeks

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen²⁰
Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin,
days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

Simplified biweekly infusional 5-FU/LV (sLV5FU2)⁹
Leucovorin 400 mg/m² IV over 2 hours on day 1,**
followed by 5-FU bolus 400 mg/m² and then 1200 mg/m²/d x 2 days
(total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks

Weekly
Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV
bolus injection 1 hour after the start of leucovorin. Repeat weekly.²¹
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week²¹

See References on [REC-F \(12 of 13\)](#)

* Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/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/m²/min. J Oncol Pract 2016;12:e548-553.

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

† 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****Capecitabine⁸**

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

Capecitabine + bevacizumab^{22,†}

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

Irinotecan

Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks^{23,24}

or Irinotecan 180 mg/m² IV over 30–90 minutes, day 1

Repeat every 2 weeks

or Irinotecan 300–350 mg/m² IV over 30–90 minutes, day 1

Repeat every 3 weeks

Irinotecan + cetuximab (KRAS/NRAS/BRAF WT only)

Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly²⁵

or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks¹³

Irinotecan + panitumumab¹⁴ (KRAS/NRAS/BRAF WT only)

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

Irinotecan + ramucirumab¹⁶

Ramucirumab 8 mg/kg IV over 60 minutes every 2 weeks

Cetuximab (KRAS/NRAS/BRAF WT only)

Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly²⁵

or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks¹³

Panitumumab²⁶ (KRAS/NRAS/BRAF WT only)

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

Regorafenib

Regorafenib 160 mg PO daily on days 1–21²⁷

or

First cycle: Regorafenib 80 mg PO daily on days 1–7, then 120 mg PO daily on days 8–14, then 160 mg PO daily on days 15–21²⁸

Subsequent cycles: Regorafenib 160 mg PO daily on days 1–21

Repeat every 28 days

Trifluridine + tipiracil²⁹

Trifluridine + tipiracil 35 mg/m² 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

Pembrolizumab³⁰ (dMMR/MSI-H only)

Pembrolizumab 2 mg/kg every 3 weeks

or Pembrolizumab 200 mg every 3 weeks

Nivolumab³¹ (dMMR/MSI-H only)

Nivolumab 3 mg/kg every 2 weeks

or Nivolumab 240 mg IV every 2 weeks

or Nivolumab 480 mg IV every 4 weeks

Nivolumab + ipilimumab³² (dMMR/MSI-H only)

Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses, then

nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks

See References on [REC-F \(12 of 13\)](#)

† 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

Trastuzumab + pertuzumab³³ (HER2-amplified and RAS WT)
Trastuzumab 8mg/kg IV loading dose on Day 1 of Cycle 1,
then 6mg/kg IV every 21 days
Pertuzumab 840mg IV loading dose on Day 1 of Cycle 1,
then 420mg IV every 21 days

Trastuzumab + lapatinib³⁴ (HER2-amplified and RAS WT)
Trastuzumab 4mg/kg IV loading dose on Day 1 of Cycle 1,
then 2mg/kg IV weekly
Lapatinib 1000mg PO daily

Irinotecan + cetuximab + vemurafenib³⁵
(*BRAF V600E* mutation positive)
Irinotecan 180 mg/m² IV every 2 weeks
Cetuximab 500 mg/m² IV every 2 weeks
Vemurafenib 960 mg PO twice daily

Irinotecan + panitumumab + vemurafenib³⁵
(*BRAF V600E* mutation positive)
Irinotecan 180 mg/m² IV every 2 weeks
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks
Vemurafenib 960 mg PO twice daily

Dabrafenib + trametinib + cetuximab³⁶
(*BRAF V600E* mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly

Dabrafenib + trametinib + panitumumab³⁶
(*BRAF V600E* mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

Encorafenib + binimetinib + cetuximab^{37,38}
(*BRAF V600E* mutation positive)
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO twice daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly

Encorafenib + binimetinib + panitumumab^{37,38}
(*BRAF V600E* mutation positive)
Encorafenib 300 mg PO daily
Binimetinib 45 mg PO twice daily
Panitumumab 6 mg/kg IV every 14 days

Larotrectinib³⁹
(*NTRK* gene fusion positive)
100 mg PO twice daily

See References on [REC-F \(12 of 13\)](#)

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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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.

Survivorship Care Planning

The oncologist and primary care provider should have defined roles in the surveillance period, with roles communicated to patient.¹

- 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.

Management of Late/Long-Term Sequelae of Disease or Treatment²⁻⁶

- For issues related to distress, pain, neuropathy, fatigue, or sexual dysfunction, [see NCCN Guidelines for Survivorship](#).
- Bowel function changes: chronic diarrhea, incontinence, stool frequency, stool clustering, urgency, cramping
 - ▶ Consider anti-diarrheal agents, bulk-forming agents, diet manipulation, pelvic floor rehabilitation, and protective undergarments.
- ▶ Management of an ostomy
 - ◇ Consider participation in an ostomy support group or coordination of care with a health care provider specializing in ostomy care (ie, ostomy nurse).
 - ◇ Screen for distress around body changes ([See NCCN Guidelines for Distress Management](#)) and precautions around involvement with physical activity ([SPA-A in the NCCN Guidelines for Survivorship](#)).

- For oxaliplatin-induced neuropathy
 - ▶ Consider duloxetine for painful neuropathy only, not effective for numbness, tingling, or cold sensitivity.⁷
 - ▶ Refer to pain management specialist for refractory cases.
 - ▶ Pregabalin or gabapentin are not recommended.
- Urogenital dysfunction after resection and/or pelvic radiation^{8,9}
 - ▶ 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.

Counseling Regarding Healthy Lifestyle and Wellness¹⁰
[See NCCN Guidelines for Survivorship](#)

- Undergo all age and gender-appropriate cancer and preventive health screenings as per national guidelines.
- 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 daily aspirin 325 mg for secondary prevention.
- Eliminate or limit alcohol consumption, no more than 1 drink/day for women, and 2 drinks/day for men.
- 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.

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[References](#)



PRINCIPLES OF SURVIVORSHIP

Colorectal Long-term Follow-up Care - References

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**American Joint Committee on Cancer (AJCC) TNM Staging Classification for Rectal Cancer 8th ed., 2017)****Table 1. Definitions for T, N, M****T Primary Tumor**

- TX** Primary tumor cannot be assessed
- T0** No evidence of primary tumor
- Tis** Carcinoma *in situ*: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
- T1** Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
- T2** Tumor invades the muscularis propria
- T3** Tumor invades through the muscularis propria into pericolorectal tissues
- T4** Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure
- T4a Tumor invades* through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
- T4b Tumor directly invades* or adheres** to adjacent organs or structures

N Regional Lymph Nodes

- NX** Regional lymph nodes cannot be assessed
- N0** No regional lymph node metastasis
- N1** One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥ 0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
- N1a One regional lymph node is positive
- N1b Two or three regional lymph nodes are positive
- N1c No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues
- N2** Four or more regional lymph nodes are positive
- N2a Four to six regional lymph nodes are positive
- N2b Seven or more regional lymph nodes are positive

M Distant Metastasis

- M0** No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs
- M1** Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
- M1a Metastasis to one site or organ is identified without peritoneal metastasis
- M1b Metastasis to two or more sites or organs is identified without peritoneal metastasis
- M1c Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

* 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 (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).

** 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 classification should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.

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**American Joint Committee on Cancer (AJCC)**
TNM Staging System for Colon Cancer 8th ed., 2017)**Table 2. Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
Stage IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
Stage IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

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NCCN Guidelines Version 2.2019 Rectal Cancer

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 08/07/18

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 indicated.

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Discussion
update in
progress

Overview

Colorectal cancer is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2018, an estimated 43,030 new cases of rectal cancer will occur in the United States (25,920 cases in men; 17,110 cases in women). During the same year, it is estimated that 50,630 people will die from rectal and colon cancer combined.¹ Despite these statistics, the incidence per 100,000 population of colon and rectal cancers decreased from 60.5 in 1976 to 46.4 in 2005.² In fact, the incidence of colorectal cancer decreased at a rate of approximately 2.9% per year or greater between 2005 and 2014.¹ The incidence rate for colorectal cancer reported by the CDC for 2011 was 40.0 per 100,000 persons.³ In addition, mortality from colorectal cancer decreased by almost 35% from 1990 to 2007,⁴ and is currently down by about 50% from peak mortality rates.¹ 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.⁵ 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. Colorectal cancer that occurs in young adult patients is clinicopathologically and genetically different from colorectal cancer in older adults, suggesting a need to develop specific treatment strategies for this population.⁶

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, surgical management, perioperative 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, 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.⁷

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 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 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).

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 cancer⁸⁻¹² 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])^{13,14} and familial adenomatous polyposis (FAP).¹⁵ 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](#). Results from a recent randomized controlled trial (RCT) 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.¹⁶

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 β activation, stromal invasion, and

angiogenesis.¹⁷ However, this classification is not yet recommended in clinical practice.

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.^{13,14,18,19} 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.²⁰ 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.²⁰

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.²¹⁻²⁴ 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

CDC²⁵⁻²⁷ and by the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Medical Pathology (AMP), and ASCO in a guideline on molecular biomarkers for colorectal cancer.²⁸ 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.^{29,30} The Cleveland Clinic recently reported on its experiences implementing such a screening approach.³¹

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, Nivolumab, and Ipilimumab: 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 mismatch repair-deficient (dMMR) tumors.³² 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](#).

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.³³⁻³⁹ Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with colorectal cancer.⁴⁰⁻⁴³ 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 overall survival (OS) (hazard ratio [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.⁴⁴ Another meta-analysis determined that the relationship between vitamin D levels and mortality is linear.⁴⁵

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.⁴⁶ A later analysis of the same study reported that the effect of vitamin D supplementation on recurrence of advanced adenomas varied significantly based on the genotype of the vitamin D receptor, indicating that only individuals with specific vitamin D receptor alleles may benefit from vitamin D supplementation for prevention of advanced adenomas.⁴⁷ Furthermore, no study has yet definitively shown that vitamin D supplementation improves outcomes in patients with colorectal cancer. Two studies have reported that supplementation did not improve survival.^{48,49} However, the randomized, double-blind, phase II SUNSHINE trial that was presented at ASCO in 2017 reported a longer PFS for previously untreated metastatic colorectal cancer patients randomized to standard treatment plus high-dose vitamin D supplementation compared to those randomized to standard treatment plus low-dose vitamin D supplementation.⁵⁰ OS data were not yet mature at the time of reporting. 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.⁵¹ 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.

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.⁵²⁻⁵⁴ 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).^{53,55-70} 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 an HR for the development of colorectal cancer of 0.63 (95% CI, 0.54–0.74) compared with those who adhered to ≤ 1 of the factors. Other large studies support the conclusion that adherence to healthy lifestyle factors can reduce the risk of colorectal cancer.^{71,72}

Some data suggest that consumption of dairy may lower risk for the development of colorectal cancer.^{73,74} 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.⁷⁵ 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.⁷⁶⁻⁷⁸ Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs may also decrease the risk for colorectal cancer.⁷⁹⁻⁸⁵ In fact, the USPSTF recommends that adults aged 50 to 59 years with a 10-year cardiovascular disease risk $\geq 10\%$ and a life expectancy of ≥ 10 years and without an increased bleeding risk take low-dose aspirin daily for at least 10 years for the primary prevention of both cardiovascular disease and CRC.⁸⁶

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption are associated with a poor prognosis.^{57,87-90} Conversely, post-diagnosis fish consumption may be associated with a better prognosis.⁹¹ A family history of colorectal cancer

increases risk while improving prognosis.⁹² Data on the effect of dairy consumption on prognosis after diagnosis of colorectal cancer are conflicting.^{93,94}

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.⁹⁵⁻¹⁰⁴ 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.¹⁰⁵ In addition, although patients with colorectal cancer and diabetes appear to have a worse prognosis than those without diabetes,^{106,107} patients with colorectal cancer and diabetes treated with metformin seem to have a survival benefit over those not treated with metformin.^{98,108,109} The data regarding the effects of metformin on colorectal cancer incidence and mortality, however, are not completely consistent, with some studies seeing no effect.^{110,111}

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).¹¹² The TNM categories reflect very similar survival outcomes for rectal and colon cancer; these diseases therefore share the same staging system.

In the 8th edition of the AJCC Cancer Staging Manual, 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.¹¹²

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).¹¹²

In rectal cancer, T stage has more prognostic value than N stage: patients with stage IIIA disease (T1-2) have longer rectal cancer-specific survival than patients with stage IIA (T3), IIB (T4a), and IIC (T4b) rectal cancer.¹¹³

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 8th edition of the AJCC Cancer Staging Manual includes the M1c category for peritoneal carcinomatosis with or without blood-borne metastasis to visceral organs.¹¹² Patients with peritoneal metastases have a shorter progression-free survival (PFS) and OS than those without peritoneal involvement.¹¹⁴

The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.¹¹²

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 margins¹¹⁵⁻¹¹⁹; 8) neoadjuvant treatment effect^{120,121}; 9) lymphovascular invasion (LVI)¹²²; 10) perineural invasion (PNI)¹²³⁻¹²⁵; and 11) the number of tumor deposits.¹²⁶⁻¹³⁰

Margins

The 8th 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.¹¹²

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer.¹³¹ 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.¹³¹ 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 (mm). 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.¹³² The panel defines a positive CRM as tumor within 1 mm from the transected margin.^{117,119,133}

Accurate pathologic assessment of the CRM of resected rectal tumor specimens is crucial, because the CRM has been shown to be a strong predictor of both local recurrence and OS,^{131,133-135} including in patients undergoing neoadjuvant therapy,^{118,136} 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.¹¹⁸ 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 CAP recommend evaluation of 12 lymph nodes to accurately identify early-stage colorectal cancers.^{112,131,137} The number of lymph nodes that can be retrieved varies with age and gender of the patient and on tumor grade or site.¹³⁸ The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify early-stage rectal cancer.¹³⁹ 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.^{140,141} 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.¹⁴² 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, $P \leq .0001$).¹⁴³⁻¹⁴⁵ In fact, retrieval of fewer lymph nodes may be a marker of a higher tumor response and better prognosis following neoadjuvant treatment.^{146,147}

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 reported.^{148,149} 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.^{149,150} In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.¹⁵¹ 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.¹⁵² Others have noted that micrometastasis found in node-negative patients did not predict outcome.¹⁵³ 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.¹⁵⁴

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.¹⁵⁵ 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.¹⁵⁶ The 8th edition of the AJCC Cancer Staging Manual notes that micrometastases have been defined as clusters of 10 to 20 tumor cells or clumps of tumor ≥ 0.2 mm in diameter and recommends that these micrometastases be considered as standard positive nodes.¹¹²

Response to Treatment

The most recent CAP Guidelines require that the pathology report comment on treatment effects of neoadjuvant therapy.¹³⁷ 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).^{120,121,137,157}

Perineural Invasion

Several studies have demonstrated that the presence of PNI is associated with a significantly worse prognosis.^{123-125,158-160} 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.¹²⁴ 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%; $P = .0005$).¹²⁵ Similar results were seen for patients with stage III disease.¹²³ 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).¹⁵⁹ 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.^{126-130,160} 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 ($P < .0001$).¹³⁰ Another retrospective study found a similar difference in 5-year

OS rates (80.3% vs. 34.9%, respectively; $P < .001$).¹⁶¹ The association of tumor deposits with decreased survival also holds in patients with rectal cancer who had neoadjuvant chemoradiation (chemoRT).^{162,163} Tumor deposits are classified as pN1c.¹¹²

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 pathology¹⁶⁴ 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).¹⁶⁵ Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis.¹³¹ The panel recommends marking the malignant 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.^{164,166} Favorable histologic features include lesions of grade 1 or 2 without angiolymphatic invasion and with a negative resection margin.¹⁶⁴ 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 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.^{164,167-169} In addition, several studies have shown that tumor budding is an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.¹⁷⁰⁻

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Rectal surgery consists of either a transanal local excision, if appropriate, or a transabdominal resection. In patients with unfavorable pathologic features, transabdominal resection should be considered in order to include lymphadenectomy. All patients who have malignant polyps removed by transanal local 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 is a cancerous lesion in the rectum, which lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI (see Figure 1). The rectum ends at the superior border of the functional anal canal, defined as the palpable upper border of the anal sphincter and puborectalis muscles of the anorectal ring.

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.¹⁷⁴ Furthermore, the risk of pelvic recurrence is higher in patients with rectal cancer compared to those with colon cancer, and locally recurrent rectal cancer is associated with a poor prognosis.¹⁷⁵⁻¹⁷⁷ Careful patient selection with respect to particular treatment options and the use of sequenced multimodality therapy that combines chemoRT, chemotherapy, and operative treatment for most patients is recommended.¹⁷⁸

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 whether to recommend preoperative chemoRT, 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, which includes total colonoscopy to evaluate for synchronous lesions or other pathologic conditions of the colon and rectum. Rigid proctoscopy can also be considered. Patients with rectal cancer also require a complete physical examination, including carcinoembryonic antigen (CEA) determination and assessment of performance status to determine operative risk.

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.

Imaging also plays a critical role in preoperative evaluation, both for evaluation of the primary tumor and to assess for the presence of distant metastases. Preoperative imaging for rectal cancer includes chest/abdominal CT and pelvic MRI or chest CT and abdominal/pelvic MRI, as described below.

Preoperative Pelvic Imaging in Rectal Cancer

The accessibility of rectal cancer to evaluation by pelvic MRI with contrast makes possible preoperative assessments of depth of tumor penetration and the presence of local lymph nodal metastases.^{179,180} Pelvic MRI has the 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.¹⁸¹⁻¹⁸⁶ The CRM by MRI is measured at the closest distance of the tumor to the mesorectal fascia. The panel defines a clear CRM as > 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane. An involved CRM, in contrast, is within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle. 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.¹⁸⁷ 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 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; $P < .05$). MRI has also been shown to be accurate for the prediction of T and N stage.¹⁸⁸ A group of experts developed consensus guidelines for standardized imaging of rectal cancer by MRI.¹⁸⁹

Only a 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.^{181,184,190} In addition, CT has poor sensitivity for the prediction of CRM status.¹⁹¹ Furthermore, CT has lower sensitivity and specificity for the prediction of lymph node involvement than MRI (CT, 55% and 74%; MRI, 66% and 76%).¹⁹⁰ Therefore, pelvic CT is not recommended for rectal staging.

A 2004 meta-analysis showed that endoscopic ultrasound (EUS) and MRI have similar sensitivities and specificities for evaluation of lymph nodes (EUS, 67% and 78%; MRI, 66% and 76%).¹⁹⁰ However, newer data suggest that EUS is not very accurate for rectal cancer staging.¹⁹² Furthermore, EUS cannot fully image high or bulky rectal tumors nor regions beyond the immediate area of the primary tumor (eg, tumor deposits, vascular invasion).¹⁸¹ Another disadvantage of EUS is a high degree of operator dependence.¹⁹⁰ At this time, the panel believes that EUS should only be used to evaluate the pelvis if MRI is contraindicated (eg, because of a pacemaker).

Preoperative Imaging for Distant Metastases

Additional information regarding the occurrence of distant metastases should be determined preoperatively through chest and abdominal imaging. Chest imaging should be by CT scan, whereas imaging of the abdomen can be performed with CT or MRI. Lung metastases occur in approximately 4% to 9% of patients with colon and rectal cancer,¹⁹³⁻¹⁹⁵ and studies have shown that 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.^{196,197}

The consensus of the panel is that a PET scan is not indicated for preoperative staging of rectal cancer. 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.

Restaging/Assessing Treatment Response

Restaging after neoadjuvant treatment is done to detect distant metastases that would change the treatment strategy, to plan the surgical approach, and, increasingly, to determine if additional therapy or resection can be avoided for select patients (see *Watch-and-Wait Nonoperative Approach for Clinical Complete Responders* and *Preoperative Chemotherapy Without Chemoradiation*, below). MRI, CT, and EUS have been used for restaging after neoadjuvant treatment, but the accuracy of these techniques for determining T stage and lymph node involvement is limited.¹⁹⁸⁻²⁰⁶ As with initial staging, the panel recommends pelvic MRI for restaging with chest and abdominal imaging to assess for distant disease. Abdominal/pelvic CT has been shown to identify resectable liver metastases in 2.2% (95% CI, 0.8%–5.1%) of patients during restaging, with false-positive findings that could cause unnecessary treatment in 1.3% (95% CI, 0.3%–3.9%).²⁰⁷ In this study, the use of restaging abdominal/pelvic CT was at the physician's discretion, and no difference was seen in recurrence-free survival for those who had an abdominal/pelvic CT before resection compared with those who did not.

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.^{205,208-210} FDG PET/CT is also being investigated for its ability to accurately determine response to neoadjuvant treatment.^{209,211}

At this time, the panel recommends chest CT, abdominal CT or MRI, and pelvic MRI for restaging.

Surgical Approaches

A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancer lesions.^{212,213} These

methods include local procedures, such as polypectomy, transanal local 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]).^{212,213}

Transanal Local Excision

Transanal local 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 local excision with negative margins.²¹⁴ In addition, full-thickness excision must be feasible.

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 local excision.²¹⁵ A small prospective, single-blinded, randomized trial compared laparoscopic surgery with laparoscopy combined with TEM in 60 patients with rectal cancer.²¹⁶ The TEM group had shorter operation times and hospital stays, and no local nor distant recurrences were seen in either group after a median follow-up of 28 months.

Both transanal local 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, poor differentiation, or invasion into the lower third of the submucosa (sm3 level),^{217,218} 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.²¹⁹ 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.²²⁰ 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.²²¹ 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.^{174,219} 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.²²² These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.^{219,223,224} A retrospective study of 282 patients undergoing either transanal local 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 ($P = .001$).²²⁴ 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 ($P = .003$).²¹⁹ More recently, an analysis of >164,000 individuals from the National Cancer Database (NCDB) 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; $P < .001$).²²⁵ 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,^{223,226} although not all studies have seen such results.²²⁷

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 neoadjuvant treatment.

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.^{174,213,228} 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.²²⁹ The TME approach is designed to radically

remove lymphatic drainage regions of tumors located above the level of the levator muscles.²³⁰ 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.²³¹ 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.²³² An extralevator APR may have benefits over a conventional APR approach, including lower rates of intraoperative perforation, CRM involvement, and local recurrence, although inconsistencies are seen between studies.^{233,234}

Pathologists play a key role in evaluating the surgical specimen, including a macroscopic assessment of both its external appearance/completeness and the CRM.^{235,236} The panel defines a positive CRM as tumor within 1 mm from the transected margin (see *Pathology*, above).^{117,119,133} 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.¹¹⁷

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.^{237,238} 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.²³⁷ Importantly, quality of life between patients with or without a permanent colostomy appears to be fairly comparable.^{239,240}

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.²⁴¹⁻²⁴⁴ 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.²⁴⁵ The phase III COLOR II trial, powered for non-inferiority, 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 return of bowel function, but with longer operation times.²⁴⁶ No differences were seen in completeness of resection, percentage of patients with a 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.²⁴¹

In the CLASICC trial comparing laparoscopically assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.²⁴⁷ 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; $P = .132$).²⁴⁸

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.²⁴⁹ 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.²⁴² Factors that may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically assisted surgery for colorectal cancer have been described,²⁵⁰ and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Two other trials, ACOSOG Z6051 and ALaCaRT, have reported pathologic outcomes.^{243,244} In Z6051, the primary endpoint was a composite of CRM >1 mm, negative distal margin, and TME completeness.²⁴³ 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.²⁴⁴ 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.

An analysis of results from >18,000 individuals in the NSDB undergoing LAR for rectal cancer found short-term oncologic outcomes to be similar between the open and laparoscopic approaches.²⁵¹ In addition, older reviews and meta-analyses consistently found the laparoscopic approach to be safe and feasible,^{242,252–265} even though a meta-analysis published in 2017 found that the risk for a non-complete mesorectal excision is significantly higher in patients receiving a laparoscopic resection compared with those receiving an open resection.²⁶⁶

Several studies have also compared outcomes of robotic-assisted resection to conventional laparoscopic resection.^{267–271} Comparable results are generally seen between the approaches in conversion to open resection, TME quality, postoperative complications, and quality of life.

In conclusion, some studies have shown that laparoscopy is associated with similar short- and long-term outcomes when compared to open surgery,^{241,242} whereas other studies have shown the laparoscopic approach to be associated with higher rates of CRM positivity and incomplete TME.^{243,244} The panel defined principles by which minimally invasive 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 experts has defined standards for the technical details of laparoscopic TME.²⁷²

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 usually 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.^{132,273,274} 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.^{132,275,276} 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,²⁷⁷ 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. The current guidelines recommend several possible sequences of therapy, depending on predicted CRM status and response to initial therapy. 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 RT preoperatively versus postoperatively for stage II/III rectal cancer.^{278,279} 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.²⁷⁸ 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.²⁸⁰ 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 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; $P = .13$).²⁸¹

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue.^{278,279,282} 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,^{278,279} this conclusion is not supported by 2 meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.^{283,284} 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.^{278,285} Improvements in preoperative staging with pelvic MRI have allowed for more accurate staging, but the risk of over-staging disease has not been eliminated.²⁷⁷ 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.

Concurrent Chemotherapy with Radiation

A number of randomized trials have evaluated the effectiveness of the addition of concurrent 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 N1-2.²⁸⁶ 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%; $P < .05$).²⁸⁶

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.²⁸⁷ Significant reductions in tumor size, pTN stage, lymphatic invasion, vascular invasion, and PNI rates were observed with use of combined-modality therapy compared with use of RT and surgery without chemotherapy.²⁸⁷ More mature results from this trial, which included 4 treatment groups (preoperative RT; preoperative chemoRT; preoperative RT plus postoperative chemotherapy; and preoperative chemoRT plus postoperative chemotherapy), however, indicated that no significant differences in OS were associated with adding 5-FU–based chemotherapy preoperatively or postoperatively.²⁸⁸

The conclusions of these trials have been supported in a 2009 systematic review that included 4 RCTs.²⁸⁹ In addition, a recent Cochrane review of 6 RCTs 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.²⁹⁰ 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.²⁹¹ Another recent meta-

analysis of 5 RCTs comparing neoadjuvant chemoRT with neoadjuvant radiotherapy came to similar conclusions.²⁷⁴

With respect to the type of chemotherapy administered concurrently with RT,²⁷⁶ 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 (RFS) 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.²⁹² 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.²⁹³ 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.^{294,295} 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.^{295,296} 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).²⁹⁴ Furthermore, in this trial capecitabine demonstrated a significant improvement in 3-year DFS (75.2% vs. 66.6%; $P = .034$).²⁹⁴ Because of these studies, capecitabine given concurrently with RT is listed in the guidelines as 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 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).²⁹⁷ 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.^{295,296} Further follow-up of these trials is necessary to see if there is a difference in local recurrence rates and 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.²⁹⁸ 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. The results did not change after longer follow-up.²⁹⁹

Results of the German CAO/ARO/AIO-04 trial have been published.^{300,301} 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%, $P = .038$)³⁰¹, but this result could be because of differences in the fluorouracil schedule between the arms.³⁰² 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 ($P = .03$).³⁰⁰ 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.³⁰³

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.³⁰⁴ 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.

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

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.³⁰⁵ 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 of cetuximab in this setting.^{306,307} 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.³⁰⁸ 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.

Another phase II study, RaP Study/STAR-03, also assessed the potential role of panitumumab in neoadjuvant chemoRT in patients with *KRAS* wild-type, cT3N0 or cT2-3N1-2, mid to low rectal cancer with a predicted negative CRM.³⁰⁹ All patients were treated with panitumumab-chemoRT followed by resection and adjuvant FOLFOX. The primary endpoint of pathologic complete response was observed in 10.9% (95% CI, 4.7–17.1) of participants, not meeting the pre-specified level of 16%.

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.³¹⁰ The 5-year OS rate was 80%, and the 5-year RFS 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.³¹¹⁻³¹³ 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 and the Total Neoadjuvant Therapy Approach

Several small trials have tested the utility of a course of neoadjuvant chemotherapy preceding chemoRT and resection.³¹⁴⁻³¹⁹ This approach is referred to as a total neoadjuvant therapy (TNT) approach. In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CAPEOX either before chemoRT or after surgery.^{316,320} 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.³¹⁸ 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.³¹⁹ The regimen was well tolerated with a pathologic complete response rate of 36%.

A single-institution retrospective cohort analysis of patients with T3/4 or node-positive rectal cancer compared the outcomes after either 1) a traditional approach of neoadjuvant chemoRT then resection with planned adjuvant chemotherapy (n = 320); or 2) a TNT approach of induction chemotherapy then chemoRT before resection (n = 308). Patients in the TNT group received a greater percentage of the planned chemotherapy

dose than those in the adjuvant chemotherapy group. The complete response rates were 36% and 21% in the TNT and adjuvant chemotherapy groups, respectively.

Possible benefits of using chemotherapy first include the early prevention or eradication of micrometastases, higher rates of pathologic complete response, minimizing the length of 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.³²¹ All 32 of the participants had an R0 resection, and the 4-year DFS was 84% (95% CI, 67%–94%). Another phase II trial, which included 60 patients with stage II/III rectal cancer (excluding cT4b) from 8 institutions, assessed the R0 resection rate after FOLFOX plus either bevacizumab or cetuximab.³²² An R0 resection was achieved in 98.3% of the participants, and the pathologic complete response rate was 16.7%.

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 response than regimens that included radiation (6.6% vs. 14.0% for 5-FU-RT and 27.5% for FOLFOX-RT).³⁰³ The rate of downstaging in the FOLFOX group was similar to the 5-FU-RT group but lower than the FOLFOX-RT group (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.³²³ The ranges of R0 resection and pathologic complete response rates were 90% to 100% and 4% to 33%, respectively.

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).

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

Technical Aspects of Radiation Therapy

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 <https://www.rtog.org/CoreLab/ContouringAtlases.aspx>).³²⁴ 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 chemoRT and surgery 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,³²⁵⁻³³⁰ it is unclear whether such longer intervals are associated with clinical benefit. Results of one NCDB analysis suggest that an interval of >8 weeks is associated with increased odds of pathologic complete response,³³¹ 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.^{332,333}

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.³³⁴ 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 5.5-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 RT (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 administered preoperatively for resectable rectal cancer showed a survival advantage and a decreased rate of local recurrence with this approach compared

with surgery alone.³³⁵ However, a follow-up study published in 2005 showed that the patients with short-course preoperative RT had increased RR for postoperative hospitalization due to bowel obstructions and other gastrointestinal complications.³³⁶ 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.³³⁷⁻³³⁹ 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.³⁴⁰ 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.^{340,341}

Long-term (12-year) follow-up of one of the short-course RT trials (the Dutch TME trial³³⁸) was reported.³⁴² The analysis showed that 10-year survival was significantly improved in patients with stage III disease and a negative CRM in the radiotherapy plus surgery group compared to the group that received surgery alone (50% vs. 40%; $P = .032$).³⁴² 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 RT and more conventional preoperative long-course chemoRT and found no differences in local recurrence or survival.³⁴³ Similarly, an Australian/New Zealand trial (Trans-Tasman

Radiation Oncology Group [TROG] trial 01.04) that randomized 326 patients to short-course RT or long-course chemoRT found no differences in local recurrence and OS rates.³⁴⁴ In addition, rates of late toxicity, distant recurrence, and RFS 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%; $P = .13$).³⁴⁵ However, no overall difference was seen in health-related quality of life between the groups.³⁴⁶ Finally, a trial compared short-course RT with long-course chemoRT with delayed surgery in both groups.³⁴⁷ 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. The 3-year DFS was better in the long-course arm than in the short course arm (75% vs. 59%; $P = .022$), with no difference in OS.³⁴⁸

A 2014 systematic review identified 16 studies (RCTs, phase II trials, and retrospective studies) that addressed the interval between short-course RT and resection of rectal cancer.³⁴⁹ 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 pCdR 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 considered as an appropriate option for patients with T3N0 or T1-3N1-2 rectal cancer. A multidisciplinary evaluation, including a discussion of the need for downstaging and the possibility of long-term toxicity, is recommended when considering short-course RT. Short-course RT is not

recommended for T4 disease at this time. The ongoing randomized RAPIDO trial (NCT01558921) is assessing DFS at 3 years with the use of preoperative short-course RT followed by 6 cycles of CAPEOX before resection in patients with clinical stage T3 or T4 rectal cancer.³⁵⁰

Response to Neoadjuvant Treatment

Fifty percent to 60% of patients are downstaged following neoadjuvant therapy, with about 20% of patients showing a pathologic complete response.³⁵¹⁻³⁵⁷ 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.³⁵⁸ 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%.³⁵⁹ A recent retrospective review of 725 patients with rectal cancer found similar results.³⁵⁵ 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. Other studies have also shown a prognostic effect of response to neoadjuvant treatment.^{360,361}

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 downstaged to ypT0-2 were more likely to benefit from adjuvant chemotherapy than patients with ypT3-

4 staging.³⁵¹ Similar results were seen from another retrospective review.³⁶² 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.

Watch-and-Wait 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 al³⁶³ 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.³⁶⁴

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.³⁶⁵ 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 watch-and-wait 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 watch-and-

wait 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.³⁶⁶⁻³⁶⁹ 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.³⁶⁷

Several systematic reviews have been published on the nonoperative approach.³⁷⁰⁻³⁷² They all show that the approach is likely safe with the use of resection in patients with tumor regrowth, but that the data are very limited.

Despite the impressive results of prospective trials, 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 watch-and-wait approach.³⁷³ 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.^{198-206,374} In addition, lymph node metastases are still seen in a subset of patients with pathologic complete response.³⁷⁵ Keeping these caveats in mind, the panel believes that a nonoperative management approach may be considered in centers with experienced multidisciplinary teams after a careful discussion with the patient of his or her risk tolerance.

The use of nonoperative management of rectal cancer has been increasing in the United States, likely representing both some early adoption of the approach described herein as well as disparities in the receipt of appropriate rectal cancer resection.³⁷⁶ An analysis of the NCDB

from 2004 through 2008 looked at all patients with clinical stage II/III rectal cancer who received neoadjuvant chemoRT only (for whom surgery was “not part of the planned first course of treatment”) or neoadjuvant chemoRT plus resection.³⁷⁷ No data were available regarding the clinical response to neoadjuvant therapy. Although the patients in this study represent a very different population than the trials discussed above, it is important to note that those with the nonoperative approach had a worse OS (HR, 1.90; 95% CI, 1.75–2.04). These results underscore the importance of careful patient selection, vigilant surveillance, and resection of recurrences for those choosing a watch-and-wait approach.

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; however, few studies have evaluated the effect of adjuvant chemotherapy in patients with rectal cancer, and its role is not well-defined.^{378,379} 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 22921.²⁸⁸ 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).²⁸⁸ 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; $P = .29$).³⁸⁰ 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.^{381,382}

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.³⁸³ The open-label phase II ADORE trial randomized 321 patients with resected rectal cancer and neoadjuvant therapy to adjuvant 5-FU/LV or FOLFOX.³⁸⁴ 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%; $P = .03$).³⁰⁰

A 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 rates of 96% and 100%, respectively.³⁸⁵ 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.³⁸⁶ 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.^{387,388} A systematic review published in 2017 identified 8 phase III trials and 1 randomized phase II trial comparing adjuvant chemotherapy with observation in patients with nonmetastatic rectal cancer treated with neoadjuvant chemoRT.³⁸⁹ The authors report that the data are not robust enough to warrant routine use of adjuvant therapy in this population.

Most database studies have also failed to see much of a benefit to adjuvant chemotherapy in this setting.³⁹⁰⁻³⁹² However, 2 similar analyses that used the NCDB from 2006 to 2013 or from 2006 and 2012 and that looked only at patients achieving a pathologic complete response after neoadjuvant chemoRT ($n = 2891$; $n = 2764$) found a significant improvement in OS with the use of adjuvant chemotherapy.^{393,394}

An 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.³⁹⁵ 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.³⁹⁶ Pathologic stage, age, and postoperative readmissions were associated with a decreased likelihood of receiving adjuvant treatment. Other database analyses show that adjuvant chemotherapy is used in 74% to 92% of patients in this setting.^{390,391}

Although conclusive data on the benefits of adjuvant therapy in patients with stage II/III rectal cancer are lacking, the panel recommends its use. Choice of regimen depends on initial clinical staging and predicted CRM status, with FOLFOX or CAPEOX as preferred or only options for higher risk patients and 5-FU/leucovorin (5-FU/LV) or capecitabine as additional options in some cases. For example, these less intensive adjuvant chemotherapy options might be especially appropriate in patients whose cancer 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 colon or rectal cancer looked at the effect of timing of adjuvant therapy

following primary tumor resection.³⁹⁷ 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.³⁹⁸ The optimal duration of adjuvant treatment in rectal cancer is still unclear.^{399,400} In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.⁴⁰¹ 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](#) for a full discussion).⁴⁰²

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.⁴⁰³ 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.⁴⁰⁴ For the low, intermediate, and high recurrence risk groups, recurrence at 3 years was 12%, 18%, and 22%, respectively. Similar results were found in other prospectively designed studies.^{405,406}

A recent prospectively designed validation study assessed this assay for predicting recurrence risk in patients with stage II and III rectal cancer.⁴⁰⁷ For patients who underwent surgery without neoadjuvant therapy in the Dutch 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 leucovorin shortage. One is the use of levo-leucovorin, which is commonly used in Europe. A dose of 200 mg/m² of levo-leucovorin is equivalent to 400 mg/m² of standard leucovorin. Another option is for practices or institutions to use lower doses of leucovorin for all doses in all patients, since the panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg leucovorin gave similar survival and 3-year recurrence rates as 25 mg leucovorin when given with bolus 5-FU to patients as adjuvant therapy following R0 resections for colorectal cancer.⁴⁰⁸ Another study showed no difference in response rate or survival in patients with metastatic colorectal cancer receiving bolus 5-FU with either high-dose (500 mg/m²) or low-dose (20 mg/m²) leucovorin.⁴⁰⁹ Also, the Mayo Clinic and NCCTG determined that there was no therapeutic difference between the use of high- (200 mg/m²) or low- (20 mg/m²) dose leucovorin with bolus 5-FU in the treatment of advanced colorectal cancer, although 5-FU doses were different in the 2 arms.⁴¹⁰ 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 local excision, as appropriate (see section on *Surgical Approaches*, above). If pathology review after local excision reveals no high-risk features, 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 pT2, additional treatment is required. The options are: 1) transabdominal resection (preferred for pT2 lesions) followed by adjuvant therapy based on pathologic stage (see *Adjuvant Treatment Recommendations for cT1-2 N0 Rectal Cancer*, below); or 2) chemoRT. For patients treated with transanal local excision and then chemoRT, options for the next phase of treatment are: 1) observation if there is no evidence of disease; 2) transabdominal resection with or without adjuvant chemotherapy; or 3) chemotherapy without resection. Chemotherapy options are listed in the guidelines. Results of a meta-analysis suggest that transanal local excision followed by chemoRT without a transabdominal resection may be associated with higher rates of local recurrence than transanal local excision followed by transabdominal resection.⁴¹¹ Careful surveillance of patients forgoing transabdominal resection in this setting is advised.

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.^{174,412,413} Following transabdominal resection of patients with clinical stage T1-2 N0 rectal cancer, patients should receive adjuvant therapy based on pathologic stage (see *Adjuvant Treatment Recommendations for cT1-2 N0 Rectal Cancer*, below). For all

patients with locoregional rectal cancer, the panel recommends perioperative therapy for a total duration of approximately 6 months.

Adjuvant Treatment Recommendations for cT1-2 N0 Rectal Cancer

Patients who had a transabdominal resection for stage cT1-2 rectal cancer are given further treatment based on the pathologic stage as delineated in detail in the guidelines. Patients with tumors staged as pT1-2, N0, M0 require no further treatment. If pathology review reveals pT3, N0, M0, chemoRT followed by chemotherapy is one option. Observation can also be considered in these patients if the tumor was well-differentiated or moderately well-differentiated carcinoma invading less than 2 mm into the mesorectum, without lymphatic or venous vessel involvement and was located in the upper rectum.⁴¹⁴

For resected patients with positive nodes and/or pT4 disease, chemotherapy and chemo RT can be given as a “sandwich regimen,” consisting of chemotherapy followed by concurrent chemoRT followed by additional chemotherapy.^{276,292,293} Alternatively, chemoRT can be the initial therapy followed by chemotherapy.

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

Recommendations for Patients with T3, N any Lesions with Clear CRM by MRI or with T1-2, N1-2 Lesions

Patients clinically staged as T3, N any with prediction of clear margins by MRI have the same treatment options as those clinically staged as T1-2, N1-2. Prediction of CRM status by MRI is discussed above (see *Preoperative Pelvic Imaging in Rectal Cancer*).

The first option for these patients is chemoRT or short-course RT followed by transabdominal resection and adjuvant chemotherapy based on initial clinical stage; specific options are listed in the guidelines. If long-course chemoRT is used, then restaging can be considered before resection. If

short-course RT is used, surgery should be within 1 week or delayed 6 to 8 weeks.

In those patients who achieve a complete clinical response to initial chemoRT or short-course RT with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a “watch and wait,” nonoperative management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance. The data supporting this approach are discussed in *Watch-and-Wait Nonoperative Approach for Clinical Complete Responders*, above.

Another option for the sequence of treatment in this population is to use a TNT approach, starting with chemotherapy followed by either chemoRT or short-course RT, then restaging and transabdominal resection.

A poor clinical response does not necessarily imply unresectability, and surgical exploration is usually appropriate when resection is being considered. 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 or short-course RT, 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](#)). FOLFOXIRI is not recommended in this setting.

Recommendations for Patients with T3, N any Lesions with Involved CRM by MRI, with T4, N any Lesions, with Locally Unresectable Disease, or Who Are Medically Inoperable

Patients in this group can start with chemoRT with restaging at 6 weeks after completion of treatment. If pelvic MRI reveals an involved CRM or bulky residual disease, then 12 to 16 weeks of chemotherapy, restaging, transabdominal resection, and additional chemotherapy are recommended. This approach has been assessed in a small study of 45 patients.⁴¹⁵ Twenty-two percent of the patients eventually underwent an R0 resection, with 3-year PFS and 5-year OS in the entire population at 30% (95% CI, 15.0–46.0) and 44.0% (95% CI, 26.0–61.0), respectively.

If a clear CRM is predicted by MRI after initial chemoRT, then transabdominal resection and adjuvant chemotherapy are recommended. Alternatively, a watch-and-wait, nonoperative approach may be considered as described above for patients with clinical stage T3, N any with clear CRM by MRI or T1-2, N1-2 lesions.

Alternatively, a TNT approach can be used in these patients. In this approach, 12 to 16 weeks of chemotherapy are followed by chemoRT, restaging, and transabdominal resection. When a TNT approach is used, resection should be performed unless there is a clear contraindication. 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](#)). FOLFOXIRI is not recommended in this setting.

For unresectable cancers, doses higher than 54 Gy may be required; the dose of RT 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),⁴¹⁶⁻⁴²⁰ 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,⁴²¹⁻⁴²³ and 80% to 90% of these patients have unresectable metastatic liver disease.^{197,422,424-426} Metastatic disease most frequently develops metachronously after treatment for locoregional colorectal cancer, with the liver as the most common site of involvement.⁴²⁷ However, 20% to 34% of patients with colorectal cancer present with synchronous liver metastases.^{196,197} 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.⁴²⁸

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.⁴²⁹ 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.⁴²⁶ Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.^{422,430} 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.^{196,431-435}

Other groups, including ESMO, have established guidelines for the treatment of metastatic colorectal cancer.⁴³⁶ 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.^{422,437} Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,^{432,435} and a recent meta-analysis reported a median 5-year survival of 38%.⁴³⁸ 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.⁴³⁹⁻⁴⁴¹ 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 disease⁴⁴² (discussed further in *Determining Resectability*).

Colorectal metastatic disease sometimes occurs in the lung.⁴²¹ Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.⁴⁴³⁻⁴⁴⁵ 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%.⁴⁴⁵ Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases^{444,446-450} and an analysis of patients who underwent hepatic

resection followed by subsequent pulmonary resection showed positive outcomes.⁴⁵¹

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.^{452,453} 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).⁴⁵⁰ A recent systematic review concluded similarly that carefully selected patients might benefit from this approach.⁴⁵⁴

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.⁴⁵⁵ 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.⁴⁵⁶⁻⁴⁵⁹ 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.⁴⁵⁶ 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.⁴⁶⁰ Panel consensus is that resection of liver or lung metastases can be considered in carefully selected patients.^{444,461,462}

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*).⁴⁶³

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 is indicated for small metastases that can be treated with margins.⁴⁶⁴⁻⁴⁶⁶ Stereotactic body RT (SBRT; also called stereotactic ablative radiotherapy [SABR])^{425,467,468} is also a reasonable option, as discussed in subsequent paragraphs. Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins⁴⁶⁵ or safely treated by SBRT. In select patients with liver-only or liver-dominant metastatic disease that cannot be resected or ablated, other local, arterially directed treatment options may be offered.⁴⁶⁹⁻⁴⁷¹

A meta-analysis of 90 studies concluded that hepatic arterial infusion chemotherapy (HAIC), yttrium-90 microsphere radioembolization, and transcatheter arterial chemoembolization (TACE) have similar efficacy in patients with unresectable hepatic colorectal metastases.⁴⁷² Local therapies are described in more detail below. The exact role of non-extirpative local therapies in the treatment of colorectal metastases remains controversial.

Hepatic Arterial Infusion of Chemotherapy

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, HAIC) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAIC and intravenous 5-FU with or without LV was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.^{426,473} 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 HAIC at later follow-up periods.^{426,474} Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAIC has been compared with systemic chemotherapy,⁴⁷⁵ although most have not shown a survival benefit of HAIC.⁴²⁶ Results of some studies also suggest that HAIC may be useful in the conversion of patients from an unresectable to a resectable status.⁴⁷⁶⁻⁴⁷⁸

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAIC.⁴³⁷ Limitations on the use of HAIC include the potential for biliary toxicity⁴²⁶ and the requirement of specific technical expertise. Panel consensus is that HAIC 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

Transhepatic Arterial Chemoembolization

TACE involves hepatic artery catheterization to locally deliver chemotherapy followed by arterial occlusion.⁴⁷⁰ A randomized trial compared the arterial delivery of irinotecan-loaded drug-eluting beads

(DEBIRI) and reported an OS benefit (22 months vs. 15 months; $P = .031$) of DEBIRI when compared to systemic FOLFIRI.⁴⁷⁹ 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.⁴⁸⁰ A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.⁴⁸¹ 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.⁴⁸²⁻⁴⁸⁷ 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.⁴⁸⁸

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; $P = .03$).⁴⁸⁹ 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.⁴⁹⁰ In the refractory setting, a CEA level ≥ 90 and LVI at the time of primary resection were negative prognostic factors for OS.⁴⁹¹ 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.⁴⁹²⁻⁴⁹⁴

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX+/- bevacizumab vs. FOLFOX+/- bevacizumab) were reported.⁴⁹⁵ 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; $P = .002$).

The FOXFIRE and FOXFIREGlobal studies were performed in the same manner as the SIRFLOX trial with the intention to compile all data and allow assessment of oncologic outcomes in a larger cohort.⁴⁹⁶ Pooled data from 1103 patients in these 3 prospective trials showed similar findings as in the SIRFLOX trial with prolongation of the liver PFS in the group treated by radioembolization but no difference in OS and PFS. Of interest was the unexpected finding of survival benefit with radioembolization plus chemotherapy compared to chemotherapy alone in the subgroup of patients with right-sided primary origin (HR, 0.67; 95% CI, 0.48–0.92). Based on these data, further investigation is needed to identify a role of radioembolization at earlier stages of disease in patients with right-sided primary origin.

Whereas very little data show any impact on patient survival and the data supporting its efficacy are limited, toxicity with radioembolization is relatively low.^{495,497-499} 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.⁵⁰⁰ Ablative techniques include radiofrequency ablation (RFA),^{465,501} 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.^{465,501-504}

A small number of retrospective studies have compared RFA and resection in the treatment of liver or lung metastases.^{440,505-509} Most of these studies have shown RFA to be relatively inferior to resection in terms of rates of local recurrence and 5-year OS.^{500,510,511} Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, lack of treatment assessment based on the ability to achieve margins, technological limitations of RFA, or a combination of these factors remains unclear.⁵⁰⁶ 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 at the time.⁵⁰⁸ 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.⁵¹²⁻⁵¹⁴

A 2012 phase II trial randomized 119 patients to receive systemic treatment alone (FOLFOX with or without bevacizumab) or systemic treatment plus RFA.⁵¹⁵ No difference in OS was initially 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; $P = .025$). However, a subsequent analysis following prolonged follow-up of the same population of this phase II RCT, showed

that OS was improved in the combined modality arm (HR, 0.58; 95% CI, 0.38–0.88, $P = .01$), with a 3-, 5-, and 8-year OS of 56.9%, 43.1%, and 35.9% for the combined modality arm compared to 55.2%, 30.3%, and 8.9% for the chemotherapy alone arm.⁵¹⁶ This study documented a long-term survival benefit for patients receiving RFA in addition to chemotherapy compared to those treated by chemotherapy alone.

Data on ablative techniques other than RFA are extremely limited.^{508,512,513,517-520} However, in a comparison of RFA with microwave ablation, outcomes were similar with no local tumor progression for metastases ablated with margins over 10 mm and a relatively better control of perivascular tumors with the use of microwave ablation ($P = .021$).⁵²¹ 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.⁴⁶⁴⁻⁴⁶⁶

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

Liver- or Lung-Directed Radiation

Local radiation therapies include arterial radioembolization with microspheres^{491,492,522-530} and conformal (stereotactic) external beam RT (EBRT).⁵³¹

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 3D conformal RT,

SBRT,^{425,467,468,532,533} and IMRT, which use computer imaging to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.⁵³⁴⁻⁵³⁷

Peritoneal Carcinomatosis

Approximately 17% of patients with metastatic colorectal cancer have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis.^{114,538} Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.^{114,538} 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 (upper rectal lesions only) if needed for obstruction or impending obstruction.⁵³⁹⁻⁵⁴¹ 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.^{542,543}

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.⁵⁴⁴⁻⁵⁴⁷ 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.⁵⁴⁸ 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.⁵⁴⁹ 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.^{423,544}

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.⁵⁰⁰

Any active metastatic systemic regimen can be used in an attempt to convert a patient's unresectable status to a resectable status, because 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.⁵⁵⁰⁻⁵⁵⁴ Studies have reported that chemotherapy-associated liver injury (including severe sinusoidal dilatation and steatohepatitis) is associated with morbidity and complications following hepatectomy for colorectal liver metastases.^{550,551,554,555} 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.⁵⁴⁶ 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,⁴²⁴ 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.⁴³¹ 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.⁵⁵⁶ 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.^{557,558} 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) trial⁵⁵⁷; and 4% versus 10%, $P = .08$ in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.⁵⁵⁸ 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 ($P = .026$).⁵⁵⁹

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.⁵⁶⁰ For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.⁵⁶⁰ 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 RCT compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable colorectal cancer metastatic to the liver.⁵⁶¹ 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; $P = .007$ for the cetuximab arm and 36.0 vs. 19.6 months; $P = .016$ for the control arm). A recent meta-analysis of 4 RCTs 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.⁵⁶²

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.⁵⁶³ 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.⁵⁶⁴ 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.^{554,565-567} Reported risks associated with chemotherapy include the potential for development of liver steatosis or steatohepatitis when oxaliplatin or irinotecan-containing chemotherapeutic regimens are administered.⁵⁵⁰ 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

Perioperative administration of chemotherapy is recommended for most patients undergoing liver or lung resection with the goal of increasing the likelihood that residual microscopic disease will be eradicated. In 2018, the panel revised its recommendations for treatment of synchronous liver and/or lung metastases, favoring a TNT approach to treating these patients. Neoadjuvant and/or adjuvant therapy may still be considered for patients with resectable metachronous metastases. A meta-analysis identified 3 randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.⁵⁶⁸ 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.⁵⁶⁹ Additional recent meta-analyses have also failed to observe an OS benefit with the addition of adjuvant chemotherapy in resectable metastatic colorectal cancer.^{570,571}

The choice of chemotherapy regimen in the perioperative setting is dependent on a number of factors, including the chemotherapy history of the patient, whether disease is synchronous or metachronous, whether the CRM is clear or involved (as evaluated by MRI), and the response rates and safety/toxicity issues associated with the 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.⁵⁷² 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.⁵⁷³ Furthermore, a multi-institutional phase II study investigating the feasibility and efficacy of preoperative mFOLFOX6 for patients with resectable liver metastases demonstrated the feasibility of this approach.⁵⁷⁴ Three-year OS and PFS rates were 81.9% and 47.4%, respectively.

The optimal sequencing of chemotherapy remains unclear, although the recommendations of the panel reflect a clinical trend towards use of a total neoadjuvant treatment approach for patients with synchronous metastases. Metachronous metastases may be treated with neoadjuvant and/or adjuvant systemic therapy.

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.^{426,575,576} 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.^{576,577} 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.⁵⁵⁰

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.⁵⁵⁰⁻⁵⁵⁴ 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 chemotherapy regimen to target metastatic disease; and a surgical approach (ie, staged or synchronous resection of metastases and rectal lesion). Advantages of an initial chemoRT approach include a possible decreased risk of pelvic failure following surgery, while a disadvantage is that preoperative pelvic RT 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.

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 a 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; $P = .28$).⁵⁷⁸ 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%; $P = .63$). The randomized phase III HEPATICA trial, which closed prematurely due to poor accrual, found that global quality-of-life scores were higher in patients receiving CAPEOX plus bevacizumab than those receiving CAPEOX alone after resection of liver metastases, but no conclusions could be drawn regarding the primary endpoint of DFS.⁵⁷⁹

A meta-analysis of RCTs published in 2011 demonstrated that the addition of bevacizumab to chemotherapy was 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.⁵⁸⁰ Venous thromboembolisms, however, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.⁵⁸¹ Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension, gastrointestinal hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is quite low.⁵⁸² The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those aged 65 years or older. Gastrointestinal perforation is a rare but important side effect of bevacizumab therapy in patients with colorectal cancer.^{578,583} Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to gastrointestinal perforation. The FDA recently approved a safety label warning of the risk for necrotizing fasciitis, sometimes fatal and usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation after bevacizumab use.⁵⁸⁴

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 drug⁵⁸⁵) between the last dose of bevacizumab and surgery. Re-initiation of bevacizumab should be delayed at least 6 to 8 weeks postoperatively.

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).⁵⁸⁶ 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.

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, nivolumab, ipilimumab, and vemurafenib. 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. 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.⁵⁸⁷⁻⁵⁹⁶ 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.⁵⁸⁸ 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.^{594,597} 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, 0.59–0.99; $P = .04$).⁵⁹⁷ 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.^{587,588,590,591,596} 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 genomic differences between right- and left-sided tumors⁵⁹⁸ 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,^{587,588,591,596} 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.⁵⁹⁹⁻⁶⁰² 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.⁶⁰³ A similar conclusion was drawn with respect to panitumumab.⁶⁰⁴ 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.^{603,605} Furthermore, cetuximab and panitumumab are only effective in approximately 10% to 20% of patients with colorectal cancer.^{603,605,606} 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.⁶⁰⁷⁻⁶¹⁶ 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*).^{617,618} The panel therefore strongly recommends *RAS* (*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 *RAS* 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,⁶¹⁹ and a guideline on molecular biomarkers for colorectal cancer developed by the ASCP, CAP, AMP, and ASCO also recommends *RAS* testing consistent with the NCCN recommendations.²⁸

The panel strongly recommends genotyping of tumor tissue (either primary tumor or metastasis) in all patients with metastatic colorectal cancer for

RAS and *BRAF*. The recommendation for *RAS* testing at this point is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *RAS* 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 *RAS* 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, *RAS* 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.^{620,621} For this reason, *RAS* 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 *RAS* 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.⁶²² No specific testing methodology is recommended.⁶²³ The three genes can be tested individually or as part of next-generation sequencing (NGS) panel.

***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.^{607,624} A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy,⁶⁰⁷⁻⁶¹⁶ 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.^{625,626} 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.⁶²⁷ At this time, however, the test is not recommended for prognostic reasons.

A retrospective study from De Roock et al⁶²⁸ 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.⁶²⁹ However, 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.⁶³⁰ 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.⁶³¹ 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.⁶³² However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. A meta-analysis of 8 RCTs came to the same conclusion: that tumors with *KRAS* G13D mutations are no more likely to respond to EGFR inhibitors than tumors with other *KRAS* mutations.⁶³³ 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 4.⁶³⁴ In the PRIME trial, 17% of 641 patients without *KRAS* exon 2 mutations were found to have mutations 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.⁶¹⁷ 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.⁶³⁵ 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 *RAS* 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 *RAS* 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.⁶²⁵ The NCCN Colon/Rectal Cancer Panel believes that *RAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *RAS* mutation should not be treated with either cetuximab or panitumumab.

***BRAF* V600E Mutations:** Although mutations in *RAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *RAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *RAS* 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).^{636,637} *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.⁶³⁶⁻⁶³⁸ 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,⁶³⁹⁻⁶⁴¹ 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.^{637,642} 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.⁶³⁸

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.⁶⁴³⁻⁶⁴⁵ 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%; $P = .0012$).⁶⁴⁶ 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.⁶⁴⁷

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).⁶⁴⁸ 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 RCTs 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.⁶⁴⁹

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.^{624,637,638,650-653} 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; $P = .0003$).⁶²⁴ 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.⁶³⁷ Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (CI, 0.33–0.73; $P = .001$).⁶⁵¹ 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.⁶³⁸ 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.⁶⁵⁴ 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; $P < .001$).

The phase II SWOG S1406 trial that tested a combination of vemurafenib, cetuximab, and irinotecan was thus tested in patients with *BRAF* V600E-mutated mCRC.⁶⁵⁵ Ninety-nine patients with *BRAF*-mutant, *RAS* wild-type tumors who received 1 or 2 prior regimens were randomized to irinotecan and cetuximab with or without vemurafenib. An abstract presented at the

2017 ASCO Annual Meeting reported that the primary endpoint of median PFS was improved in the vemurafenib arm (4.4 vs. 2.0 months; HR, 0.42; 95% CI, 0.26–0.66; $P < .001$). Disease response was also improved with addition of vemurafenib, with response rates of 16% versus 4% ($P = .08$) and disease control rates of 67% versus 22% ($P = .001$). Grade 3/4 adverse events that were higher in the vemurafenib arm included neutropenia (28% vs. 7%), anemia (13% vs. 0%), and nausea (15% vs. 0%).

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, unless given with a BRAF inhibitor (eg, vemurafenib). The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis⁶⁵⁶) 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, or *BRAF* status can be determined by NGS.

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%).^{657,658} Specific molecular diagnostic methods have been proposed for HER2 testing in colorectal cancer,⁶⁵⁹ and various therapeutic approaches are being tested in patients with tumors that have HER2 overexpression (eg, trastuzumab plus lapatinib, trastuzumab plus pertuzumab).^{658,660} These approaches are currently considered investigational, and enrollment in a clinical trial is encouraged.

Evidence does not support a prognostic role of HER2 overexpression.⁶⁶¹ However, initial results indicate HER2 overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.^{657,662} 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 inhibitor was similar regardless of HER2 status.⁶⁵⁷ 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, Nivolumab, and Ipilimumab: MSI Status

The percentage of stage IV colorectal tumors characterized as MSI-H (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.⁶⁶³⁻⁶⁶⁵ 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.⁶⁶⁶ 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.⁶⁶⁷

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.⁶⁶⁸

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,⁶⁶⁹ which was studied with or without the CTLA-4 blocking antibody, ipilimumab,⁶⁷⁰ in patients with metastatic colorectal cancer in the phase II, multi-cohort CheckMate-142 trial.^{671,672} One cohort of this trial included 74 patients with dMMR colorectal cancer who were treated with nivolumab. ORR for these patients was 31.1% (95% CI, 20.8–42.9) with 69% of patients having disease control for at least 12 weeks. Median duration of response had not yet been reached at the time of data collection. PFS and OS were 50% and 73%, respectively, at 1 year. Grade 3 or 4 drug-related AEs occurred in 20% of patients, with increased amylase and increased lipase most common.⁶⁷¹ Another cohort of the CheckMate-142 included 119 patients with dMMR colorectal cancer who were treated with nivolumab in combination with ipilimumab. For this cohort, ORR was 55% (95% CI, 45.2–63.8) and the disease control rate for at least 12 weeks was 80%. PFS and OS were 71% and 85%, respectively, at 1 year. In addition, significant, clinically meaningful improvements were observed in patient reported outcomes of functioning, symptoms, and quality of life. Grade 3 to

4 treatment-related AEs occurred in 32% of patients, but were manageable.⁶⁷²

While the accelerated FDA approvals for pembrolizumab, nivolumab, and nivolumab in combination with ipilimumab were for dMMR metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan,^{667,669,670} a number of the patients on the above-mentioned trials had not received all three prior therapies. For the nivolumab monotherapy cohort of the CheckMate-142 trial, 37% of patients received nivolumab in first- or second-line and 28% of patients had not received all three indicated prior therapies before treatment with nivolumab.⁶⁷¹ For the nivolumab plus ipilimumab cohort, 24% of patients received the combination in first- or second-line and 31% of patients had not received all three indicated prior therapies before treatment with nivolumab plus ipilimumab.⁶⁷² Based on these data, the panel recommends pembrolizumab, nivolumab, or nivolumab plus ipilimumab as subsequent-line treatment options in patients with metastatic MMR-deficient colorectal cancer. These therapies are only options for patients who have not previously received a checkpoint inhibitor. Clinical trials are ongoing to confirm the benefit of these drugs in this setting.

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.^{668,671-673} The most common immune-mediated side effects are to the skin, liver, kidneys, gastrointestinal tract, lungs, and endocrine systems.⁶⁷⁴⁻⁶⁷⁶ Pneumonitis, occurring in approximately 3% to 7% of patients on checkpoint inhibitor therapy, is one of the most serious side effects of PD-1 inhibitors.^{674,677-679}

Recommendations for Treatment of Resectable Synchronous Metastases

When patients present with colorectal cancer and synchronous liver only or lung only metastases, the panel now recommends a TNT approach, with choice of preoperative therapy based on the predicted status of the CRM by MRI. Upfront systemic treatment has the goal of early eradication of micrometastases, whereas the goal of short-course RT or long-course chemoRT is local control of disease prior to surgery/local therapy. Those with a predicted clear CRM should receive chemotherapy as described in the guidelines followed by short-course RT or long-course chemoRT. Those with a CRM predicted to be involved can receive 1) chemotherapy followed by long-course chemoRT or 2) short-course RT or long-course chemoRT followed by chemotherapy. As in other settings, the total perioperative therapy should not exceed 6 months. Restaging should be performed before resection.

There is NCCN Member Institutional variation in the choice of neoadjuvant therapy approach for resectable synchronous metastases. Standard practice at some institutions is to start with chemotherapy and then to stratify further treatment based on the degree of metastatic disease and the response to initial therapy. If the risk of distant failure is deemed to be the greater concern, resection would be the next course of treatment. If local failure appears more likely, then RT would be given before surgery.

Resection of the primary tumor and liver can be done in a simultaneous or staged approach following neoadjuvant treatment.⁶⁸⁰⁻⁶⁸⁷ 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.⁶⁸⁸⁻⁶⁹⁰ In addition, neoadjuvant short-course radiation

of T1-T3 primary rectal tumors is an option in this setting.⁶⁹¹ 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.

If a patient is treated with short-course RT, surgery should be within 1 week or delayed 6 to 8 weeks. For the remaining patients, 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 synchronous liver only or lung only metastases or who are medically inoperable are treated with intensive 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 should be considered for patients with potentially convertible disease.⁶⁹² These patients should be re-evaluated for resection after 2 months of chemotherapy and every 2 months thereafter while undergoing such therapy. Patients who become resectable should receive short-course RT (preferred) or long-course chemoRT followed by immediate or delayed staged or synchronous resection and/or local therapy for metastases and resection of the rectal lesion. Patients who remain unresectable after initial systemic therapy should proceed to second-line systemic therapy for advanced or metastatic disease. Short-course RT (preferred) or long-course chemoRT can be given prior to second-line therapy if progression of the primary tumor occurred during first-line treatment.

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.⁶⁹³ Other retrospective analyses have also shown a potential benefit.^{694,695} 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.⁶⁹⁶ 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,⁴⁶³ 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.⁶⁹⁷ However, a different systematic review concluded that, while data are not strong, resection of the primary tumor may provide a survival benefit.⁶⁹⁸ Another systematic review and meta-analysis identified 5 studies that compared open to laparoscopic palliative colectomies in this setting.⁶⁹⁹ The laparoscopic approach resulted in shorter lengths of hospital stays ($P < .001$), fewer postoperative complications ($P = .01$), 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 is therefore not recommended. Diversion can be considered for obstructing lesions.

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](#)).

Recommendations for Treatment of Metachronous Metastases

In a single-institution, retrospective analysis of 735 patients with stage II/III rectal cancer treated with preoperative chemoRT followed by TME, the 5-year rates of liver and lung recurrences were 6.3% and 10.2%, respectively.⁷⁰⁰ Resection of liver-only and lung-only recurrences resulted in comparable survival (5.3 years and 5.1 years, respectively; $P = .39$).

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.^{701,702} 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.⁷⁰³ 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.⁷⁰⁴

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) of *RAS* and *BRAF* genotype should be performed (see *Perioperative Cetuximab and Panitumumab for Resectable Metastatic Disease: 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 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](#)). In the case of liver metastases only, HAIC 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.⁷⁰⁵ Quality of life is an outcome that is rarely measured but is of unquestioned clinical relevance.⁷⁰⁶ 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.⁷⁰⁶ PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.⁷⁰⁶⁻⁷⁰⁸ GRUPO Español Multidisciplinar en Cáncer Digestivo (GEMCAD) recently proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.⁷⁰⁹

A recent study, in which individual patient data from 3 RCTs 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).⁷⁰⁷ 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.^{710,711} 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,⁷¹² and a recent study found that 95% of recurrences occurred in the first 5 years.⁷¹³

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 studies⁷¹⁴⁻⁷¹⁶ and in multiple meta-analyses of RCTs designed to compare low-intensity and high-intensity programs of surveillance.⁷¹⁷⁻⁷²¹ In the final analysis of the 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.²⁷⁶ 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.⁷²²

Results from a recent RCT 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).⁷²³ 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.⁷²³

The CEAwatch trial compared usual follow-up care to CEA measurements every 2 months, with imaging performed if CEA increases were seen

twice, in 3223 patients treated for non-metastatic colorectal cancer at 11 hospitals in the Netherlands.⁷²⁴ 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. However, no OS or disease-specific survival benefit was seen.⁷²⁵ Another randomized trial of 1228 patients found that more intensive surveillance led to earlier detection of recurrences than a less intensive program (less frequent colonoscopy and liver ultrasound and the absence of an annual chest x-ray) but also did not affect OS.⁷²⁶

The randomized phase III PRODIGE 13 trial will compare 5-year OS after intensive radiologic 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.⁷²⁷ Meta-analyses support the conclusion that more intensive surveillance of patients with resected colorectal cancer results in earlier detection of recurrences, without any effect on survival.^{718,719}

Patients who had resection of metastatic colorectal cancer can undergo subsequent curative-intent resection of recurrent disease (see *Surgical Management of Colorectal Metastases*, above), and therefore should undergo post-treatment surveillance. 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.⁷²⁸

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 panel recommendations for post-treatment surveillance pertain to patients who have undergone successful treatment (ie, no known residual disease) and are separated into three groups: 1) those who received transanal local excision only; 2) patients with stage I disease and full surgical staging; and 3) patients with stage II through IV disease.

For all three groups, 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.⁷²⁹ More frequent colonoscopies may be indicated in patients who present with colorectal cancer before age 50.⁷²⁹ 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,⁷³⁰ 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.⁷²⁹

Proctoscopy with EUS or MRI is recommended to evaluate the rectal anastomosis for local recurrence in patients treated with transanal local excision only. 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.⁷³¹ In these 112

patients, 20 anoscopies, 44 proctoscopies, and 495 flexible sigmoidoscopies were performed.

For the stage II-IV group, history and physical examination is recommended 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,⁷³² 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.^{717,732,733} 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.^{717,734} 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.⁷³⁵ Those scanned once per year survived a median of 54 months versus 43 months for those scanned 3 to 4 times per year ($P = .08$), 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.^{734,736} 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).^{737,738} 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.^{713,739} The American Society of Colon and Rectal Surgeons also released surveillance guidelines, which are also very similar to NCCN surveillance recommendations.⁷⁴⁰ 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.

All patients with rectal cancer should be counseled for family history. For patients with suspected Lynch syndrome, FAP, or attenuated FAP, see the [NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal](#).

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.⁷⁴¹ 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 cutoff of 10 ng/mL were calculated at 68% (95% CI, 53%–79%) and 97% (95% CI,

90%–99%), respectively.^{742,743} In the first 2 years post-resection, a CEA cutoff of 10 ng/mL is estimated to detect 20 recurrences, miss 10 recurrences, and result in 29 false positives.

A PET/CT scan may be considered in the scenario of an elevated CEA with negative, good-quality CT scans. A systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.⁷⁴⁴ 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. An analysis of outcomes of 88 patients treated for colorectal cancer under surveillance who had normal or equivocal conventional imaging results with an elevated CEA found that PET/CT had a sensitivity of 88% and a specificity of 88% for the detection of recurrences.⁷⁴⁵

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,⁷⁴⁶ 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.⁷⁴⁷ In a more recent, single-institution, retrospective analysis of 735 patients with stage II/III rectal cancer treated with preoperative chemoRT followed by TME, locoregional recurrence rate at 5 years was 4.6%, occurring at a median 24.7 months.⁷⁰⁰

The panel recommends that patients with unresectable lesions be treated with chemotherapy with or without radiation according to their ability to tolerate therapy. Debulking that results in gross residual cancer is not recommended. Potentially resectable isolated pelvic/anastomotic recurrence should be managed with preoperative chemoRT followed by resection (preferred if chemoRT was not previously given) or by resection followed by adjuvant chemoRT. IORT or brachytherapy should be considered with resection if it can be safely delivered.^{418,748-750}

A recent retrospective study found that re-resection was not associated with improved survival in patients with isolated locoregional recurrence (3.6 years with surgery vs. 3.2 years without surgery; $P = .353$).⁷⁰⁰ Older studies have shown that patients with disease recurrence at the anastomotic site are more likely to be cured following re-resection than those with an isolated pelvic recurrence.^{751,752} 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.⁷⁵² Studies of patients who previously received pelvic radiation show that re-irradiation can be effective, with acceptable rates of toxicity.⁷⁵³⁻⁷⁵⁵ 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.⁷⁵³ IMRT can be used in this setting of re-irradiation.

Survivorship

The panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.⁷⁵⁶ 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](#)). Additional health monitoring 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.⁷⁵⁷

Other recommendations include monitoring for late sequelae of rectal cancer or of the treatment of rectal cancer, such as bowel function changes (eg, patients with stoma).⁷⁵⁸⁻⁷⁶³ Urogenital dysfunction following resection and/or pelvic irradiation is common.^{758,764-766} 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.⁷⁶⁷⁻⁷⁷² Specific management interventions to address side effects of colorectal cancer have been described,⁷⁷³ and a survivorship care plan for patients with colorectal cancer has been published.⁷⁷⁴

The [NCCN Guidelines for Survivorship](#) 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 American Cancer Society (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.⁷⁵⁷

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.⁷⁷⁵ 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.⁷⁷⁶ 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.⁷⁷⁷ In addition, recent evidence suggests that both pre- and post-diagnosis physical activity decrease 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.⁷⁷⁸ Similar results were seen in other studies and in recent meta-analyses of prospective studies.⁷⁷⁹⁻⁷⁸²

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/m² or greater had an increased risk of disease recurrence and death.⁷⁸³ Recent analyses confirm the increased risk for recurrence and death in obese patients.⁷⁸⁴ 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.⁷⁸⁵ 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.⁷⁸⁶ A meta-analysis of prospective cohort studies found that pre-diagnosis obesity was associated with increased colorectal cancer-specific and all-cause mortality.⁷⁸⁷ Other analyses confirm the increased risk for recurrence and death in obese patients.^{784,788-791}

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.⁷⁹² 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/m².⁷⁹³ However, several possible explanations for this so-called “obesity paradox” have been suggested.⁷⁹⁴ 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](#)).

A diet consisting of more fruits, vegetables, poultry, and fish, less red meat, more whole grains, and fewer refined grains and concentrated

sweets was found to be associated with an improved outcome in terms of cancer recurrence or death.⁷⁹⁵ 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.⁹⁴

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.⁷⁹⁶ 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.⁷⁹⁷ 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).⁸⁷

A discussion of lifestyle characteristics that may be associated with a decreased risk of colorectal cancer recurrence, such as those recommended by the ACS,⁷⁹⁸ 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.⁷⁹⁹

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; eliminate or limit alcohol consumption to no more than 1 drink/day for women and 2 drinks/day for men; and quit smoking.⁸⁰⁰ 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.⁸⁰¹

Secondary Chemoprevention for Colorectal Cancer Survivors

Limited data suggest a link between post-colorectal-cancer-diagnosis statin use and increased survival.^{111,802,803} 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; $P < .001$).⁸⁰²

Abundant data show that low-dose aspirin therapy after a diagnosis of colorectal cancer decreases the risk of recurrence and death.⁸⁰⁴⁻⁸¹⁰ 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).⁸⁰⁴ 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.^{806,811-816} In addition, a meta-analysis of 15 RCTs showed that while non-aspirin NSAIDs were better for preventing recurrence, low-dose aspirin was safer and thereby had a more favorable risk to benefit profile.⁸¹⁷

Based on these data, the panel believes that survivors of colorectal cancer can consider taking 325 mg aspirin daily 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.⁸¹⁸

Summary

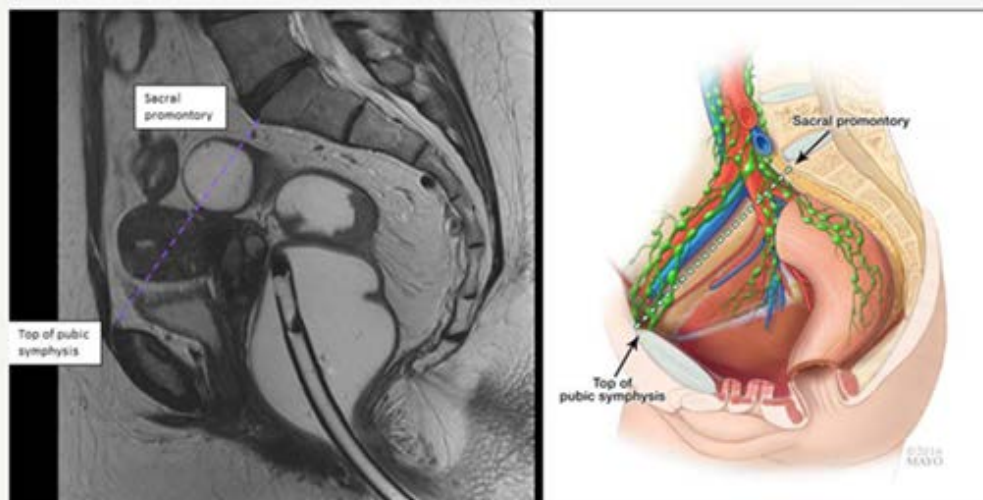
The NCCN Rectal Cancer Panel believes that a multidisciplinary approach, including representation from gastroenterology, medical oncology, surgical oncology, radiation oncology, and radiology is necessary for treating patients with rectal cancer. Adequate pathologic assessment of the resected lymph nodes 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 local 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 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.

Figure 1. Definition of Rectum



“Rectum” is defined as the portion of bowel located below the pelvic inlet (an imaginary line drawn from the sacral promontory to the top of the pubic symphysis) as determined by a dedicated MRI of the pelvis

- Upper rectum: above the **anterior peritoneal reflection**
- Mid-rectum: at the anterior peritoneal reflection
- Lower-rectum: below the anterior peritoneal reflection

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