National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Rectal Cancer

Version 2.2025 — March 31, 2025

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NCCN Rectal Cancer Panel Members
Summary of the Guidelines Updates

Clinical Presentations and Primary Treatment:
- Pedunculated or Sessile Polyp (Adenoma) with Invasive Cancer (REC-1)
- Workup for Rectal Cancer Without Suspected or Proven Distant Metastases/Rectal Cancer With Suspected or Proven Distant Metastases (REC-2)
- Staging and Treatment for Rectal Cancer Without Suspected or Proven Distant Metastases (REC-3)
- Treatment After Transanal Local Excision of T1, N0 (REC-4)
- Treatment After Transabdominal Resection of T1–2, N0 (REC-5)

Treatment for pMMR/MSS Rectal Cancer
- pMMR/MSS:T3, N Any; T1–2, N1–2; T4, N Any or Locally Unresectable or Medically Inoperable (REC-6)
- pMMR/MSS: Suspected or Proven Metastatic Synchronous Adenocarcinoma (REC-7)

Surveillance and Recurrence
- Surveillance Following Operative Management (REC-10)
- Surveillance Following Nonoperative Management (REC-10A)
- Recurrence and Workup (REC-11)
- pMMR/MSS: Metachronous Metastases (REC-12)

Treatment for dMMR/MSI-H Rectal Cancer
- dMMR/MSI-H or *POLE/POLD1* Mutation: T3, N Any; T1–2, N1–2; T4, N Any or Locally Unresectable or Medically Inoperable (REC-14)
- dMMR/MSI-H or *POLE/POLD1* Mutation: Suspected or Proven Metastatic Synchronous Adenocarcinoma (REC-15)
- dMMR/MSI-H or *POLE/POLD1* Mutation: Resectable Metachronous Metastases (REC-17)

Principles of Imaging (REC-A)
Principles of Pathologic and Molecular Review (REC-B)
Principles of Surgery and Locoregional Therapies (REC-C)
Principles of Perioperative Therapy (REC-D)
Principles of Radiation Therapy (REC-E)
Systemic Therapy for Advanced or Metastatic Disease (REC-F)
Principles of Survivorship (REC-G)
Principles of Nonoperative Management (REC-H)
Staging (ST-1)
Abbreviations (ABBR-1)

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2025 of the NCCN Guidelines for Rectal Cancer from Version 1.2025 include:

REC-2
- Workup
  - Rectal cancer without suspected or proven distant metastases
    - Bullet 3 added: Consider PIK3CA testing for stage II-III
- Footnote k added: Testing for DPYD genetic variants should be considered prior to fluoropyrimidine therapy. After discussions regarding risk assessment, patients may choose DPYD genetic testing. However, no specific test is recommended at this time and there are insufficient data to inform dose adjustments for many of the DPYD variants. See DPYD Testing and Fluoropyrimidine-Associated Toxicity Discussion section in the NCCN Guidelines for Colon Cancer for more information.

REC-3A
- Footnote t added: For stage II-III disease, if PIK3CA mutation, add aspirin 100-162 mg PO daily for 3 years following surgery. (Also for REC-5, REC-6, REC-14)

REC-16
- Footnote xx modified: Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, dostarlimab-gxly, cemiplimab-rwlc, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr. *Combination PD-L1/CTLA-4 blockade has been associated with improved survival in unresectable or metastatic CRC, but also higher toxicity.* (Also for REC-17)

REC-F 4 of 13
- Footnote w modified: Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, dostarlimab-gxly, cemiplimab-rwlc, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr. Nivolumab + ipilimumab combination is category 2B when intensive therapy is not recommended due to toxicity concerns. *Combination PD-L1/CTLA-4 blockade has been associated with improved survival in unresectable or metastatic CRC, but also higher toxicity.* Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab. This applies to all areas of the Guideline where nivolumab is listed.

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Updates in Version 1.2025 of the NCCN Guidelines for Rectal Cancer from Version 5.2024 include:

TOC
- Reorganized and updated section headers

REC-2
- Rectal cancer with suspected or proven distant metastases
  - Qualifier modified: Deficient MMR (dMMR)/MSI-high (MSI-H) or POLE/POLD1 mutation *with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb]* (Also for REC-3A, REC-11, REC-11A, REC-14, REC-15, REC-16, REC-17, REC-F)

REC-3
- Rectal cancer without suspected or proven distant metastases
  - This page has been extensively revised and split into two pages
  - Footnote removed: In select cases (eg, requiring an APR), these may be treated with neoadjuvant therapy with the goal of organ preservation (as in the bottom pathway in the above flowchart).

REC-3A
- New page added for additional content from REC-3

REC-4
- Pathologic findings after transanal local excision for T1, N0
  - Pathway for pT1, NX with high-risk features or pT2, NX has been revised.
- Footnote removed: A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged ≥70 years has not been proven. (Also for REC-5)
- Footnote t revised: Circulating tumor DNA (ctDNA) is ~~emerging as~~ a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care *and treatment decision-making* ~~is~~ *are* not recommended based on ctDNA results. Participation in clinical trials is encouraged. (Also for REC-5)

REC-6
- pMMR/MSS T3, N any; T1–2, N1–2; T4, N any or Locally unresectable or medically inoperable: Total Neoadjuvant Therapy
  - Restage with sigmoidoscopy ± MRI
    - Pathway modified: Tumor regression ≤20% *or high-risk features remain*
      - Language modified:
        - *Consider* long-course chemo/RT
        - *Consider* short-course RT

REC-8
- pMMR/MSS Resectable synchronous liver only and/or lung only metastases: Neoadjuvant Treatment
  - Top pathway:
    - Chemotherapy: FOLFIRINOX added as an option
    - Language modified: Consider holding radiation if ~~complete~~ response to neoadjuvant therapy
  - Footnote aa modified: Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or stereotactic body RT [SBRT]). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E). *For small lesions (≤3 cm), thermal ablation is equivalent to resection.* (Also for REC-9, REC-12, REC-13, REC-16, REC-17)

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Updates in Version 1.2025 of the NCCN Guidelines for Rectal Cancer from Version 5.2024 include:

REC-9
- pMMR/MSS Unresectable synchronous liver only and/or lung only metastases or medically inoperable
  - Footnote bb added: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. (Also for REC-13)
  - Footnote removed: An FDA-approved biosimilar is an appropriate substitute for bevacizumab. (Also for REC-13, REC-F)

REC-10
- Surveillance Following Operative Management
  - Stage II–IV
    - Colonoscopy recommendation modified: Colonoscopy in 1 y after surgery except if no *complete* preoperative colonoscopy ~~due to obstructing lesion~~, *then* colonoscopy in 3–6 mo
    - Footnote ee revised: *ctDNA is not recommended for surveillance.* ~~ctDNA is emerging as a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care is not recommended based on ctDNA results. Participation in clinical trials is encouraged.~~

REC-11
- Recurrence
  - Documented metachronous metastases by CT, MRI, and/or biopsy
    - dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb], footnote added: Patients who are not candidates for immunotherapy should be treated as recommended for pMMR/MSS disease. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

REC-12
- pMMR/MSS Resectable Metachronous Metastases
  - Pathways modified: Resection ~~(preferred)~~ and/or Local therapy (Also for REC-17)
  - Footnote nn modified: Hepatic artery infusion ± systemic *chemotherapy (VEGFi contraindicated)* ~~5-FU/leucovorin~~ (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure. (Also for REC-13, REC-17)

REC-13
- Footnote removed: An FDA-approved biosimilar is an appropriate substitute for trastuzumab. (Also for REC-F)

REC-15
- Footnote mm modified: Patients ~~with dMMR/MSI-H or POLE/POLD1 mutation disease~~ who are not candidates for immunotherapy should be treated as recommended for pMMR/MSS disease. (REC-17)

REC-16
- Checkpoint inhibitor immunotherapy options added to footnote vv: Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, ~~or~~ dostarlimab-gxly, *cemiplimab-rwlc, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr.* (Also for REC-17)

REC-17
- dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb], Resectable Metachronous Metastases
  - No previous immunotherapy; Initial Treatment
    - The order of treatment options has been flipped with checkpoint inhibitor immunotherapy on top

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Updates in Version 1.2025 of the NCCN Guidelines for Rectal Cancer from Version 5.2024 include:

REC-A 1 of 4
- Principles of Imaging
  - Initial Workup/Staging
    - Bullet 2 revised: Pelvis MRI with or without contrast or endorectal ultrasound (only if MRI is contraindicated ~~[eg, pacemaker]~~)

REC-B 6 of 11
- Principles of Pathologic and Molecular Review
  - HER2 Testing
    - Bullet 3 revised: Anti-HER2 therapy with signal transduction inhibition (eg, trastuzumab/pertuzumab, trastuzumab/tucatinib, trastuzumab/lapatinib) is ~~only~~ indicated *for patients with HER2 IHC 3+, IHC2+/ISH+, or NGS amplified cancer that are also RAS and BRAF wild-type.* ~~in HER2-amplified tumors that are also RAS and BRAF wild-type.~~

REC-B 7 of 11
- POLE/POLD1
  - Bullet 4 modified: NGS of CRCs arising in patients with either germline or somatic ED PVs demonstrate an ~~ultramutator~~ *ultra-hypermutated* phenotype identified as extremely high tumor mutational burden (TMB>*50 mut/Mb* ~~>100 mut/Mb~~).

REC-C 1 of 8
- Principles of Surgery and Locoregional Therapies
  - TME
    - Sub-bullets updated:
      - Minimally invasive approaches (eg, laparoscopic, robotic) for resection of rectal cancer have been shown to be safe.
      - There are no significant differences in disease-free survival and recurrence rates with minimally invasive approaches when compared to open resection.
    - Sub-bullet removed: Some studies have shown that minimally-invasive approaches (e.g. laparoscopic, robotic) are associated with similar short- and long-term outcomes when compared to open surgery, whereas other studies have shown that laparoscopy is associated with higher rates of circumferential margin positivity and incomplete TME. Therefore, minimally invasive resection may be considered based on the following principles

REC-C 3 of 8
- External Beam Radiation Therapy (EBRT)
  - Sub-bullet 2, diamond 2 revised: ~~Consider SBRT for patients with oligometastatic disease.~~ *SBRT or other hypofractionated regimens with BED10>100 Gy are preferred in the context of oligometastatic disease to provide durable local control. Final dosing should also take into account adjacent normal organs.*
- Hepatic Arterial Infusion (HAI) Eligibility
  - Bullet 10 revised: HAI chemotherapy cannot be delivered with concurrent bevacizumab *or other VEGF inhibitors*

REC-C 6 of 8
- References updated

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Updates in Version 1.2025 of the NCCN Guidelines for Rectal Cancer from Version 5.2024 include:

REC-E 1 of 2
- Principles of Radiation Therapy
  - General Principles
    - Bullet 2 revised: In patients with a limited number of liver or lung metastases, ablative 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.~~ *Ablative radiotherapy can be considered for patients with unresectable metastasis or in patients preferring a nonoperative approach.*
  - Treatment Information
    - Bullet 6 revised: *SBRT or other hypofractionated regimens with BED10>100 Gy are preferred in the context of oligometastatic disease to provide durable local control. Final dosing should also take into account adjacent normal organs.* ~~SBRT can be used alone or in conjunction with other metastatic-directed therapies for patients with oligometastatic disease.~~ SBRT can be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver/lung and liver/lung radiation tolerance can be respected. There should be no other systemic disease or it should be minimal and addressed in a comprehensive management plan. ~~RT dosing to consider, depending on the ability to meet normal organ constraints and underlying liver/lung function:~~
      - ~~SBRT: 30–60 Gy (typically in 3–5 fractions).~~
      - ~~Hypofractionation: 37.5–67.5 Gy in 10–15 fractions.~~

REC-E 2 of 2
- Target Volumes
  - RT dosing revised: Small bowel dose should be limited to ~~50~~ *Dmax 55* Gy, V45 Gy should be ~~<195~~ *≤150* cc ~~for a bowel bag avoidance~~, or V~~15~~ *50* should be ~~<120~~ *≤30* cc for individual small bowel loops, if possible.
    - Reference added: Alvarez JA, Shi Q, Dasari A, et al. Alliance A022104/NRG-GI010: The Janus Rectal Cancer Trial: a randomized phase II/III trial testing the efficacy of triplet versus doublet chemotherapy regarding clinical complete response and disease-free survival in patients with locally advanced rectal cancer. Supplement 2. Protocol update to Alliance A022104. BMC Cancer 2024;24:901.

REC-F 1 of 13
- Continuum of Care - Systemic Therapy for Advanced or Metastatic Disease
  - The initial systemic therapy algorithms have been revised and updated to a table format.
    - Initial Therapy
      - Intensive Therapy Recommended
        - Encorafenib + (cetuximab or panitumumab) + FOLFOX regimen added as a category 2A recommendation for BRAF V600E mutation positive

REC-F 2 of 13
- Second-line and Subsequent Therapy Options (if not previously given)
  - Biomarker-directed therapy
    - Encorafenib + (cetuximab or panitumumab) + FOLFOX regimen added as a category 2B recommendation for BRAF V600E mutation positive

REC-F 3 of 13
- Any line of therapy: dMMR/MSI-H or POLE/POLD1 mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb]
  - Treatment option added for top and bottom pathways: or Nivolumab + ipilimumab (if checkpoint inhibitor monotherapy was previously received)

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Updates in Version 1.2025 of the NCCN Guidelines for Rectal Cancer from Version 5.2024 include:

REC-F 4 of 13
- Footnotes
  - Footnote c added: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. (Also for REC-F 5 through 9 of 13)
  - Footnote s added: BRAF V600E regimen may be given with FOLFOX as subsequent line therapy if no previous treatment with oxaliplatin or BRAF-targeting regimen.
  - Footnote w modified: Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, ~~or~~ dostarlimab-gxly, c*emiplimab-rwlc, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr.* Nivolumab + ipilimumab combination is category 2B when intensive therapy is not recommended due to toxicity concerns. Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab. This applies to all areas of the Guideline where nivolumab is listed.

REC-F 8 of 13 and **REC-F 9 of 13**
- Regimen and dosing updated

REC-F 10 of 13 through **REC-F 13 of 13**
- References updated

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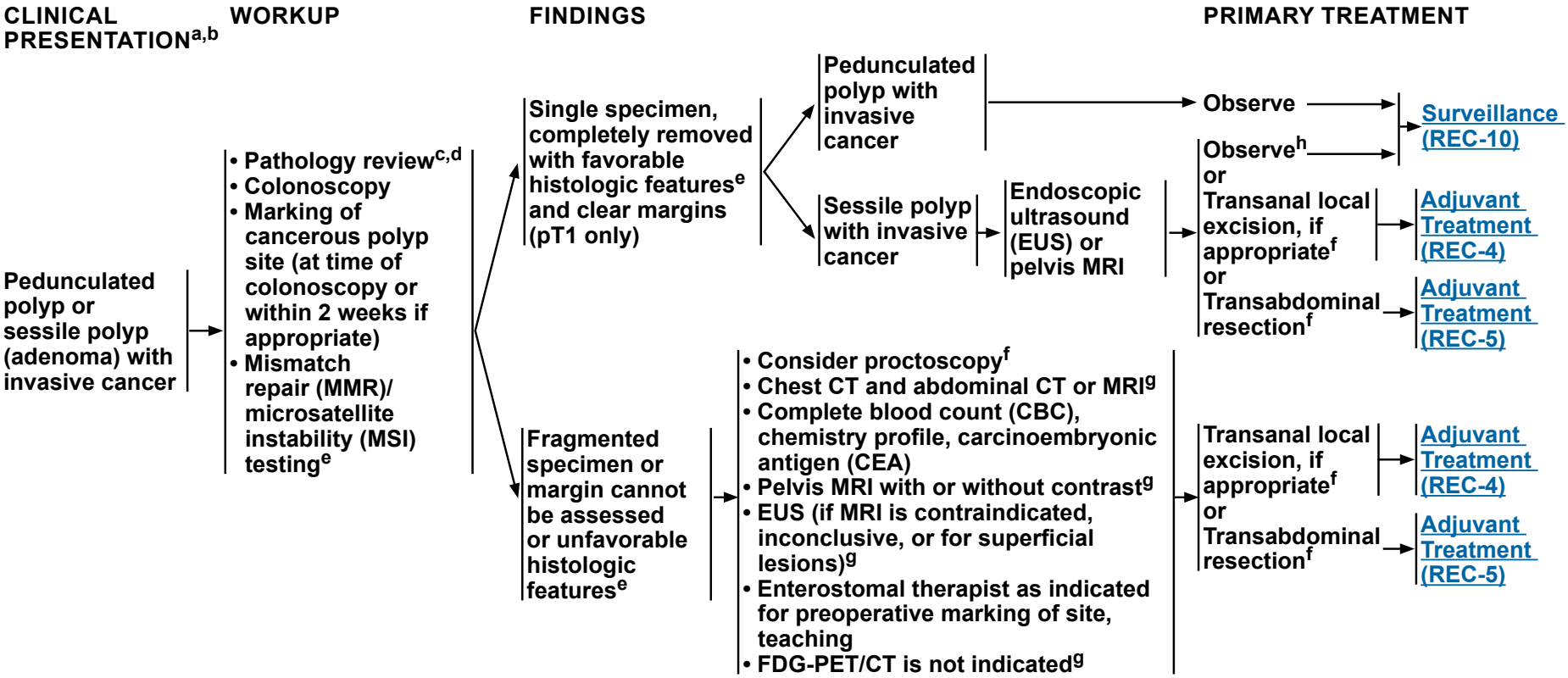

[a] All patients with rectal cancer should be counseled for family history. Patients with suspected Lynch syndrome (LS), familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[b] For melanoma histology, see the NCCN Guidelines for Melanoma: Cutaneous.
[c] Confirm the presence of invasive cancer (pT1). pTis has no biological potential to metastasize.
[d] It has not been established if molecular markers (other than MSI-H/dMMR) are useful in treatment determination (predictive markers) and prognosis. Compton CC, et al. Arch Pathol Lab Med 2000;124:979-994.
[e] Principles of Pathologic Review (REC-B).
[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[h] 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 pedunculated malignant polyps. See Principles of Pathologic Review (REC-B) - Endoscopically removed malignant polyp.

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

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CLINICAL PRESENTATION[a,b] | **WORKUP[k]**

Rectal cancer without suspected or proven distant metastases[i,j] →

- Biopsy
- MMR/MSI testing[e]
- Consider *PIK3CA* testing for stage II-III
- Pathology review
- Colonoscopy
- Consider proctoscopy[f]
- Chest CT and abdominal CT or MRI[g]
- CBC, chemistry profile, CEA
- Pelvis MRI with or without contrast[g]
- Endorectal ultrasound (if MRI is contraindicated or inconclusive, or for superficial lesions)[g]
- Enterostomal therapist as indicated for preoperative marking of site, teaching
- FDG-PET/CT is not indicated[g]
- Multidisciplinary team evaluation, including formal surgical evaluation
- Fertility risk discussion/counseling in appropriate patients

→ REC-3

Rectal cancer with suspected or proven distant metastases[i] →

- Colonoscopy
- Consider proctoscopy
- Chest CT and abdominal CT or MRI[g]
- Pelvis MRI with or without contrast[g]
- CBC, chemistry profile, CEA
- Molecular testing, including[e,l]:
  - *RAS* and *BRAF* mutations; HER2 amplifications; MMR or MSI status (if not previously done)
  - Testing should be conducted as part of broad molecular profiling, which would identify rare and actionable mutations and fusions such as *POLE/POLD1*, *RET*, and *NTRK*.
- Biopsy, if clinically indicated
- Consider FDG-PET/CT (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases[g]
  - Consider MRI of liver for patients who are potentially resectable
- If potentially resectable, then multidisciplinary team evaluation, including a surgeon experienced in the resection of hepatobiliary or lung metastases

→ **Proficient MMR (pMMR)/ microsatellite stable (MSS)** → REC-7

→ **Deficient MMR (dMMR)/MSI-high (MSI-H) or *POLE/ POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb]** → REC-15

[a] All patients with rectal cancer should be counseled for family history. Patients with suspected LS, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[b] For melanoma histology, see the NCCN Guidelines for Melanoma: Cutaneous.
[e] Principles of Pathologic Review (REC-B).
[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[i] For tools to aid optimal assessment and care 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] Testing for *DPYD* genetic variants should be considered prior to fluoropyrimidine therapy. After discussions regarding risk assessment, patients may choose *DPYD* genetic testing. However, no specific test is recommended at this time and there are insufficient data to inform dose adjustments for many of the *DPYD* variants. See *DPYD* Testing and Fluoropyrimidine-Associated Toxicity Discussion section in the NCCN Guidelines for Colon Cancer for more information.
[l] Tissue- or blood-based NGS panels have the ability to pick up rare and actionable mutations and fusions.

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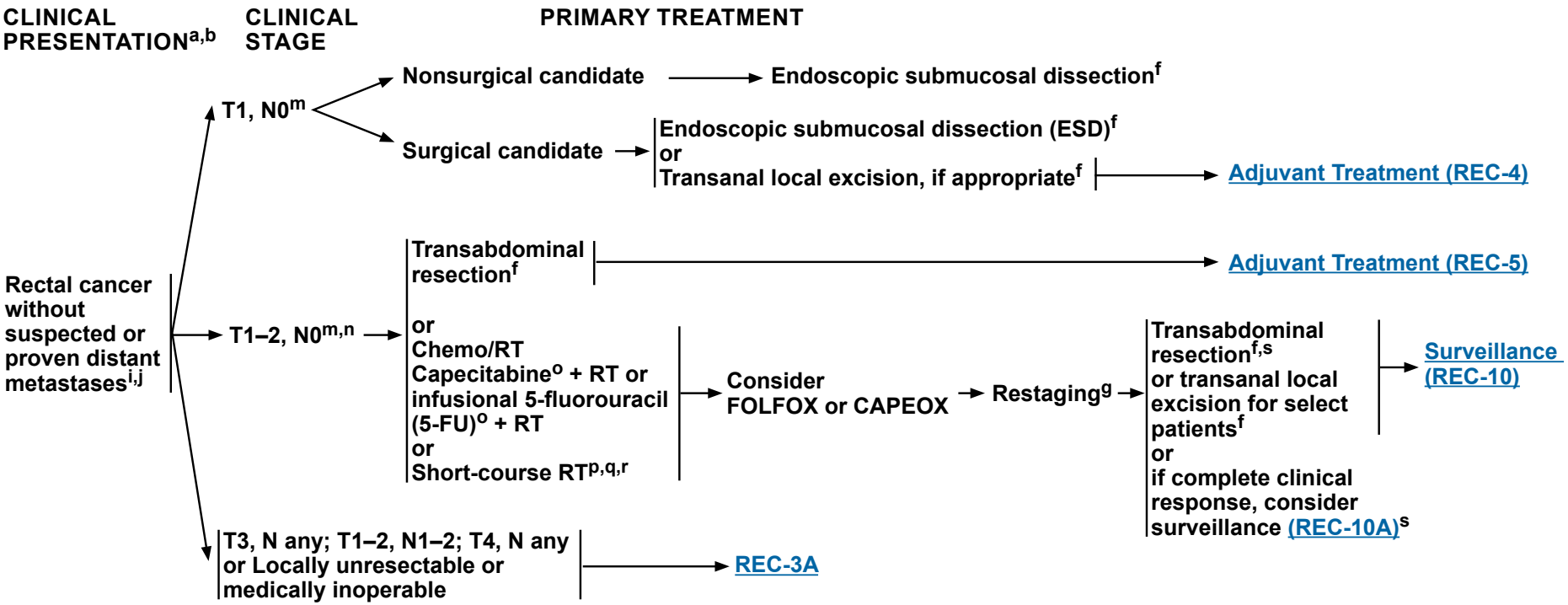

[a] All patients with rectal cancer should be counseled for family history. Patients with suspected LS, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[b] For melanoma histology, see the NCCN Guidelines for Melanoma: Cutaneous.
[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[i] For tools to aid optimal assessment and care 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.
[m] T1–2, N0 should be based on assessment of pelvis MRI (preferred) or endorectal ultrasound.
[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] Principles of Radiation Therapy (REC-E).
[q] 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.
[r] While short-course RT can be considered for preoperative radiation, for high-risk rectal cancer (clinical tumor stage cT4a or cT4b, extramural vascular invasion (EMVI), clinical nodal stage cN2, involved mesorectal fascia (MRF), or enlarged lateral lymph nodes considered to be metastatic), the 5-year follow-up of the RAPIDO trial now indicates a statistically higher locoregional recurrence rate (10%) in the experimental arm of short-course RT → chemotherapy → surgery versus control arm (6%) of chemoRT → surgery → adjuvant chemotherapy.
[s] In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination (DRE), rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) 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 (NOM) should involve a careful discussion with the patient of their risk tolerance. See Principles of Nonoperative Management (REC-H).

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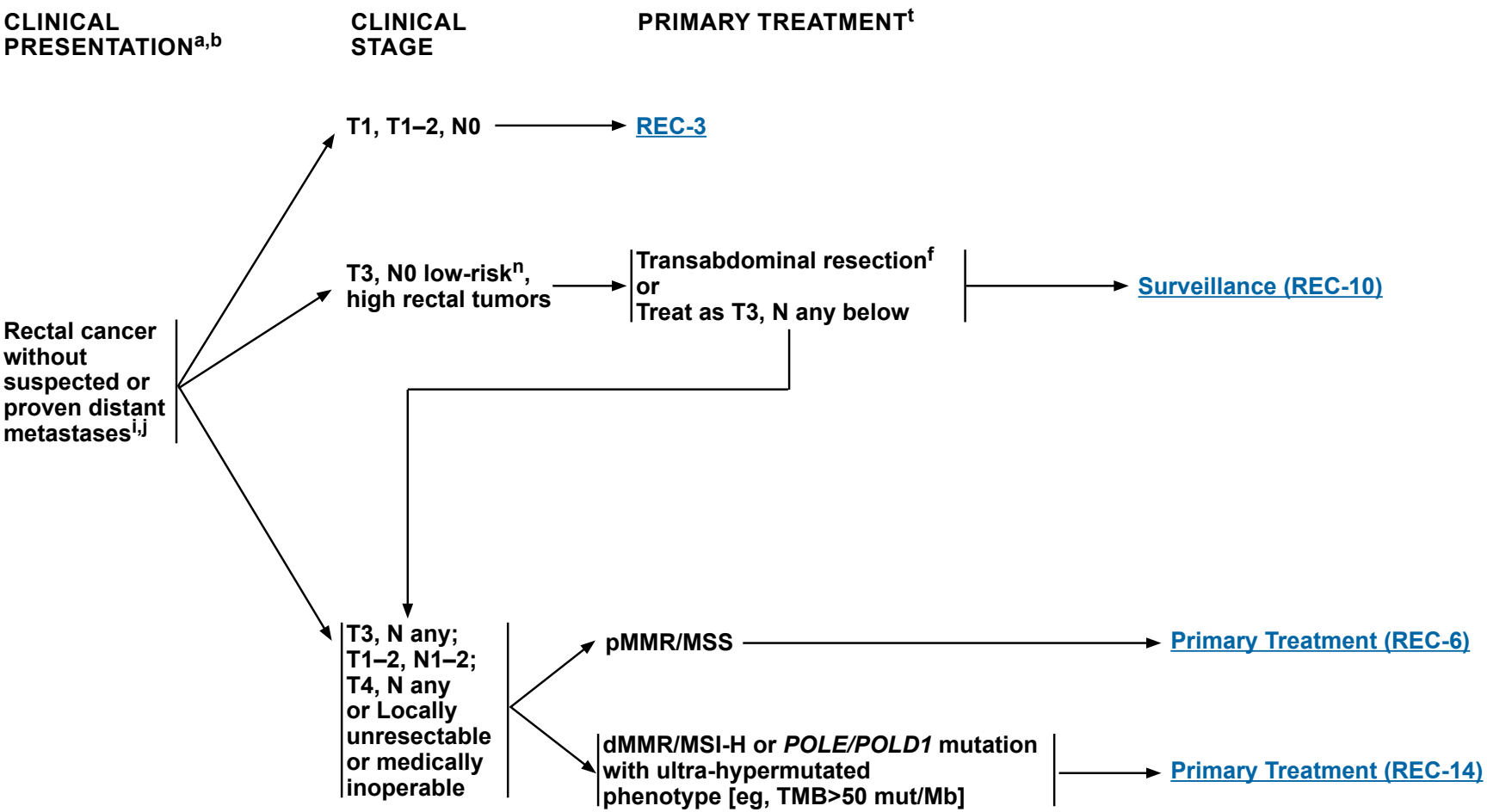

[a] All patients with rectal cancer should be counseled for family history. Patients with suspected LS, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[b] For melanoma histology, see the NCCN Guidelines for Melanoma: Cutaneous.
[f] Principles of Surgery and Locoregional Therapies (REC-C).
[i] For tools to aid optimal assessment and care 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.
[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).
[t] For stage II-III disease, if *PIK3CA* mutation, add aspirin 100-162 mg PO daily for 3 years following surgery.

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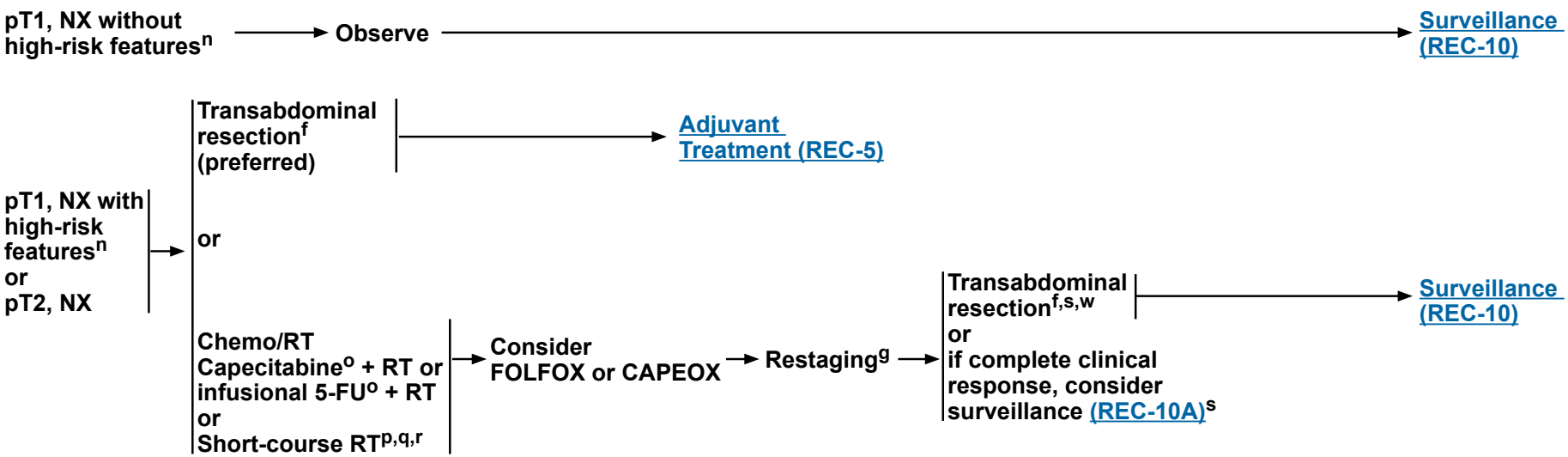
PATHOLOGIC FINDINGS AFTER TRANSANAL LOCAL EXCISION FOR T1, N0

ADJUVANT TREATMENT[g,p,u,v] (UP TO 6 MO PERIOPERATIVE TREATMENT)



[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[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] Principles of Radiation Therapy (REC-E).
[q] 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.
[r] While short-course RT can be considered for preoperative radiation, for high-risk rectal cancer (clinical tumor stage cT4a or cT4b, EMVI, clinical nodal stage cN2, involved MRF, or enlarged lateral lymph nodes considered to be metastatic), the 5-year follow-up of the RAPIDO trial now indicates a statistically higher locoregional recurrence rate (10%) in the experimental arm of short-course RT → chemotherapy → surgery versus control arm (6%) of chemoRT → surgery → adjuvant chemotherapy.
[s] In those patients who achieve a complete clinical response with no evidence of residual disease on DRE, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) 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 NOM should involve a careful discussion with the patient of their risk tolerance. See Principles of Nonoperative Management (REC-H).
[u] Principles of Perioperative Therapy (REC-D).
[v] Circulating tumor DNA (ctDNA) is a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care and treatment decision-making are not recommended based on ctDNA results. Participation in clinical trials is encouraged.
[w] For select patients who may be candidates for intraoperative RT (IORT), see Principles of Radiation Therapy (REC-E).

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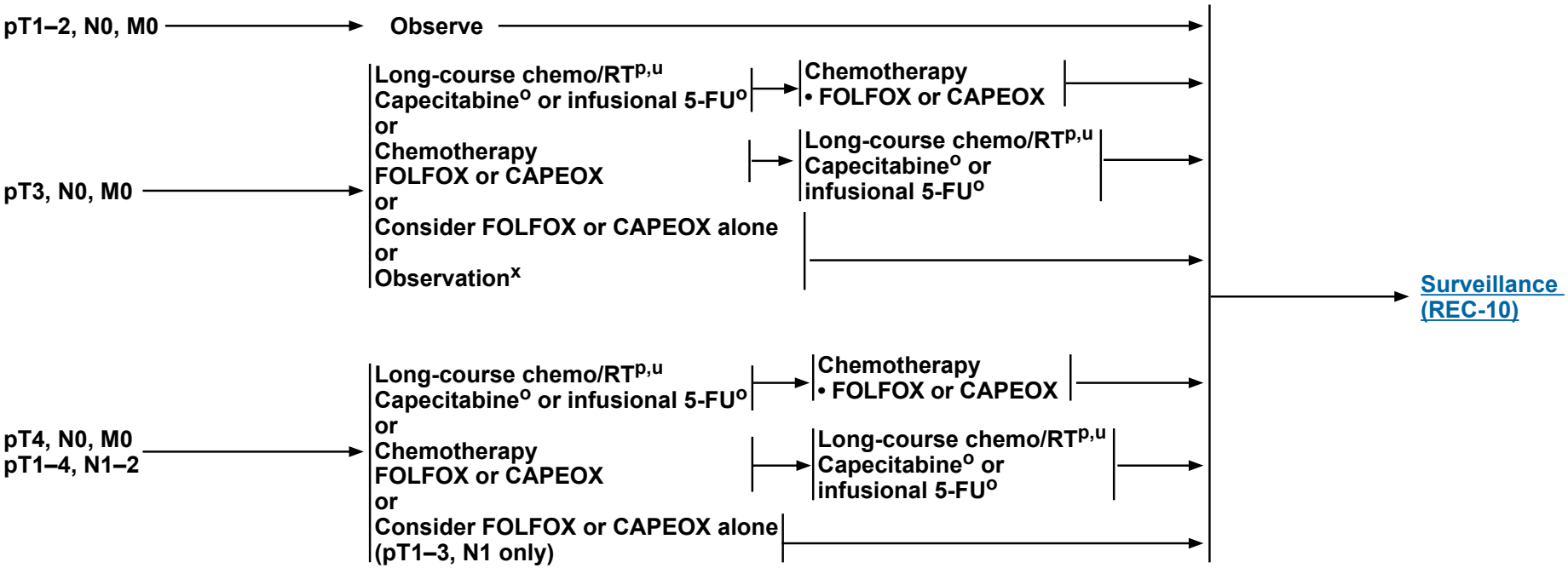

[g] Principles of Imaging (REC-A).
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p] Principles of Radiation Therapy (REC-E).
[t] For stage II-III disease, if *PIK3CA* mutation, add aspirin 100-162 mg PO daily for 3 years following surgery.
[u] Principles of Perioperative Therapy (REC-D).
[v] ctDNA is a prognostic marker; however, there is currently insufficient evidence to recommend routine use of ctDNA assays outside of a clinical trial. De-escalation of care and treatment decision-making are not recommended based on ctDNA results. Participation in clinical trials is encouraged.
[x] 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 the upper rectum. Willett CG, et al. Dis Colon Rectum 1999;42:167-173.

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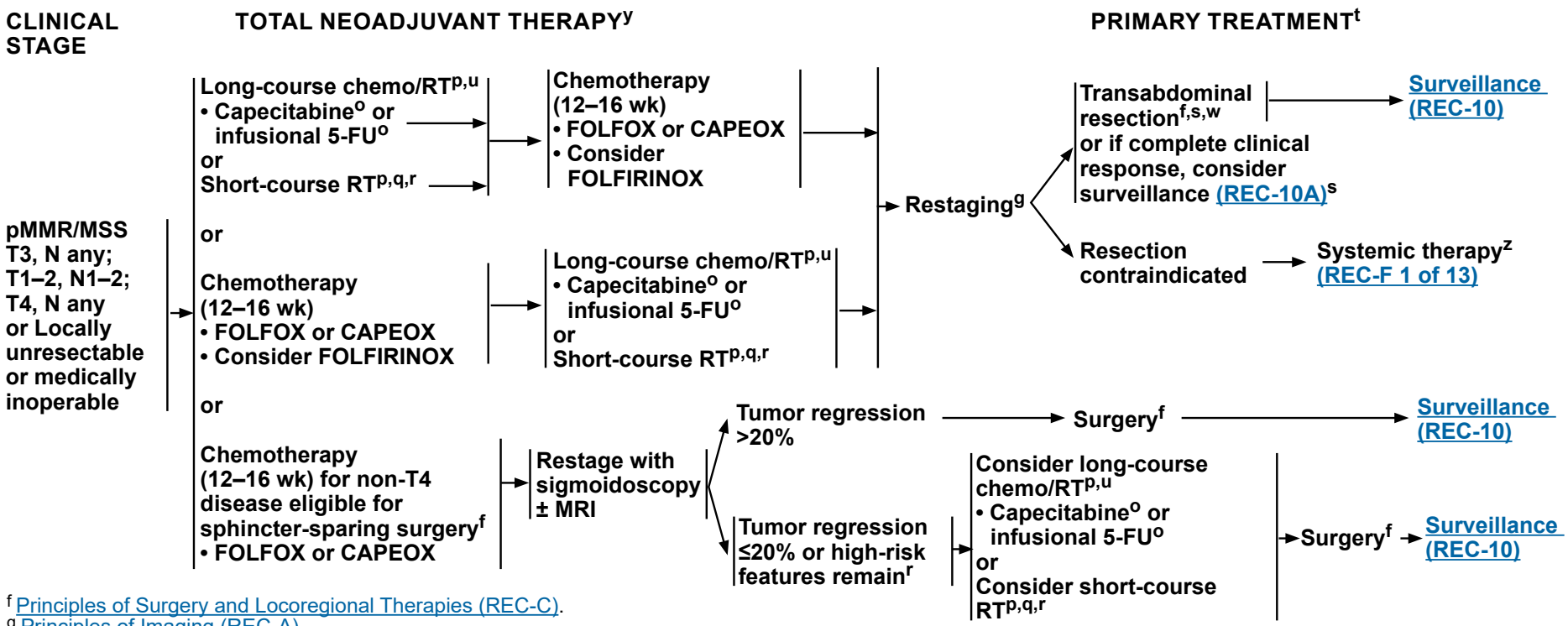

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p] Principles of Radiation Therapy (REC-E).
[q] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.
[r] While short-course RT can be considered for preoperative radiation, for high-risk rectal cancer (clinical tumor stage cT4a or cT4b, EMVI, clinical nodal stage cN2, involved MRF, or enlarged lateral lymph nodes considered to be metastatic), the 5-year follow-up of the RAPIDO trial now indicates a statistically higher locoregional recurrence rate (10%) in the experimental arm of short-course RT → chemotherapy → surgery versus control arm (6%) of chemoRT → surgery → adjuvant chemotherapy.
[s] In those patients who achieve a complete clinical response with no evidence of residual disease on DRE, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) 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 NOM should involve a careful discussion with the patient of their risk tolerance. See Principles of Nonoperative Management (REC-H).
[t] For stage II-III disease, if *PIK3CA* mutation, add aspirin 100-162 mg PO daily for 3 years following surgery.
[u] Principles of Perioperative Therapy (REC-D).
[w] For select patients who may be candidates for IORT, see Principles of Radiation Therapy (REC-E).
[y] In select cases (eg, a patient who is not a candidate for intensive therapy) neoadjuvant therapy with chemo/RT or RT alone may be considered prior to surgery.
[z] FOLFIRINOX is not recommended in this setting.

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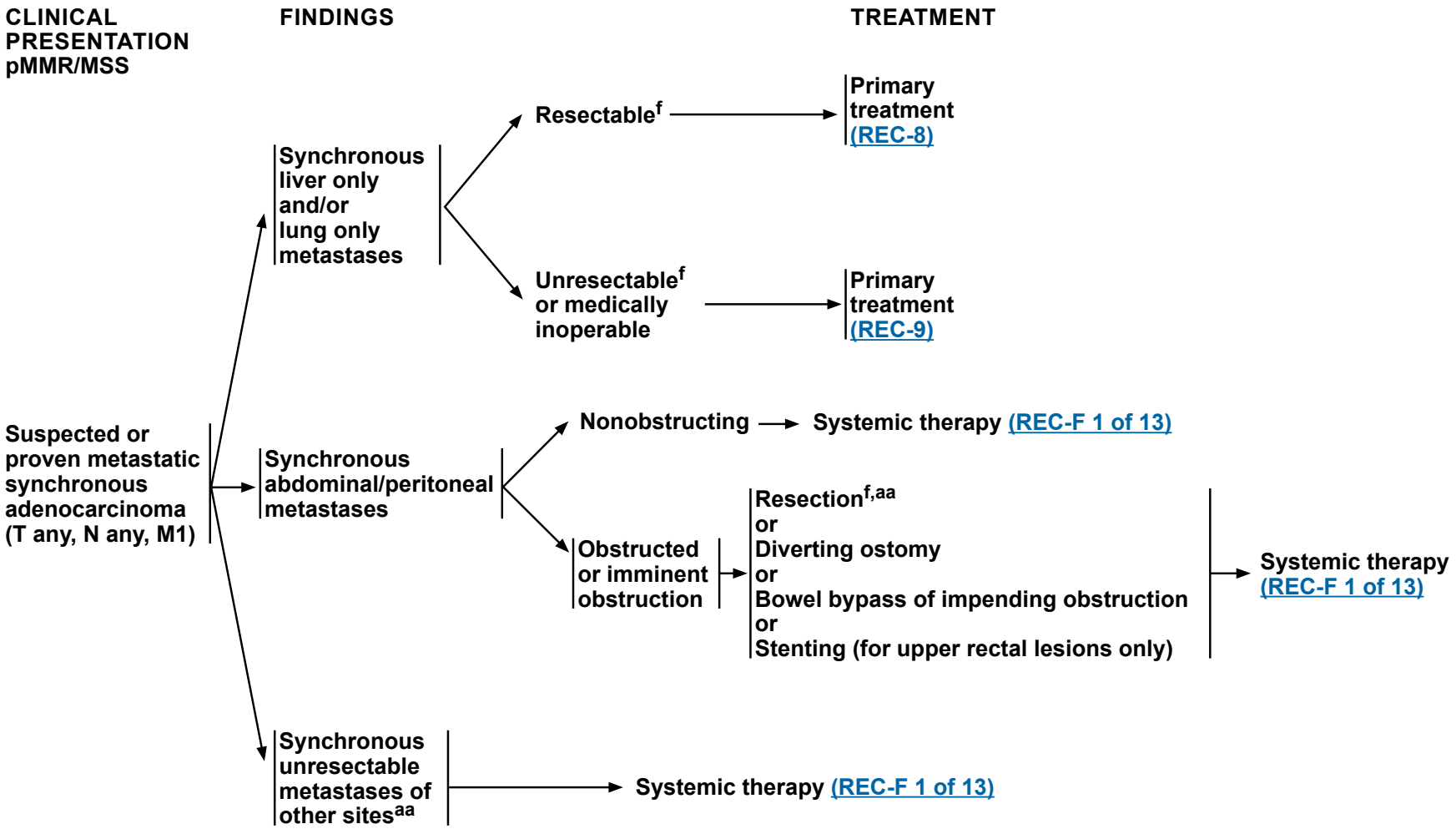

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[aa] Consider resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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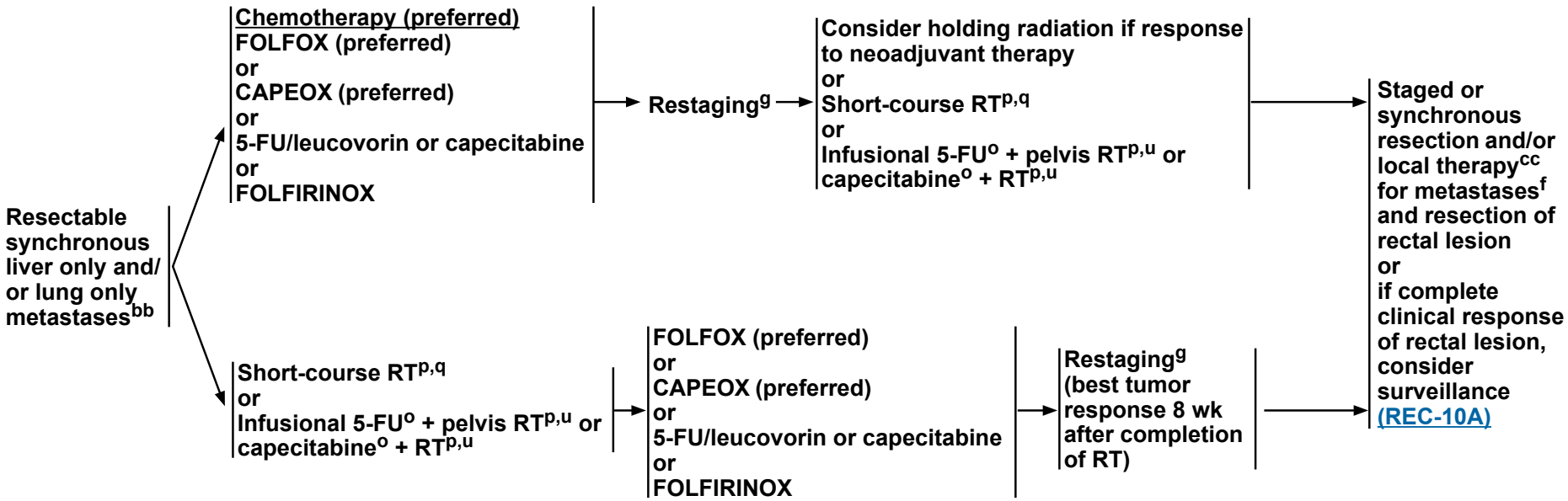
FINDINGS pMMR/MSS

NEOADJUVANT TREATMENT



[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] 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.
[p] Principles of Radiation Therapy (REC-E).
[q] 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.
[u] Principles of Perioperative Therapy (REC-D).
[bb] If obstructing lesion, consider diversion or resection (REC-7).
[cc] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or stereotactic body RT [SBRT]). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.

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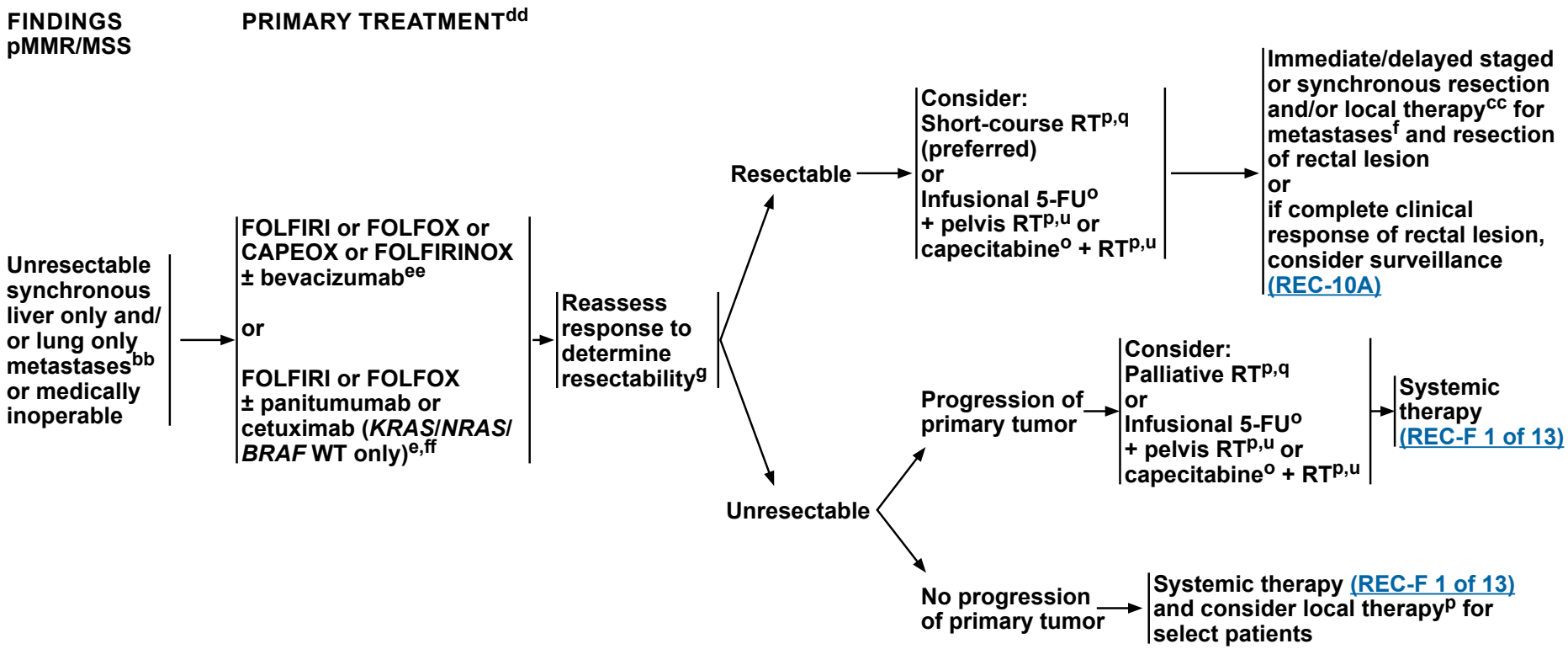

[e] Principles of Pathologic Review (REC-B).
[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p] Principles of Radiation Therapy (REC-E).
[q] Evaluation 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.
[u] Principles of Perioperative Therapy (REC-D).
[bb] If obstructing lesion, consider diversion or resection (REC-7).

[cc] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.
[dd] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[ee] 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 to 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.
[ff] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.

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SURVEILLANCE FOLLOWING OPERATIVE MANAGEMENT[g]

Low-risk polyps removed by polypectomy →
- Physical exam and proctoscopy every 3–6 mo for the first 2 y
- Colonoscopy[a] at 1 y after polypectomy

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,[hh] repeat in 3 y, then every 5 y[ii]

Stage I with full surgical staging →
- Colonoscopy[a] at 1 y after surgery
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma,[hh] repeat in 3 y, then every 5 y[ii]

Stage II–IV[gg] →
- History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- CEA[jj] every 3–6 mo for 2 y, then every 6 mo for a total of 5 y
- Chest/abdomen/pelvis (C/A/P) 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,kk] in 1 y after surgery except if no complete preoperative colonoscopy, then colonoscopy in 3–6 mo
  - If advanced adenoma, repeat in 1 y
  - If no advanced adenoma,[hh] repeat in 3 y, then every 5 y[ii]
- FDG-PET/CT is not recommended
- Principles of Survivorship (REC-G)

→ **Serial CEA elevation or documented recurrence** → Workup and Treatment (REC-11)

For surveillance following ESD, see REC-C 5 of 8

[a] All patients with rectal cancer should be counseled for family history. Patients with suspected LS, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[g] Principles of Imaging (REC-A).
[gg] ctDNA is not recommended for surveillance.
[hh] Villous polyp, polyp >1 cm, or high-grade dysplasia.
[ii] Kahi CJ, et al. Gastroenterology 2016;150:758-768.
[jj] If patient is a potential candidate for resection of isolated metastasis.
[kk] In patients with stage IV disease managed nonoperatively with complete clinical response, initiate colonoscopy surveillance from first documentation of complete response.

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SURVEILLANCE FOLLOWING NONOPERATIVE MANAGEMENT

- History and physical examination every 3–6 months for 2 years and then every 6 months for a total of 5 years
- CEA every 3–6 months for 2 years, then every 6 months for a total of 5 years
- DRE and proctoscopy or flexible sigmoidoscopy every 3–4 months for 2 years, then every 6 months for a total of 5 years
- MRI rectum every 6 months for up to 3 years
- CT chest/abdomen every 6–12 months for a total of 5 years, CT pelvis to be included once no longer doing MRI
- Colonoscopy at 1 year following completion of therapy
  - If advanced adenoma, repeat in 1 year
  - If no advanced adenoma, repeat in 3 years, then every 5 years
- Principles of Nonoperative Management (REC-H)

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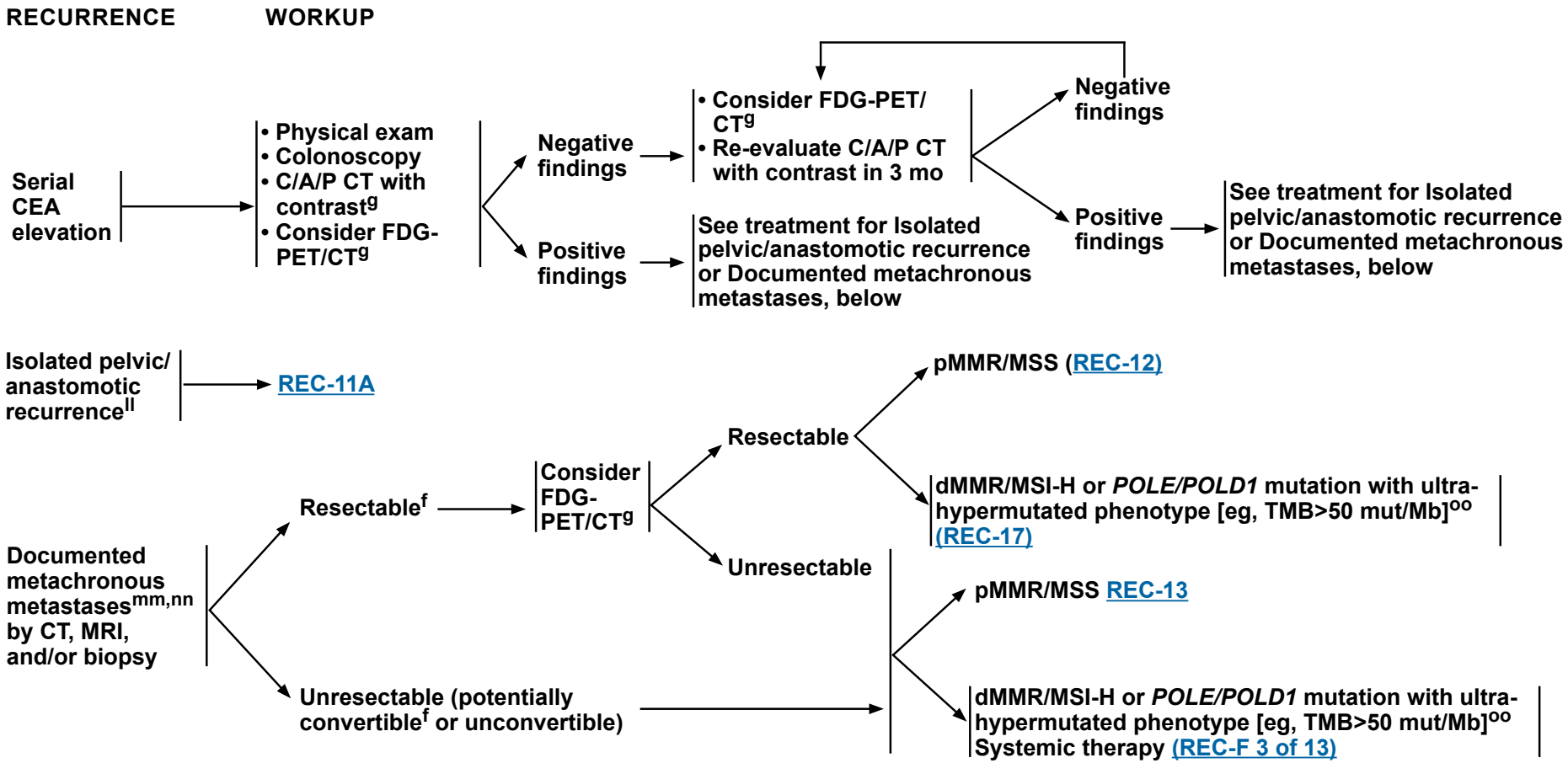

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[ll] If previous RT given (short course or chemoradiation), see Principles of Radiation Therapy (REC-E) for further guidance.
[mm] Determination of tumor gene status for *RAS* and *BRAF* mutations and HER2 amplifications (individually or as part of tissue- or blood-based next-generation sequencing [NGS] panel). See Principles of Pathologic Review (REC-B)- *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing. NGS panels have the ability to pick up rare and actionable mutations and fusions.
[nn] Patients should be evaluated by a multidisciplinary team including surgical consultation for patients with potentially resectable disease.
[oo] Patients who are not candidates for immunotherapy should be treated as recommended for pMMR/MSS disease. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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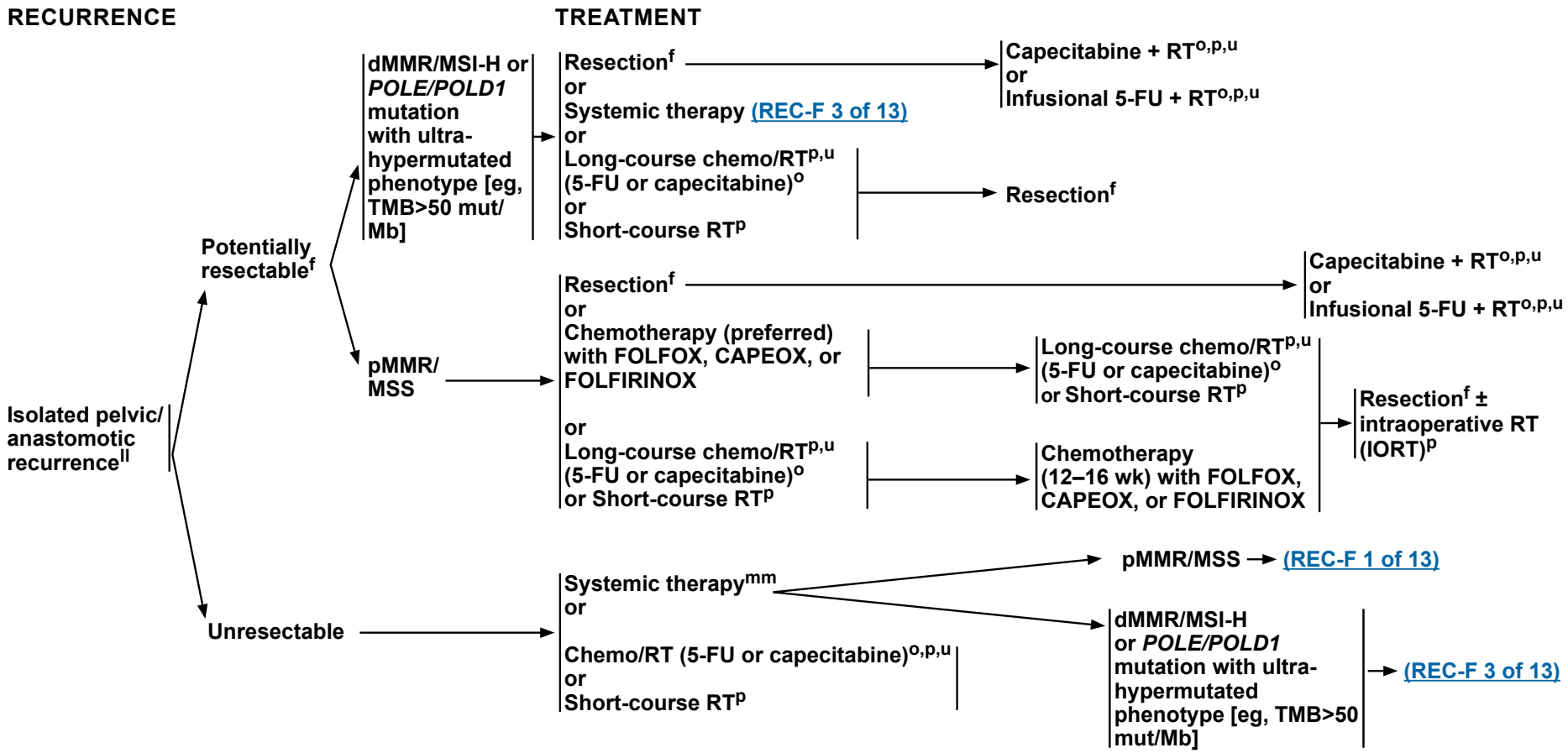

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p] Principles of Radiation Therapy (REC-E).
[u] Principles of Perioperative Therapy (REC-D).

[ll] If previous RT given (short course or chemoradiation), see Principles of Radiation Therapy (REC-E) for further guidance.
[mm] Determination of tumor gene status for *RAS* and *BRAF* mutations and HER2 amplifications (individually or as part of tissue- or blood-based NGS panel). See Principles of Pathologic Review (REC-B)- *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing. NGS panels have the ability to pick up rare and actionable mutations and fusions.

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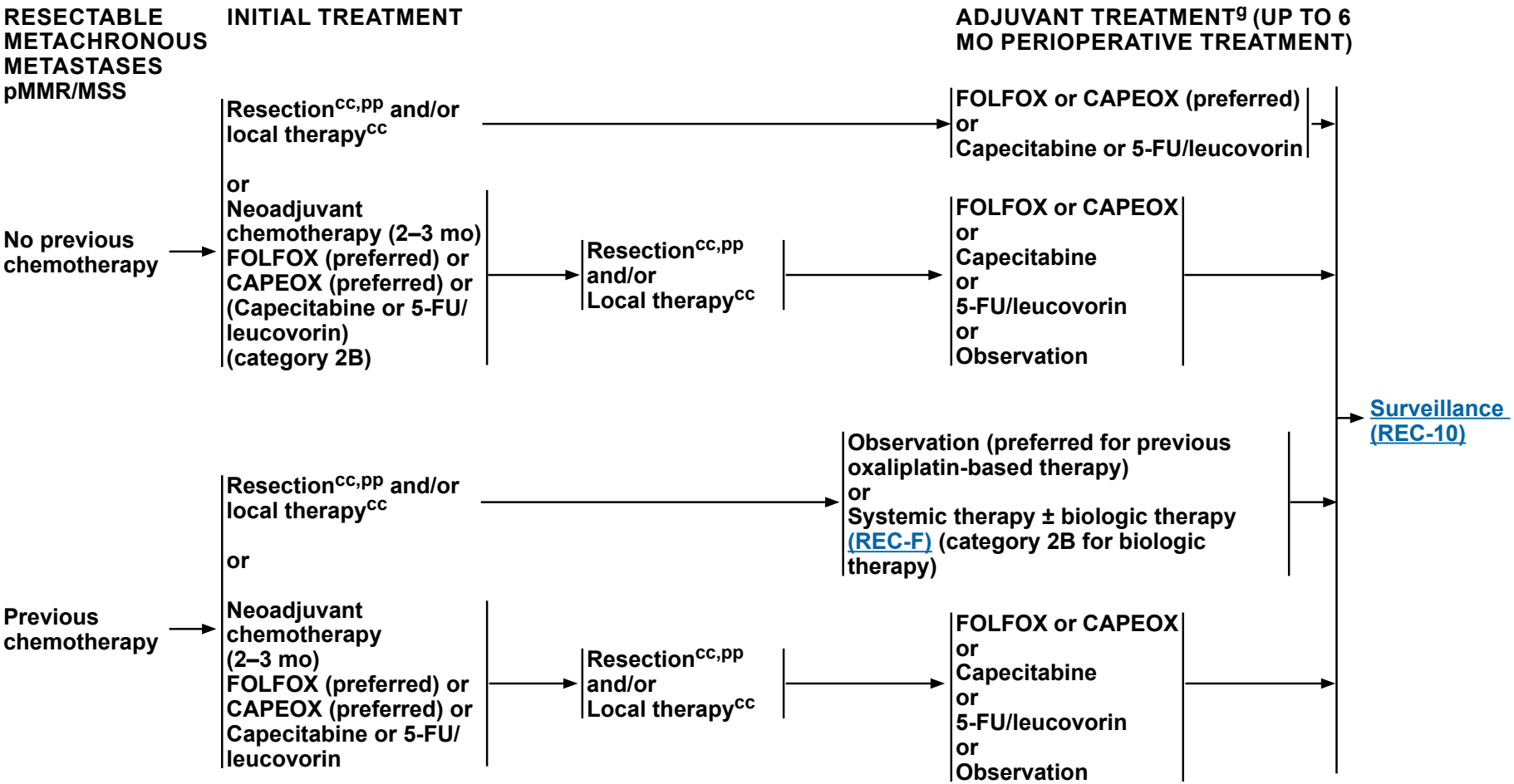

[g] Principles of Imaging (REC-A).
[cc] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.
[pp] Hepatic artery infusion ± systemic chemotherapy (VEGFi contraindicated) (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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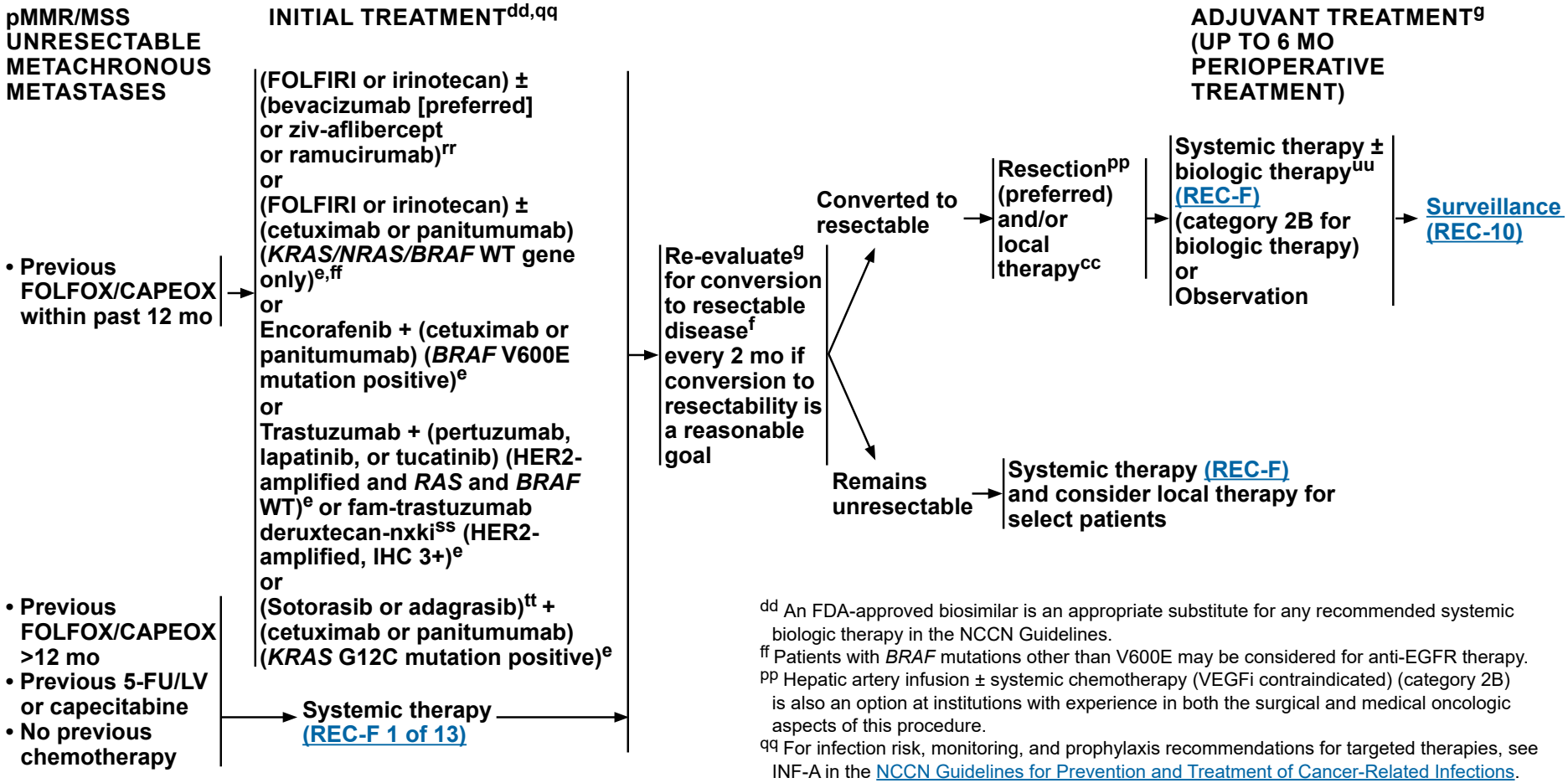

[e] Principles of Pathologic Review (REC-B) 5 of 11).
[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[cc] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.

[dd] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[ff] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.
[pp] Hepatic artery infusion ± systemic chemotherapy (VEGFi contraindicated) (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[qq] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[rr] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[ss] Some activity was seen after a previous HER2-targeted regimen. May not be indicated in patients with underlying lung issues due to lung toxicity (3.5% report of drug-related deaths from interstitial lung disease on the DESTINY-CRC01 trial).
[tt] If patient is unable to tolerate EGFR inhibitor due to toxicity, single-agent adagrasib or sotorasib can be considered.
[uu] Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.

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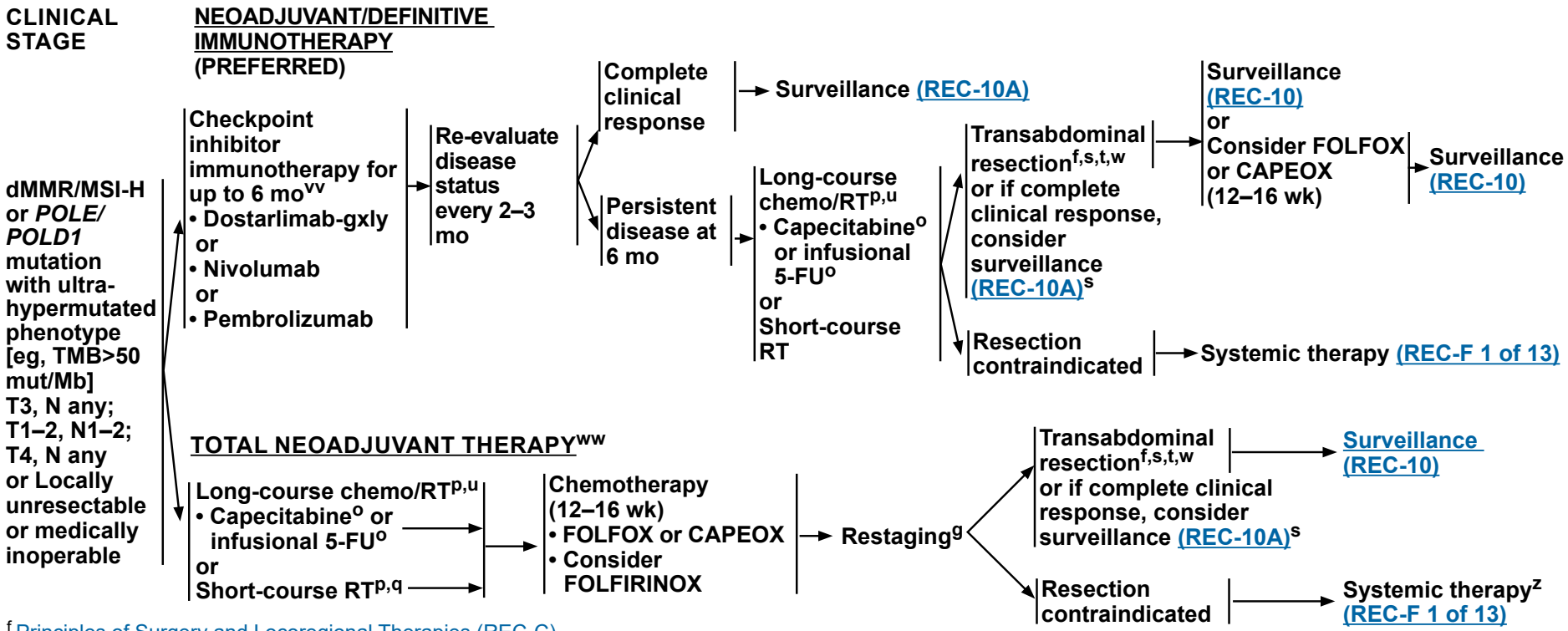

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] Principles of Imaging (REC-A).
[o] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.
[p] Principles of Radiation Therapy (REC-E).
[q] Evaluation for short-course RT should be in a multidisciplinary setting, with a discussion of the need for downstaging and the possibility of long-term toxicity.
[s] In those patients who achieve a complete clinical response with no evidence of residual disease on DRE, rectal MRI, and direct endoscopic evaluation, a "watch and wait," nonoperative (chemotherapy and/or RT) 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 NOM should involve a careful discussion with the patient of their risk tolerance. See Principles of Nonoperative Management (REC-H).
[t] For stage II-III disease, if *PIK3CA* mutation, add aspirin 100-162 mg PO daily for 3 years following surgery.
[u] Principles of Perioperative Therapy (REC-D).
[w] For select patients who may be candidates for IORT, see Principles of Radiation Therapy (REC-E).
[z] FOLFIRINOX is not recommended in this setting.
[vv] If no previous treatment with a checkpoint inhibitor.
[ww] In select cases (eg, a patient who is not a candidate for intensive therapy) neoadjuvant therapy with chemo/RT or RT alone may be considered prior to surgery.

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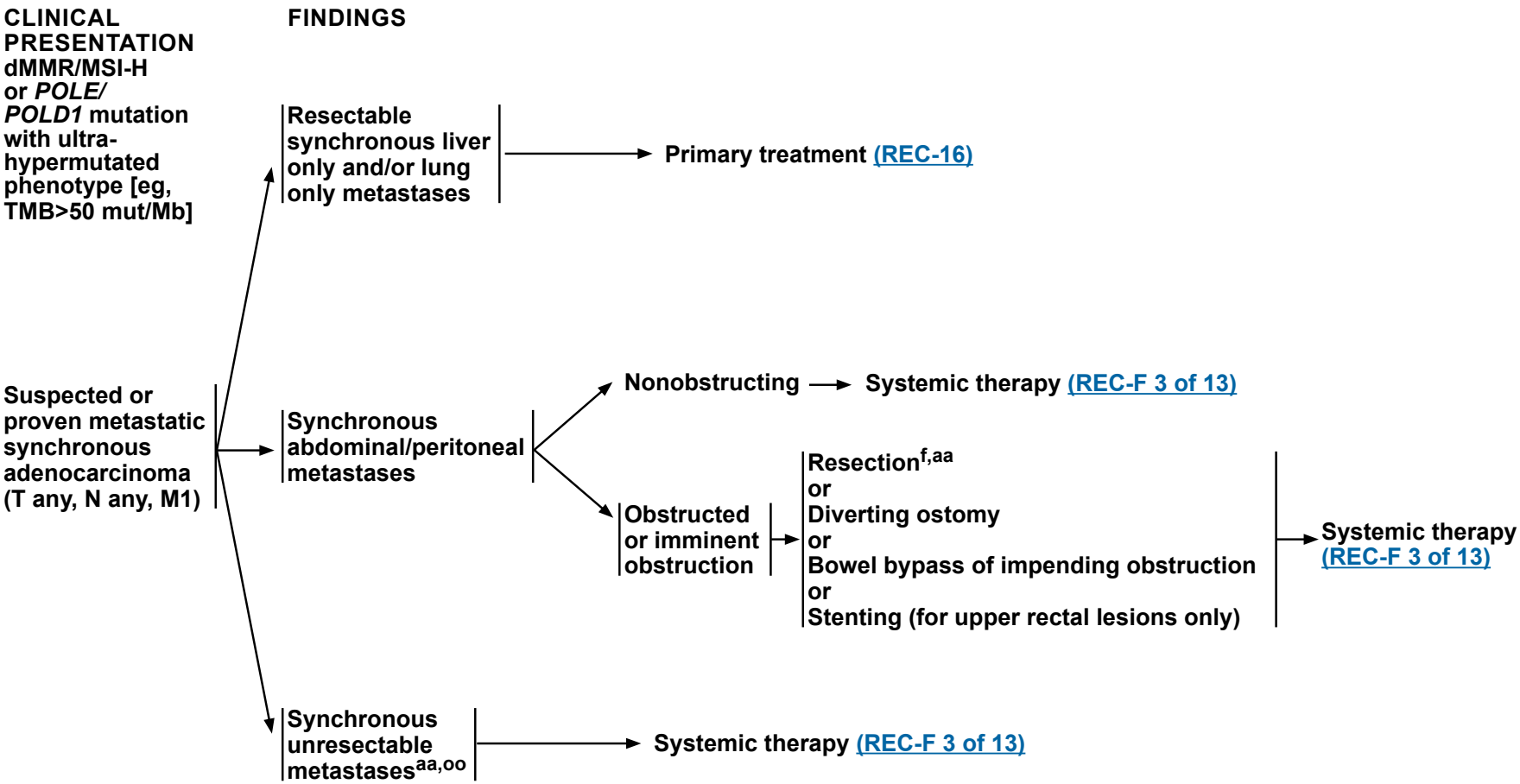

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[aa] Consider resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.
[oo] Patients who are not candidates for immunotherapy should be treated as recommended for pMMR/MSS disease. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

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FINDINGS

dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb]

NEOADJUVANT TREATMENT

Resectable synchronous liver only and/or lung only metastases[bb] → **Checkpoint inhibitor immunotherapy (preferred)[vv,xx,yy,zz]** → **Restaging[g]** → **Consider holding radiation if complete response to neoadjuvant therapy**
or
Short-course RT[p,q] (preferred)
or
Infusional 5-FU[o] + pelvis RT[p,u] or capecitabine[o] + RT[p,u] → **Staged or synchronous resection and/or local therapy[cc] for metastases[f] and resection of rectal lesion**

or

Surveillance (REC-10A) if complete response to immunotherapy

[f] Principles of Surgery and Locoregional Therapies (REC-C).
[g] 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.
[p] Principles of Radiation Therapy (REC-E).
[q] 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.
[u] Principles of Perioperative Therapy (REC-D).
[bb] If obstructing lesion, consider diversion or resection (REC-7).
[cc] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.
[vv] If no previous treatment with a checkpoint inhibitor.
[xx] Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, dostarlimab-gxly, cemiplimab-rwlc, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr. Combination PD-L1/CTLA-4 blockade has been associated with improved survival in unresectable or metastatic CRC, but also higher toxicity.
[yy] Data are limited and the risk of early progression may be higher than with chemotherapy. Andre T, et al. N Engl J Med 2020;383:2207-2218.
[zz] For patients with a contraindication to checkpoint inhibitor immunotherapy, neoadjuvant chemotherapy with FOLFOX, CAPEOX, or FOLFIRINOX is an option.

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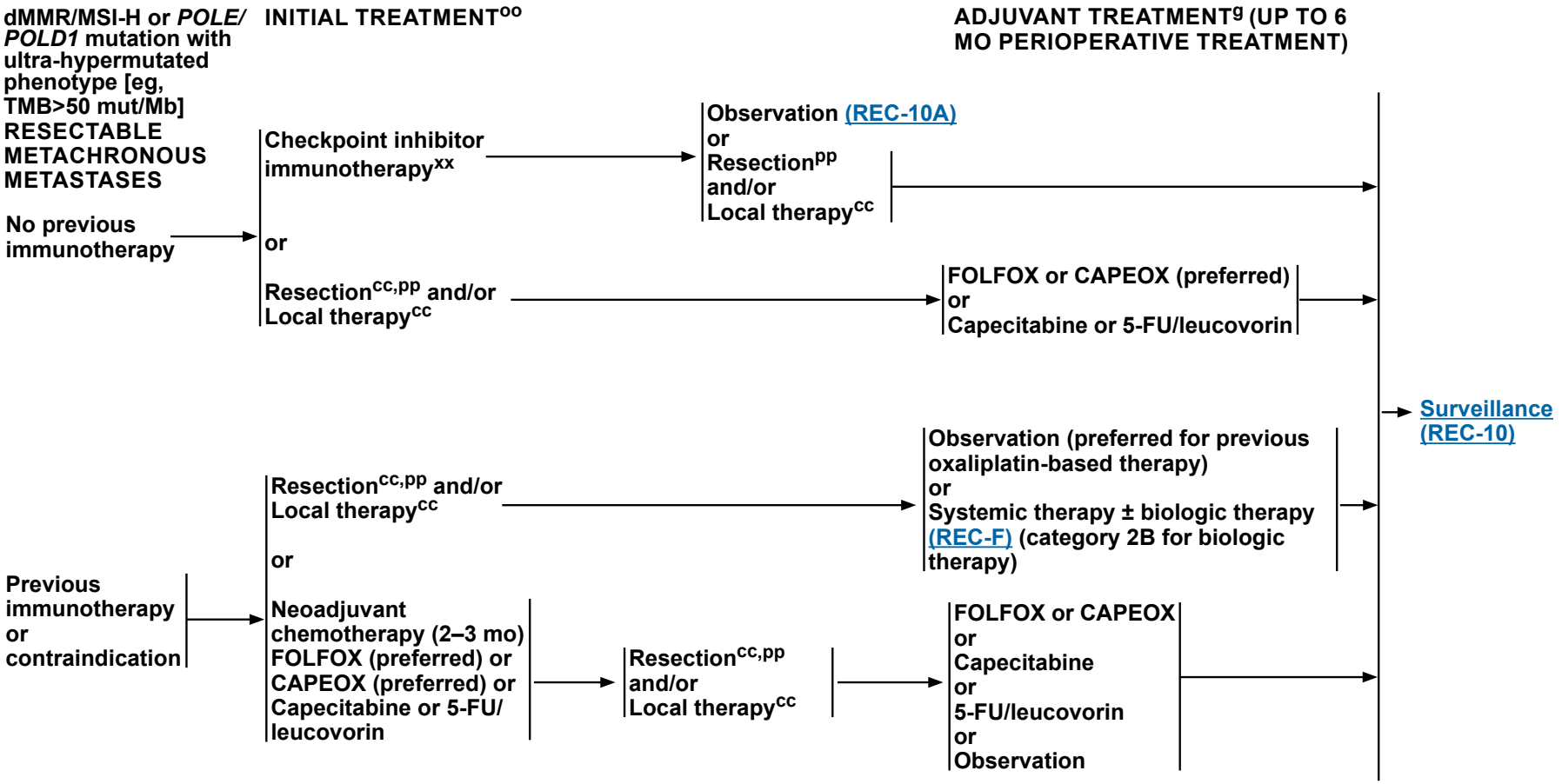

[g] Principles of Imaging (REC-A).

[cc] Resection is preferred over locally ablative procedures (eg, image-guided thermal ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.

[oo] Patients who are not candidates for immunotherapy should be treated as recommended for pMMR/MSS disease. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[pp] Hepatic artery infusion ± systemic chemotherapy (VEGFi contraindicated) (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

[xx] Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, dostarlimab-gxly, cemiplimab-rwlc, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr. Combination PD-L1/CTLA-4 blockade has been associated with improved survival in unresectable or metastatic CRC, but also higher toxicity.

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PRINCIPLES OF IMAGING[1-3]

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 (IV) iodinated contrast and oral contrast material unless contraindicated.
  - IV contrast is not required for the chest CT (but usually given if performed with abdominal CT).
  - If IV iodinated contrast material is contraindicated because of significant contrast allergy, then MRI examination of the abdomen with IV gadolinium-based 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 MRI without IV contrast or consider FDG-PET/CT imaging.
- Pelvis MRI with or without contrast or endorectal ultrasound (only if MRI is contraindicated)
  [See Pelvis MRI Requirements (REC-A 3 of 4) and Reporting (REC-A 4 of 4)]
  - Assess T and N stage of the primary rectal tumor.
  - Pelvis MRI or CT can be used for workup of synchronous metastatic disease.
  - Pelvis MRI can be performed with or without IV gadolinium contrast per institutional preferences.
  - Pelvis 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 (eg, widespread metastases, plan for permanent colonic diversion).
  - The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.
- FDG-PET/CT is not routinely indicated.
  - FDG-PET/CT does not supplant a contrast-enhanced diagnostic CT or MRI and should only be used to evaluate an equivocal finding on a contrast-enhanced CT or MRI or in patients with strong contraindications to IV contrast administration.
- Consider FDG-PET/CT (skull base to mid-thigh):
  - If potentially surgically curable M1 disease in selected cases.
  - In patients considered for image-guided liver-directed therapies for liver metastases (ie, thermal ablation, radioembolization).[4-8]
- If liver-directed therapy or surgery is contemplated, a hepatic MRI with IV routine extracellular or hepatobiliary GBCA is preferred over CT to assess exact number and distribution of metastatic foci for local treatment planning.

References on (REC-A 2 of 4)

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PRINCIPLES OF IMAGING[1-3]

Restaging

- **Chest CT and abdominal CT or MRI and pelvis 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**
- **FDG-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:**
  - **C/A/P CT every 6 to 12 months (category 2B for frequency <12 months) for a total of 5 years.**
  - **MRI or EUS of the rectum every 3 to 6 months for 2 years, then every 6 months for a total of 5 years (for patients with transanal local excision only).**
  - **FDG-PET/CT examination is not recommended.**
- **Stage IV disease:**
  - **C/A/P CT every 3 to 6 months (category 2B for frequency <6 months) x 2 years, then every 6 to 12 months for a total of 5 years.**
  - **MRI or EUS of the rectum every 3 to 6 months for 2 years, then every 6 months for a total of 5 years (for patients with transanal excision only).**
- **FDG-PET/CT is not indicated with the exception of selected patients who are considered for image-guided liver-directed therapies for hepatic metastases (ie, thermal ablation, radioembolization) or serial CEA elevation during follow-up.**

[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;257:674-684.
[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.
[4] Mauri G, Gennaro N, De Beni S, et al. Real-time US-^{18}FDG-PET/CT image fusion for guidance of thermal ablation of ^{18}FDG-PET-positive liver metastases: the added value of contrast enhancement. Cardiovasc Intervent Radiol 2019;42:60-68.
[5] Sahin DA, Agcaoglu O, Chretien C, et al. The utility of PET/CT in the management of patients with colorectal liver metastases undergoing laparoscopic radiofrequency thermal ablation. Ann Surg Oncol 2012;19:850-855.
[6] Shady W, Kishore S, Gavane S, et al. Metabolic tumor volume and total lesion glycolysis on FDG-PET/CT can predict overall survival after (90)Y radioembolization of colorectal liver metastases: a comparison with SUVmax, SUVpeak, and RECIST 1.0. Eur J Radiol 2016;85:1224-1231.
[7] Shady W, Sotirchos VS, Do RK, et al. Surrogate imaging biomarkers of response of colorectal liver metastases after salvage radioembolization using 90Y-loaded resin microspheres. AJR Am J Roentgenol 2016;207:661-670.
[8] Cornelis FH, Petre EN, Vakiani E, et al. Immediate postablation ^{18}F-FDG injection and corresponding SUV are surrogate biomarkers of local tumor progression after thermal ablation of colorectal carcinoma liver metastases. J Nucl Med 2018;59:1360-1365.

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PRINCIPLES OF IMAGING
Pelvic MRI Requirements[3]

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	• **Slice thickness 1–3 mm (no more than 4 mm). 3D T2-weighted sequences are not adequate substitutes** • **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[a]**

[a] IV contrast can be administered (after completion of non-contrast scans) if dynamic contrast-enhanced (DCE) MRI and/or perfusion assessment is needed for tumor response evaluation, currently performed primarily in investigational setting.
[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 IMAGING
Pelvic MRI Reporting[3]

At presentation (before neoadjuvant therapy)	• 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 MRF and the smallest distance (mm) between the tumor and the MRF and its location[b] • N-stage • Presence/absence of suspicious extramesorectal lymph nodes • Additional findings that can be provided in synoptic report: ▸ 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)
After neoadjuvant therapy	• 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[b] • The smallest distance (mm) between the remaining tumor and the MRF and its location • Additional findings that can be provided in synoptic report: ▸ 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)

[b] Circumferential resection margin (CRM) measured at the closest distance of the tumor to the MRF. Clear CRM: Greater than 1 mm from MRF and levator muscles and not invading into the intersphincteric plane. Involved CRM: within 1 mm of MRF; or, for lower third rectal tumors, within 1 mm from levator muscle; or, for anal canal lesions, invasion into or beyond the intersphincteric plane.
[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 PATHOLOGIC AND MOLECULAR 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 looks closely 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, pT1, grade 1 or 2, no lymphatic or venous invasion, or negative margins.[8,9]**
- **Unfavorable histopathologic features: >3 cm in size, >pT1, with grade 3, or lymphovascular invasion, positive margin, tumor budding, or sm3 (lower one third of the submucosa) 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 11)
Lymph Node Evaluation on REC-B (4 of 11)
Sentinel Lymph Node Evaluation on REC-B (4 of 11)
KRAS, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 11)
HER2 Testing and *NTRK* Fusions on REC-B (6 of 11)
References on REC-B (8 of 11)

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PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW

Pathologic Stage

- The following parameters should be reported:
  - Grade of the cancer
  - Depth of penetration (pT), the pT stage, is based on viable tumor. Acellular mucin pools are not considered to be residual tumor in those patients 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 patients treated with neoadjuvant therapy.
  - Status of proximal, distal, circumferential (radial), and mesenteric margins[11,12]
  - Circumferential resection margin (CRM)[13-17]
  - Neoadjuvant treatment effect[15,16,18-20]
  - Lymphovascular invasion[15,16,21]
  - Perineural invasion (PNI)[22-24]
  - Tumor deposits[25,26]
- 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, Eighth 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, Eighth Edition and the CAP Guidelines is that as modified from Ryan R, et al. Histopathology 2005;47:141-146 and Gavioli M, et al. Dis Colon Rectum 2005;48:1851-1857.
  - 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 the 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.[15,16,18-20]

Pathologic Stage (continued) on REC-B (3 of 11)
Lymph Node Evaluation on REC-B (4 of 11)
Endoscopically Removed Malignant Polyps, Transanal Local Excision, Rectal Cancer Appropriate for Resection on REC-B (1 of 11)
KRAS, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 11)
HER2 Testing and *NTRK* Fusions on REC-B (6 of 11)
References on REC-B (8 of 11)

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PRINCIPLES OF PATHOLOGIC AND MOLECULAR 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.[21-26]**
- **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.**
- **Tumor budding - In recent years, tumor budding has been identified as a new prognostic factor in colon cancer. Recently, there was an international consensus conference on tumor budding reporting.[27] A tumor bud is defined as a single cell or a cluster of ≤4 cells detected by hematoxylin and eosin (H&E) at the advancing edge of the invasive carcinoma. The total number of buds should be reported from a selected hot spot measuring 0.785 mm (20x ocular in most microscopes/via a conversion factor). Budding is separated into three tiers: low tier (0–4 buds), intermediate tier (5–9 buds), and high tier (10 or more buds). Two recent studies[28,29] using this scoring system have shown tumor budding to be an independent prognostic factor for stage II colon cancer. An American Society of Clinical Oncology (ASCO) guideline for stage II colon cancer designates tumor budding as an adverse (high-risk) factor.[30] Several studies have shown that high-tier tumor budding in pT1 colorectal cancers (CRCs), including malignant polyps, is associated with an increased risk of lymph node metastasis; however, methodologies for assessing tumor budding and grade were not uniform.[31-35]**

Endoscopically Removed Malignant Polyps, Transanal Local Excision, Rectal Cancer Appropriate for Resection on REC-B (1 of 11)
Pathologic Stage on REC-B (2 of 11)
Lymph Node Evaluation on REC-B (4 of 11)
KRAS, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 11)
HER2 Testing and *NTRK* Fusions on REC-B (6 of 11)
References on REC-B (8 of 11)

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PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW

Lymph Node Evaluation

- **The AJCC and CAP recommend examination of a minimum of 12 lymph nodes to accurately stage rectal cancer.[11,12,36] Sampling of 12 lymph nodes may not be achievable in patients who received preoperative chemotherapy. The literature lacks consensus as to the minimum number of lymph nodes needed to accurately identify stage II cancer. The minimum number of nodes has been reported as >7, >9, >13, >20, and >30.[36-44] 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 minimum number to accurately identify stage II rectal cancer.[40,43] The number of lymph nodes retrieved can vary with patient age, gender, tumor grade, and tumor site.[37] 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, $P < .001$).[45,46] If 12 lymph nodes is considered the number needed to accurately stage stage II tumors, then only 20% of patients treated with neoadjuvant therapy had adequate lymph node sampling.[46] To date, the number of lymph nodes needed to accurately stage neoadjuvant-treated cases is unknown. However, it is not known what the clinical significance of this is in the neoadjuvant setting, as postoperative therapy is indicated in all patients who receive preoperative therapy regardless of the surgical pathology results.**

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry (IHC)

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).[47] The AJCC Cancer Staging Manual, Eighth Edition[47] defines clumps of tumor cells ≥0.2 mm but ≤2 mm in diameter or clusters of 10 to 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 of isolated tumor cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.[48-55] 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 not shown this survival difference. In some of these studies, what are presently defined as isolated tumor cells were considered to be micrometastases.[51-55]**

Evaluation of Mesorectum (total mesorectal excision, TME)

- **The pathologist should evaluate the quality (completeness) of the mesorectum (only for low rectal cancer - distal 2/3).[56-58]**

Endoscopically Removed Malignant Polyps, Transanal Local Excision, Rectal Cancer Appropriate for Resection on REC-B (1 of 11)
Pathologic Stage on REC-B (2 of 11)
KRAS, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 11)
HER2 Testing and *NTRK* Fusions on REC-B (6 of 11)
References on REC-B (8 of 11)

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PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW

Methods of Testing

- **The testing can be performed on formalin-fixed paraffin-embedded tissue (preferred) or blood-based assay.**
- **Repeat molecular testing should not be performed after standard cytotoxic chemotherapy as significant molecular changes are rarely observed. Changes in the molecular profile can more commonly be seen after targeted therapies and repeat testing may be considered to guide future targeted therapy decisions.**

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

- **All patients with metastatic CRC should have tumor genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of a next-generation sequencing (NGS) panel (preferred). Patients with any known *KRAS* mutation (exons 2, 3, and 4) or *NRAS* mutation (exons 2, 3, and 4) should not be treated with either cetuximab or panitumumab, unless given as part of a regimen targeting a *KRAS* G12C mutation.[59-61] *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely.[62-64]**
- ***BRAF* V600E mutation testing via IHC is also an option.**
- **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 the primary CRCs and/or the metastasis, as literature has shown that the *KRAS, NRAS,* and *BRAF* mutations are similar in both specimen types.[65]**

Microsatellite Instability or Mismatch Repair Testing

- **Universal MMR[a] or MSI[a] testing is recommended in all newly diagnosed patients with rectal cancer. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.**
- **The presence of a *BRAF* V600E mutation in the setting of *MLH1* absence would preclude the diagnosis of Lynch syndrome (LS) in the vast majority of patients. However, approximately 1% of cancers with *BRAF* V600E mutations (and loss of *MLH1*) are LS. Caution should be exercised in excluding patients with a strong family history from germline screening in the case of *BRAF* V600E mutations.[66]**
- **MMR or MSI testing should be performed only in CLIA-approved laboratories.**
- **Testing for MSI may be accomplished by polymerase chain reaction (PCR) or a validated NGS panel, the latter especially in patients with metastatic disease who require genotyping of *RAS* and *BRAF*.**
- **IHC refers to staining tumor tissue for protein expression of the four MMR genes known to be mutated in 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/intact) 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 or *MLH1* promoter methylation. The presence of *BRAF* V600E mutation or *MLH1* promoter methylation is consistent with sporadic cancer. However, caution should be exercised in excluding patients from germline screening based on *BRAF* V600E mutations in the setting of a strong family history.[66]**

HER2 Testing and *NTRK* Fusions on REC-B (6 of 11)

References on REC-B (8 of 11)

[a] IHC for MMR and DNA analysis for MSI are different assays and measure different biological effects caused by deficient MMR function.

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HER2 Testing

- **Diagnostic testing is via IHC, fluorescence in situ hybridization (FISH), or next-generation sequencing (NGS).**
- **Positive by IHC is defined as: 3+ staining in more than 50% of tumor cells. 3+ staining is defined as an intense membrane staining that can be circumferential, basolateral, or lateral. Those that have a HER2 score of 2+ should be reflexed to FISH testing.[67-69] HER2 amplification by FISH is considered positive when the HER2:CEP17 ratio is ≥2 in more than 50% of the cells.[67-69] NGS is another methodology for testing for HER2 amplification.[70]**
- **Anti-HER2 therapy with signal transduction inhibition (eg, trastuzumab/pertuzumab, trastuzumab/tucatinib, trastuzumab/lapatinib) is indicated for patients with HER2 IHC 3+, IHC2+/ISH+, or NGS amplified cancer that are also *RAS* and *BRAF* wild-type. Fam-trastuzumab deruxtecan-nxki is only indicated in HER2-amplified tumors (IHC 3+).**

***NTRK* Fusions**

- ***NTRK* fusions are extremely rare in CRCs.[71] The overall incidence is approximately 0.35% in a cohort of 2314 CRCs, with *NTRK* fusions confined to those tumors that are pan–wild-type *KRAS, NRAS*, and *BRAF*. In one study of eight CRCs harboring *NTRK* fusions, seven were found in the small subset that were dMMR (MLH-1)/MSI-H.[72] *NTRK* fusions are more frequently found among patients with dMMR.**
- ***NTRK* inhibitors have been shown to have activity ONLY in those cases with *NTRK* fusions, and NOT with *NTRK* point mutations.**
- **Methodologies for detecting *NTRK* fusions are IHC,[73] FISH, DNA-based NGS, and RNA-based NGS.[72,74] In one study, DNA-based sequencing showed an overall sensitivity and specificity of 81.1% and 99.9%, respectively, for detection of *NTRK* fusions when compared to RNA-based sequencing and IHC showed an overall sensitivity of 87.9% and specificity of 81.1%. Since approximately one in five tumors identified as having an *NTRK* fusion by IHC will be a false positive, tumors that test positive by IHC should be confirmed by RNA NGS. That same study commented that RNA-based sequencing appears to be the optimal way to approach *NTRK* fusions, because the splicing out of introns simplifies the technical requirements of adequate coverage and because detection of RNA-level fusions provides direct evidence of functional transcription.[74] However, selection of the appropriate assay for *NTRK* fusion detection depends on tumor type and genes.**

References on REC-B (8 of 11)

KRAS, NRAS, and *BRAF* Mutation Testing and Microsatellite Instability or Mismatch Repair Testing on REC-B (5 of 11)

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POLE/POLD1

- Polymerase genes, *POLE* and *POLD1*, encode proteins tasked with proofreading functions to recognize and correct mispaired bases incorporated during DNA replication. Pathogenic variants (PVs) within the exonuclease domains (ED) of *POLE* and *POLD1* result in loss of this proofreading function leading to subsequent acquisition of numerous single nucleotide variants (SNVs).[75,76]
- Germline PVs within the ED of *POLE* and *POLD1* predispose patients to multiple colorectal adenomas and carcinomas, resulting in polymerase proofreading-associated polyposis (PPAP)[75,76] (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric).
- Somatic *POLE* PVs occur in approximately 2%–8% of patients with predominately MSS/pMMR CRC while somatic *POLD1* PVs are extremely rare.[75,77]
- NGS of CRCs arising in patients with either germline or somatic ED PVs demonstrate an ultra-hypermutated phenotype identified as extremely high tumor mutational burden (TMB>50 mut/Mb). TMB is calculated as the total number of somatic mutations per coding area of the tumor genome. Although calculations vary according to assay performed, TMB>10 mut/Mb is generally regarded as TMB-high (TMB-H).[77,78]
- *POLE/POLD1* PVs can be identified through single gene assays (PCR or Sanger sequencing). However, TMB calculation requires a larger NGS panel, which often includes concurrent *POLE/POLD1* sequencing. As such, performing a large NGS assay on CRC tumor tissue has the advantage of not only identifying *POLE/POLD1* PVs but also provides direct evidence of loss of proofreading function (TMB-H).[77-79]
- Patients with CRC harboring *POLE/POLD1* PVs have a more favorable prognosis, likely secondary to immune responses stimulated by the presence of numerous neoantigens produced as a consequence of aberrant proofreading function. Similarly, for these patients disease responds well to immune checkpoint inhibitor therapy.[79-84]

***RET* Fusions**

- *RET* is a receptor tyrosine kinase that plays a critical role in the development and maintenance of neural and genitourinary tissues, primarily through downstream MAPK and PI3K signaling pathways.[85]
- Germline activating mutations in *RET* lead to multiple endocrine neoplasia type 2 (MEN2) (see NCCN Guidelines for Neuroendocrine and Adrenal Tumors) and loss of function mutations are associated with Hirschsprung disease and congenital abnormalities of the kidney and urinary tract.[85]
- Somatic activating alterations in *RET* include point mutations as well as gene rearrangements and have been identified in a variety of tumors.[85,86]
- In patients with CRC, activating *RET* fusions involving the C-terminal kinase domain lead to constitutive upregulation of *RET* kinase activity and subsequent promotion of cell proliferation and survival. The most common gene fusion partners reported include *KIF5B*, *CCDC6*, and *NCOA4*.[85-88]
- The *RET*-targeted inhibitor, selpercatinib, is FDA-approved for patients with solid tumors harboring activating *RET* fusions.[89]
- The presence of *RET* fusions can be interrogated through a variety of techniques, including IHC, FISH, PCR, and either DNA- or RNA-based NGS assays. RNA-based NGS assays are fusion agnostic and as such have the advantage of identifying *RET* fusions involving any partner gene.[86-88]

References on REC-B (8 of 11)

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES

Workup

- Independent evaluation by the treating surgeon with either proctosigmoidoscopy or flexible sigmoidoscopy is recommended for all rectal tumors. Critical characteristics to be documented, in conjunction with digital rectal examination (DRE), include tumor size, distances from the anal verge and the anorectal ring, orientation within the rectal lumen (eg, anterior-posterior, laterality) and/or degree of circumferential involvement, extent of obstruction, extent of fixation to the rectal wall, degree of sphincter involvement, and sphincter tone.

Transanal Local Excision[1]

- Criteria
  - <30% circumference of bowel; <3 cm in size; clear surgical margin (>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
  - Surgical technique includes full thickness excision of rectal wall with goal of ≥10 mm excision margin with an intact non-fragmented specimen.
- 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 endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS).
- Local excision could be a viable option for patients who have a strong but incomplete response and are unable or unwilling to undergo standard TME surgery. The most suitable candidates would be those meeting the near complete response (nCR) criteria as outlined in the Principles of Nonoperative Management section (endoscopy, DRE, and MRI).
- The efficacy of local excision for patients who have achieved a clinical complete response (cCR) is not yet fully established. According to current data, cCR, as determined through MRI, DRE, and endoscopy, typically correlates with a durable response. Therefore, implementing local excision might introduce unnecessary risks without clear benefits. Given this uncertainty and potential for added risk, local excision is not routinely recommended for patients who have achieved a clear cCR.

Transabdominal Resection: Abdominoperineal resection or low anterior resection or coloanal anastomosis using TME

- Management principles
  - The treating surgeon should be experienced in rectal cancer surgery, and specifically with TME. For patients with predicted positive margins based on preoperative imaging, or lateral pelvic lymph node involvement, the surgeon should be experienced in extended resections beyond the TME plane and have a multidisciplinary team available if necessary.[2]
  - The treating surgeon should assess the distal margin before initiating treatment by DRE ± rigid or flexible endoscopy, particularly for non-palpable lesions.
  - Anticipated circumferential margins should be assessed by MRI (see Principles of Imaging, REC-A) prior to any required neoadjuvant therapy, and again considered prior to surgery. If margins are involved, assessment for feasibility of resection beyond the TME plane is required. Such an extended resection (± reconstruction) should involve careful preoperative planning and may require a multidisciplinary team.
  - For adequately staged, low-risk, upper-rectal T3, N0 tumors, surgery alone is an appropriate treatment option.
  - Remove primary tumor with adequate circumferential and distal margins.
  - Treat draining lymphatics by TME.
  - 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.
- TME is a standard component of radical rectal cancer surgery. TME reduces the positive radial margin and local recurrence rates.
  - Extend 4 to 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 to 2 cm may be acceptable.
  - Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.
  - Minimally invasive approaches (eg, laparoscopic, robotic) for resection of rectal cancer have been shown to be safe.[3,4]
  - There are no significant differences in disease-free survival and recurrence rates with minimally invasive approaches when compared to open resection.[5-7]
    - ◊ The surgeon should have experience performing minimally invasive proctectomy with TME.
    - ◊ 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[8,9]
  - 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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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES

Locoregional Therapies

- **Image Guided Tumor Ablation[10]**
  - **Thermal ablation creates tumor cell death through deposition of tumoricidal heat (radiofrequency or microwave) or cold (cryoablation) in the tumor and surrounding margins.**
  - **Non-thermal ablation such as irreversible electroporation creates tumor cell death through electrical pulses that create irreversible membrane pores and cellular lysis/destruction.**

- **Liver Tumor Ablation[10-12]**
  - **Thermal ablation can be considered alone, or in conjunction with surgery, in appropriately selected patients with small metastases that can be treated with margins. All original sites of disease need to be amenable to thermal ablation or resection.**
  - **Image guided thermal ablation may be considered in selected surgical candidates or medically non-surgical candidates with small tumors that can be completely ablated with margins.**
  - **Image guided thermal ablation can be considered in selected patients with recurrence after hepatectomy or ablation as long as all visible disease can be ablated with margins.[10-12]**
  - **Image guided non-thermal ablation (irreversible electroporation) can be considered in patients that cannot be safely resected or ablated with margins due to proximity to central bile ducts or other structures that cannot be protected.**

- **Lung Tumor Ablation[13-15]**
  - **Ablative techniques may be considered alone or in conjunction with resection for resectable disease. All original sites of disease need to be amenable to thermal ablation or resection.**
  - **Image guided thermal ablation can also be considered when unresectable and amenable to complete thermal ablation.**
  - **Image guided thermal ablation may be considered in selected surgical candidates with small tumors that can be completely ablated with margins.**
  - **Image guided thermal ablation may be considered for recurrences after surgery or prior ablation as long as all visible disease is amenable to thermal ablation.**

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES

- **Arterially Directed Embolic Therapy**
  - **Hepatic Transarterial Radioembolization (TARE) with Yttrium-90 (Y-90) Microspheres[16,17]**
    - **Y-90 radioembolization (radiation lobectomy approach) can be considered instead of portal vein embolization when hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume or when there is borderline resectable disease that would benefit from tumor downsizing and remnant hypertrophy.**
    - **Hepatic TARE with Y-90 microspheres can be considered in selected patients with chemotherapy-resistant/refractory disease and with predominant hepatic metastases.**
    - **Radiation segmentectomy approach can be used for limited volume liver disease that is not amenable to resection or thermal ablation.**
  - **Transarterial Chemoembolization (TACE)[18]**
    - **TACE involves hepatic artery catheterization to locally deliver chemotherapy in combination with arterial embolization.**
    - **TACE for hepatic metastatic tumors can be considered in highly selected cases with chemotherapy-resistant/refractory disease, preserved liver function, and with predominant hepatic metastases.**
    - **The most commonly accepted variation for the treatment of metastatic colorectal cancer involves the use of drug eluted bead TACE (DEB-TACE) using irinotecan as the chemotherapeutic agent (DEBIRI).**
    - **DEBIRI can be used along with irinotecan-based chemotherapy for unresectable liver dominant disease.**

- **External Beam Radiation Therapy (EBRT)**
  - **EBRT to the metastatic site can be considered in appropriately selected cases in which the patient has a limited number of metastases, including the liver or lung or other select locations; or the patient is symptomatic; or in the setting of a clinical trial.**
  - **The possible techniques include three-dimensional conformal RT (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactive body radiation therapy (SBRT).**
    - **SBRT is an advanced technique of hypofractionated RT with photons that delivers large ablative doses of radiation. SBRT in the management of liver or lung metastases can be an alternative to ablation/embolization techniques or when these therapies have failed or are contraindicated.[19-24]**
    - **SBRT or other hypofractionated regimens with BED10>100 Gy are preferred in the context of oligometastatic disease to provide durable local control. Final dosing should also take into account adjacent normal organs. (see REC-E)**

- **Hepatic Arterial Infusion (HAI)**
  - **Eligibility:**
    - **Multidisciplinary experience with HAI therapy**
    - **Candidate for major surgery**
    - **Unresectable colorectal liver metastases or resectable colorectal liver metastases at high risk for recurrence**
    - **Treated with at least one line of systemic chemotherapy**
    - **No extrahepatic disease; primary tumor may be in place**
    - **Suitable hepatic arterial anatomy**
    - **No portal hypertension**
    - **No active viral hepatitis**
    - **Direct Bilirubin ≤1.5 mg/dL, Alkaline Phos <2X ULN.**
    - **HAI chemotherapy cannot be delivered with concurrent bevacizumab or other VEGF inhibitors**
    - **No prior radiation to the liver**

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES
CRITERIA FOR RESECTABILITY OF METASTASES AND LOCOREGIONAL THERAPIES WITHIN SURGERY

Liver

- Hepatic resection is the treatment of choice for resectable liver metastases from CRC.[25]
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[26,27]
- There should be no unresectable extrahepatic sites of disease.[28-30]
- Partial debulking (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.
  - Staged procedures can be performed as liver-first or primary-first approaches.[31]
- In the setting of neoadjuvant therapy, placement of pre-treatment fiducial marker(s) in smaller lesions may be considered.
- Re-resection and re-ablation can be considered in selected patients.[32]
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches using preoperative portal vein embolization or staged liver resections can be considered.
- At the time of surgery, ablative techniques may be considered alone or in conjunction with resection.[25] All original sites of disease should be amenable to thermal ablation or resection.
- Thermal ablation may be considered in selected surgical candidates with small tumors that can be completely ablated with margins.
- Arterially directed catheter therapy, and in particular yttrium-90 microsphere radioembolization, is an option in selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- Ablative EBRT may be considered in selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable or can be percutaneously ablated with margins.

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[33-36]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[37-40]
- Re-resection and re-ablation can be considered in selected patients.[41]
- Ablative techniques may be considered alone or in conjunction with resection for resectable disease. All original sites of disease need to be amenable to thermal ablation or resection.
- Ablative techniques can also be considered when unresectable and amenable to complete thermal ablation.
- Thermal ablation may be considered in selected surgical candidates with small tumors that can be completely ablated with margins.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Ablative EBRT may be considered in selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable or can be percutaneously ablated.

Evaluation for Conversion to Resectable or Ablatable Disease

- Re-evaluation for resection and/or ablation should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.[42-45]
- Metastatic tumor(s) with a higher likelihood of being converted to resectable and/or ablatable are those in which the initial disease is confined to limited sites.
- When considering whether disease has been converted to resectable and/or ablatable, all original sites need to be amenable to treatment.[46] Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[47]

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES
ENDOSCOPIC SUBMUCOSAL DISSECTION (ESD)

Therapeutic Principles

- ESD is a minimally invasive, organ-preserving procedure that can provide curative resection for early rectal cancers by removing these lesions en bloc.
- ESD usually involves using an injection with submucosal dissection of the lesion to achieve complete en bloc resection.
- ESD can provide either curative resection after en bloc removal or, if not curative, can provide an accurate pathologic staging of disease.

Pre-ESD Endoscopic Evaluation

- Successful curative resection of rectal lesions requires a thorough assessment of the lesion, including subclassification of laterally spreading tumor (LST), as well as vessel, surface, and pit pattern.[48]
- The morphology of all lesions should be described using the Paris classification, which has been shown to correlate to the likelihood of invasive cancer.[49]
- ESD should be performed at a high-volume center by an experienced endoscopist or surgeon.[48]
- EUS or MRI should be used in the rectum prior to resection when suspicious features of deep submucosal invasion are present.[48]

Criteria for Resection

- ESD with en bloc resection should be considered for rectal lesions at risk for submucosally invasive cancer[50,51]
  - Type V Kudo pit pattern
  - Depressed component (Paris 0–IIc)
  - Complex morphology (0–Is or 0–IIa+Is)
  - Nongranular, laterally spreading tumor ≥20 mm in size
  - Granular, laterally spreading tumor ≥30 mm in size
- Residual or recurrent colorectal adenomas
- Rectal lesions that have surface features (vascular or pit pattern) suggestive of advanced dysplasia or early submucosally invasive carcinoma

Curative Resection

- Based on both the Japanese[52] and European[48] guidelines, resection of rectal lesions can be considered curative when:
  - Negative circumferential and deep vertical tumor margins
  - Submucosal invasion depth <1000 µm
  - Absence of lymphovascular invasion
  - Absent or grade 1 (low-grade) tumor budding
  - Well (G1) to moderately (G2) differentiated tumor histology
    - ◊ If a removed lesion does not meet the above criteria, a multidisciplinary team including an endoscopist, surgeon, and pathologist should use a shared decision-making process to decide whether to proceed with surgery versus intensive surveillance.

Surveillance After ESD[50]

- Risk of lymph node metastasis after curative resection of superficial T1 rectal cancer with submucosal invasion <1000 µm is estimated to be 3%–6%.
- Flexible sigmoidoscopy is recommended 3–6 months after ESD assuming prior colonoscopy.
- Second follow-up endoscopy is recommended 3–6 months after first surveillance exam or colonoscopy if 1 year from ESD.
- Surveillance using flexible sigmoidoscopy is recommended every 6 months for a total of 5 years from ESD.
- EUS or pelvis MRI with contrast is recommended every 3–6 months for 2 years, then every 6 months to complete 5 years.

Surgery vs. ESD

- Prior retrospective studies have found that ESD and TEM/TAMIS do not differ in terms of outcomes, including local recurrence, R0 resection rate, and adverse events.[53-55]
- The decision between surgery and ESD should be determined based on the patient's candidacy for surgery, availability of expertise in ESD, and patient preference.

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES – REFERENCES

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PRINCIPLES OF PERIOPERATIVE THERAPY

Not every patient with rectal cancer requires trimodality treatment—trials with adaptive designs have demonstrated some patients will have favorable outcomes with selective usage of radiation or selective usage of surgery, based on reassessment of response during therapy.[1,2] The regimens used in patients who will undergo or have undergone surgery include both concurrent chemotherapy/RT and chemotherapy alone. Perioperative treatment is recommended for up to a total of 3 to 6 months.

Perioperative Chemotherapy:

- **mFOLFOX 6[3,4,5]**
  Oxaliplatin 85 mg/m² IV, day 1,[a] leucovorin 400 mg/m² IV day 1,[b] 5-FU 400 mg/m² IV bolus on day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 months perioperative therapy.
- **CAPEOX[6,7]**
  Oxaliplatin 130 mg/m² IV day 1.[a] Capecitabine 1000 mg/m² PO twice daily for 14 days every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy.
- **FOLFIRINOX[8,c]**
  Oxaliplatin 85 mg/m² IV on day 1,[a] leucovorin 400 mg/m² IV over 2 hours on day 1,[b] irinotecan 180 mg/m² IV over 30–90 minutes on day 1, 5-FU 400 mg/m² IV push day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks.
- **Modified FOLFIRINOX[9,c]**
  Oxaliplatin 85 mg/m² IV on day 1,[a] leucovorin 400 mg/m² IV over 2 hours on day 1,[b] irinotecan 150 mg/m² IV over 30–90 minutes on day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks.

Dosing Schedules for Concurrent Chemotherapy/RT:

- **RT + continuous infusion 5-FU[10]**
  5-FU 225 mg/m² IV over 24 hours daily on days 1–5 or days 1–7 for 5 weeks with RT
- **RT + capecitabine[11,12]**
  Capecitabine 825 mg/m² PO BID, Monday–Friday, on days of radiation treatment only, throughout the duration of RT (typically 28–30 treatment days)
- **RT + 5-FU/leucovorin[13,d]**
  5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during weeks 1 and 5 of RT

[a] 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.
[b] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[c] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of 5-FU (3200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with 5-FU. The dose of 5-FU (2400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.
[d] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

References on REC-D (2 of 2)

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PRINCIPLES OF RADIATION THERAPY

General Principles

- **Chemotherapy with a fluoropyrimidine in oral or continuous venous infusion form should be delivered concurrently with conventionally fractionated RT.**
- **In patients with a limited number of liver or lung metastases, ablative radiotherapy to the metastatic site can be considered in selected cases. Ablative radiotherapy can be considered for patients with unresectable metastasis or in patients preferring a nonoperative approach. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3D conformal RT, IMRT, or SBRT.**

Treatment Information

- **Image-guided RT (IGRT) with kilovoltage (kV) imaging or cone-beam CT imaging should be routinely used during the course of treatment with IMRT and SBRT.**
- **IMRT is preferred for reirradiation of previously treated patients with recurrent disease, patients treated postoperatively due to increased acute or later toxicity,[1] or in unique anatomical situations (eg, coverage of external iliac lymph nodes for T4 tumors invading anterior pelvic organs or inguinal lymph nodes for low-lying tumors involving the anal canal or avoidance of small bowel).**
- **In patients with locally recurrent disease after prior pelvis RT, consider use of hyperfractionated pelvic re-irradiation if re-treatment is planned.[2]**
- **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.**
- **SBRT or other hypofractionated regimens with BED10>100 Gy are preferred in the context of oligometastatic disease to provide durable local control. Final dosing should also take into account adjacent normal organs. SBRT can be considered for larger lesions or more extensive disease, if there is sufficient uninvolved liver/lung and liver/lung radiation tolerance can be respected. There should be no other systemic disease or it should be minimal and addressed in a comprehensive management plan.**

Treatment Information – Target Volumes, RT Dosing; Supportive Care REC-E 2 of 2

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PRINCIPLES OF RADIATION THERAPY

Treatment Information

- **Target Volumes**
  - **Target volume definition should be performed per ICRU 50 recommendations.**
  - **Gross tumor volume (GTV) should include all primary tumor and involved lymph nodes, using information from physical examination, endoscopic findings, diagnostic imaging, and the simulation planning study for delineation. Clinical target volume (CTV) should include the GTV plus areas at risk for microscopic spread from the primary tumor and at-risk nodal areas. A consensus atlas may be helpful to review when defining elective nodal CTVs.[3]**
  - **At-risk nodal regions include mesorectal, presacral, posterior obturator nodes, and internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures. Consider including the inguinal nodes for low-lying tumors involving the anal canal.**
  - **Fusion of the pelvis MRI is strongly recommended to optimally define gross disease.**
  - **If using 3D conformal radiation, multiple RT fields should be used (generally a 3- or 4-field technique). Prone positioning, full bladder, and other techniques to minimize the volume of small bowel in the fields are encouraged.**
  - **For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.**
- **RT Dosing**
  - **45–54 Gy in 25–30 fractions to the pelvis.**
    - **For resectable cancers, after 45 Gy a tumor bed boost with a 2-cm margin of 5.4 to 9.0 Gy in 3 to 5 fractions could be considered for preoperative radiation.**
    - **Small bowel max point dose should be limited to Dmax 55 Gy, V45 Gy should be ≤150 cc, or V50 should be ≤30 cc for individual small bowel loops.[4]**
    - **For unresectable cancers, doses higher than 54 Gy may be required, if technically feasible.**
  - **Short-course RT (25 Gy in 5 fractions) can also be considered for patients for preoperative radiation.**
    - **For high-risk rectal cancer (clinical tumor stage cT4a or cT4b, EMVI, clinical nodal stage cN2, involved MRF, [tumor or lymph node 1 mm or less from the MRF] or enlarged lateral lymph nodes considered to be metastatic), the 5-year follow-up of the RAPIDO trial now indicates a statistically higher locoregional recurrence rate (10%) in the experimental arm of short-course RT → chemotherapy → surgery versus control arm (6%) of chemoRT → surgery → adjuvant chemotherapy.[5]**

Supportive Care

- **Patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis.**
- **Patients of childbearing potential should be counseled about the effects of premature menopause and consideration should be given to referral for discussion of hormone replacement strategies.**
- **Patients of childbearing potential should be counseled that an irradiated uterus cannot carry a fetus to term.**
- **Patients should be counseled on sexual dysfunction, potential for future low testosterone levels, and infertility risks and given information regarding sperm banking or oocyte, egg, or ovarian tissue banking, as appropriate, prior to treatment.**

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb] that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

INITIAL THERAPY[d]	
Intensive Therapy Recommended	**Intensive Therapy NOT Recommended**
• FOLFOX[e] ± bevacizumab • CAPEOX[e] ± bevacizumab • FOLFIRI[f] ± bevacizumab • FOLFIRINOX[e,f,g,h] ± bevacizumab • *KRAS/NRAS/BRAF* WT[i]: ▸ FOLFOX[e] + (cetuximab or panitumumab)[j] ▸ CAPEOX[e] + (cetuximab or panitumumab)[j] ▸ FOLFIRI[f] + (cetuximab or panitumumab)[j] • *BRAF* V600E mutation positive[j]: ▸ Encorafenib + (cetuximab or panitumumab) + FOLFOX[e] • If disease progression, see REC-F 2 of 13	• 5-FU ± leucovorin ± bevacizumab • Capecitabine ± bevacizumab • *KRAS/NRAS/BRAF* WT[i]: ▸ (Cetuximab or panitumumab)[j] (category 2B) • HER2-amplified and *RAS and* BRAF WT[j]: ▸ Trastuzumab + [pertuzumab or lapatinib or tucatinib][k] • If disease progression and improvement in functional status, ▸ Consider initial therapy in first column[l] ▸ OR if previous fluoropyrimidine, see REC-F 2 of 13 • If disease progression and no improvement in functional status, see Best supportive care NCCN Guidelines for Palliative Care

For dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb], see REC-F 3 of 13

Footnotes on REC-F 4 of 13

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c,m]
pMMR/MSS (or dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb] that is ineligible for or progressed on checkpoint inhibitor immunotherapy)

SECOND-LINE AND SUBSEQUENT THERAPY OPTIONS (if not previously given)[d,n]		
Previous oxaliplatin-based therapy without irinotecan	**Previous therapy with oxaliplatin and irinotecan**	**Biomarker-directed therapy**
• FOLFIRI[f] or irinotecan[f] • FOLFIRI[f] + (bevacizumab[o] [preferred] or ziv-aflibercept[o,p] or ramucirumab[o,p]) • Irinotecan[f] + (bevacizumab[p] [preferred] or ziv-aflibercept[o,p] or ramucirumab[o,p]) • If *KRAS/NRAS/BRAF* WT[i]: ▸ FOLFIRI[f] + (cetuximab or panitumumab)[j,q] ▸ (Cetuximab or panitumumab)[j,q] ± irinotecan[f] • Biomarker-directed therapy (see Biomarker-directed therapy)	• If *KRAS/NRAS/BRAF* WT[i]: ▸ (Cetuximab or panitumumab)[j,q] ± irinotecan[f] • Biomarker-directed therapy (see Biomarker-directed therapy) • For disease that has progressed through all available regimens: ▸ Fruquintinib ▸ Regorafenib ▸ Trifluridine + tipiracil ± bevacizumab (bevacizumab combo preferred) • Best supportive care (NCCN Guidelines for Palliative Care)	• *BRAF* V600E mutation positive[j] ▸ Encorafenib + (cetuximab or panitumumab)[r] ▸ (Encorafenib + [cetuximab or panitumumab] + FOLFOX[e])[s] (category 2B) • HER2-amplified and *RAS* and *BRAF* WT[j] ▸ (Trastuzumab + [pertuzumab or lapatinib or tucatinib])[k] • HER2-amplified (IHC 3+) ▸ Fam-trastuzumab deruxtecan-nxki[t] • *KRAS* G12C mutation positive[j] ▸ (Sotorasib or adagrasib)[u] + (cetuximab or panitumumab) • *NTRK* gene fusion-positive ▸ Entrectinib ▸ Larotrectinib ▸ Repotrectinib[v] • *RET* gene fusion-positive ▸ Selpercatinib
Previous irinotecan-based therapy without oxaliplatin	**Previous therapy without oxaliplatin or irinotecan**	
• FOLFOX[e] or CAPEOX[e] • FOLFOX[e] + bevacizumab • CAPEOX[e] + bevacizumab • If *KRAS/NRAS/BRAF* WT[i]: ▸ FOLFOX[e] + (cetuximab or panitumumab)[j] ▸ CAPEOX[e] + (cetuximab or panitumumab)[j] ▸ (Cetuximab or panitumumab)[j,q] ± irinotecan[f] • Biomarker-directed therapy (see Biomarker-directed therapy)	• FOLFOX[e] or CAPEOX[e] • (FOLFOX or CAPEOX)[e] + bevacizumab • FOLFIRI[f] or irinotecan[f] • (FOLFIRI or irinotecan)[f] + (bevacizumab[o] [preferred] or ziv-aflibercept[o,p] or ramucirumab[o,p]) • Irinotecan[f] + oxaliplatin[e] ± bevacizumab • FOLFIRINOX[e,h] ± bevacizumab • If *KRAS/NRAS/BRAF* WT[i]: ▸ FOLFIRI[f] + (cetuximab or panitumumab)[j,q] ▸ (Cetuximab or panitumumab)[f,q] ± irinotecan[f] • Biomarker-directed therapy (see Biomarker-directed therapy)	

Footnotes on REC-F 4 of 13

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CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb]
Any line of therapy

Candidate for immunotherapy and no prior immunotherapy received → **Checkpoint inhibitor immunotherapy[*,w,x,y]** → **Re-evaluate disease status every 2–3 mo** →

Surveillance (REC-10A)
or
Surgery ± RT
or
Continue immunotherapy[w]
or
Nivolumab + ipilimumab (if checkpoint inhibitor monotherapy was previously received)
or
Systemic therapy (REC-F 1 of 13)

Prior immunotherapy received →

Systemic therapy (REC-F 1 of 13)
or
Nivolumab + ipilimumab (if checkpoint inhibitor monotherapy was previously received)

Footnotes on REC-F 4 of 13

[*] Patients should be followed closely for 10 weeks to assess for response.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – FOOTNOTES

[a] For chemotherapy references, see Chemotherapy Regimens and References (REF-F [5 of 13]).
[b] For infection risk, monitoring, and prophylaxis recommendations for targeted therapies, see INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[d] C/A/P CT with contrast or chest CT and abdomen/pelvis MRI with contrast to monitor progress of therapy. FDG-PET/CT should not be used. See Principles of Imaging (REC-A).
[e] Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.
[f] Irinotecan should be used with caution in patients with Gilbert syndrome or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. Guidelines for use in clinical practice have not been established.
[g] FOLFIRINOX should be strongly considered for patients with excellent performance status.
[h] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of 5-FU (3200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with 5-FU. The dose of 5-FU (2400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.
[i] Patients with BRAF mutations other than V600E may be considered for anti-EGFR therapy.
[j] Principles of Pathologic Review (REC-B).
[k] If no previous treatment with HER2 inhibitor.
[l] The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.
[m] 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. See Principles of Surgery and Locoregional Therapies (REC-C).
[n] 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.
[o] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[p] 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.
[q] Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
[r] In the second-line setting for *BRAF* V600E mutation-positive tumors, there is phase 3 evidence for better efficacy with targeted therapies over FOLFIRI.
[s] *BRAF* V600E regimen may be given with FOLFOX as subsequent line therapy if no previous treatment with oxaliplatin or BRAF-targeting regimen.
[t] Some activity was seen after a previous HER2-targeted regimen. May not be indicated in patients with underlying lung issues due to lung toxicity (3.5% report of drug-related deaths from interstitial lung disease on the DESTINY-CRC01 trial).
[u] If patient is unable to tolerate EGFR inhibitor due to toxicity, single-agent adagrasib or sotorasib can be considered.
[v] On the TRIDENT-1 trial, repotrectinib showed activity in both NTRK TKI-naïve and NTRK TKI-pretreated patients.
[w] Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, dostarlimab-gxly, cemiplimab-rwlc, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr. Nivolumab + ipilimumab combination is category 2B when intensive therapy is not recommended due to toxicity concerns. Combination PD-L1/CTLA-4 blockade has been associated with improved survival in unresectable or metastatic CRC, but also higher toxicity. Nivolumab and hyaluronidase-nvhy is not approved for concurrent use with IV ipilimumab; however, for nivolumab monotherapy, nivolumab and hyaluronidase-nvhy subcutaneous injection may be substituted for IV nivolumab. Nivolumab and hyaluronidase-nvhy has different dosing and administration instructions compared to IV nivolumab. This applies to all areas of the Guideline where nivolumab is listed.
[x] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[y] If disease response, consider discontinuing checkpoint inhibitor after 2 years of treatment.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS[c]

mFOLFOX 6[1,2,3]
Oxaliplatin 85 mg/m² IV day 1[z]
Leucovorin 400 mg/m² IV day 1[aa]
5-FU 400 mg/m² IV bolus on day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

mFOLFOX 7[4]
Oxaliplatin 85 mg/m² IV day 1[z]
Leucovorin 400 mg/m² IV day 1[aa]
5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

FOLFOX + bevacizumab[5,bb]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFOX + panitumumab[6] (*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFOX + cetuximab[7] (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks (preferred for every 2 weeks)

CAPEOX[8]
Oxaliplatin 130 mg/m² IV day 1[z]
Capecitabine 1000[cc] mg/m² twice daily PO for 14 days
Repeat every 3 weeks

CAPEOX + bevacizumab[8,bb]
Oxaliplatin 130 mg/m² IV day 1[z]
Capecitabine 1000[cc] mg/m² PO twice daily for 14 days
Bevacizumab 7.5 mg/kg IV day 1
Repeat every 3 weeks

CAPEOX + cetuximab[9-11] (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks (preferred for every 2 weeks)

CAPEOX + panitumumab[9-11] (*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI[12,13]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin[aa] 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1
5-FU 400 mg/m² IV bolus day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks

FOLFIRI + bevacizumab[14,bb]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

FOLFIRI + cetuximab (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² IV over 2 hours first infusion, followed by 250 mg/m² IV over 60 minutes weekly[15]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[16] (preferred for every 2 weeks)

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[z] 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.
[aa] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[bb] 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).
[cc] 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.

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References on REC-F (10 of 13)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS[c]

FOLFIRI + panitumumab[17] (*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept[18]
Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ramucirumab[19]
Ramucirumab 8 mg/kg over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRINOX[20,h]
Oxaliplatin 85 mg/m² IV on day 1,[z] leucovorin 400 mg/m² IV over 2 hours on day 1, irinotecan 165–180 mg/m² IV over 30–90 minutes on day 1, 5-FU 400 mg/m² IV push day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion.
Repeat every 2 weeks

Modified FOLFIRINOX[21-23,h]
Oxaliplatin 85 mg/m² IV on day 1,[z] leucovorin 400 mg/m² IV over 2 hours on day 1, irinotecan 150 mg/m² IV over 30–90 minutes on day 1, 5-FU 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46 hours) continuous infusion. Repeat every 2 weeks

FOLFIRINOX or mFOLFIRINOX + bevacizumab[24,bb]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

IROX[25]
Oxaliplatin 85 mg/m² IV,[z]
followed by irinotecan 200 mg/m² over 30–90 minutes every 3 weeks

IROX + bevacizumab[bb]
Bevacizumab 7.5 mg/kg IV on day 1
Repeat every 3 weeks

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[26]
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/leucovorin (sLV5FU2)[12]
Leucovorin[aa] 400 mg/m² IV over 2 hours on day 1,
followed by 5-FU bolus 400 mg/m² followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks
Weekly Leucovorin 20 mg/m² IV over 2 hours on day 1, 5-FU 500 mg/m² IV bolus injection 1 hour after the start of leucovorin. Repeat weekly[27]
or
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week[27]

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[h] FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of 5-FU (3200 mg/m² over 48 hours). Patients in the United States have been shown to have greater toxicity with 5-FU. The dose of 5-FU (2400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.
[z] 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.
[aa] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[bb] 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).

Continued

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS[c]

Bolus or infusional 5-FU + bevacizumab[bb]
Bevacizumab 5 mg/kg IV on day 1
Repeat every 2 weeks

Capecitabine[28,cc]
Capecitabine 850–1250 mg/m² PO twice daily for 14 days
Repeat every 3 weeks

Capecitabine + bevacizumab[29,bb]
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[30,31]
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)
Cetuximab 400 mg/m² first infusion, followed by 250 mg/m² IV weekly[32]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[16]
(preferred for every 2 weeks)

Irinotecan + panitumumab[17,33]
(*KRAS*/*NRAS*/*BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + bevacizumab[34,bb]
Irinotecan 180 mg/m² IV, day 1
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks
or
Irinotecan 300–350 mg/m² IV, day 1
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan + ramucirumab[19]
Ramucirumab 8 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + ziv-aflibercept
Irinotecan 180 mg/m² IV, day 1
Ziv-aflibercept 4 mg/kg IV, day 1
Repeat every 2 weeks

Cetuximab (*KRAS/NRAS/BRAF* WT)
Cetuximab 400 mg/m² first infusion, followed by 250 mg/m² IV weekly[32]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[16]
(preferred for every 2 weeks)

Panitumumab[35] (*KRAS/NRAS/BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib
Regorafenib 160 mg PO daily on days 1–21[36]
or
First cycle: Regorafenib 80 mg PO daily on days 1–7, followed by 120 mg PO daily on days 8–14, followed by 160 mg PO daily on days 15–21[37]
Subsequent cycles: Regorafenib 160 mg PO daily on days 1–21
Repeat every 28 days

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[bb] 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).
[cc] 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.

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References on REC-F (10 of 13)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS[c]

Trifluridine + tipiracil ± bevacizumab[38,39]
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
Bevacizumab 5 mg/kg on days 1 and 15
Repeat every 28 days

Pembrolizumab[40] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])
Pembrolizumab 2 mg/kg IV every 3 weeks
or Pembrolizumab 200 mg IV every 3 weeks
or Pembrolizumab 400 mg IV every 6 weeks

Nivolumab[41] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every 2 weeks
or Nivolumab 480 mg IV every 4 weeks

Nivolumab + ipilimumab[42] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])
Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses, followed by Nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 4 weeks

Dostarlimab-gxly[43] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])
Dostarlimab-gxly 500 mg IV every 3 weeks for 4 doses followed by 1000 mg IV every 6 weeks

Cemiplimab-rwlc[44,45] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])
350 mg IV on day 1
Repeat every 3 weeks

Retifanlimab-dlwr[46,47] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])
500 mg IV on day 1
Repeat every 4 weeks

Tislelizumab-jsgr[48-51] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])
200 mg IV on day 1
Repeat every 3 weeks

Toripalimab-tpzi[52,53] (dMMR/MSI-H or *POLE/POLD1* mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb])
3 mg/kg IV on day 1
Repeat every 2 weeks

Trastuzumab + pertuzumab[54]
(HER2-amplified and *RAS* and *BRAF* WT)
Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
Pertuzumab 840 mg IV loading dose on day 1 of cycle 1, followed by 420 mg IV every 21 days

Trastuzumab + lapatinib[55]
(HER2-amplified and *RAS* and *BRAF* WT)
Trastuzumab 4 mg/kg IV loading dose on day 1 of cycle 1, followed by 2 mg/kg IV weekly
Lapatinib 1000 mg PO daily

Trastuzumab + tucatinib[56]
(HER2-amplified and *RAS* and *BRAF* WT),
Trastuzumab 8 mg/kg IV loading dose on day 1 of cycle 1, followed by 6 mg/kg IV every 21 days
Tucatinib 300 mg PO twice daily

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

Continued
References on REC-F (10 of 13)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS[c]

Fam-trastuzumab deruxtecan-nxki[57] (HER2-amplified, IHC 3+)
Fam-trastuzumab deruxtecan-nxki 5.4 mg/kg IV on day 1
Repeat every 21 days

Encorafenib + cetuximab[58-60]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Cetuximab 400 mg/m² IV followed by 250 mg/m² IV weekly
or Cetuximab 500 mg/m² IV every 2 weeks

Encorafenib + panitumumab[58-60]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

Encorafenib + FOLFOX + cetuximab[61]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Cetuximab 500 mg/m² IV day 1
Oxaliplatin 85 mg/m² IV day 1
Leucovorin 400 mg/m² IV day 1
5-FU 400 mg/m² IV bolus on day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

Encorafenib + FOLFOX + panitumumab[61]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Panitumumab 6mg/kg IV every day 1
Oxaliplatin 85 mg/m² IV day 1
Leucovorin 400 mg/m² IV day 1
5-FU 400 mg/m² IV bolus on day 1, followed by 1200 mg/m²/day x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

Larotrectinib[62] (*NTRK* gene fusion-positive)
100 mg PO twice daily

Entrectinib[63] (*NTRK* gene fusion-positive)
600 mg PO once daily

Repotrectinib[64] (*NTRK* gene fusion-positive)
160 mg PO daily for first 14 days,
Then increase to 160 mg PO twice daily

Selpercatinib[65] (*RET* gene fusion-positive)
- **Patients ≥50 kg: 160 mg PO twice daily**
- **Patients <50 kg: 120 mg PO twice daily**

Adagrasib + cetuximab[66] (*KRAS* G12C mutation positive)
Adagrasib 600 mg PO BID
Cetuximab 500 mg/m² IV every 2 weeks

Adagrasib + panitumumab (*KRAS* G12C mutation positive)
Adagrasib 600 mg PO BID
Panitumumab 6 mg/kg IV every 2 weeks

Sotorasib + cetuximab (*KRAS* G12C mutation positive)
Sotorasib 960 mg PO daily
Cetuximab 500 mg/m² IV every 2 weeks

Sotorasib + panitumumab[67] (*KRAS* G12C mutation positive)
Sotorasib 960 mg PO daily
Panitumumab 6 mg/kg IV every 2 weeks

Fruquintinib[68]
5 mg PO daily on days 1–21
Repeat every 28 days

[c] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.

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References on REC-F (10 of 13)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE – REFERENCES

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PRINCIPLES OF SURVIVORSHIP – COLORECTAL LONG-TERM FOLLOW-UP CARE

Colorectal Cancer Surveillance

- See REC-10.
- 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 the 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
  - Delineation of appropriate timing of transfer of care with specific responsibilities identified for primary care physician and oncologist
  - Health behavior recommendations
  - Fertility counseling

Management of Late/Long-Term Sequelae of Disease or Treatment[2-6]

- 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, and 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 (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 Wellness[10]
(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.
- Drink alcohol sparingly, if at all.
- 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.

References on REC-G (2 of 2)

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PRINCIPLES OF NONOPERATIVE MANAGEMENT

To provide nonoperative management (NOM) for patients with rectal cancer, the multidisciplinary team's diagnostic skills are crucial. They must accurately assess clinical, radiologic, and pathologic findings, determining patient eligibility for NOM and closely monitoring progress. The team's expertise extends to tracking treatment responses, identifying surgical needs promptly, and adjusting the management plan as necessary. Additionally, the team should maintain a comprehensive understanding of the watchful waiting literature and surveillance methodology, adeptly treating patients with complete or near-complete clinical responses and regularly monitoring for potential tumor recurrence or progression. Given this, NOM is recommended only at centers with experienced multidisciplinary teams and for patients committed to intensive surveillance.

Criteria for Complete Clinical Response

- High-definition flexible endoscopy[1]
  - Pale smooth scar with or without telangiectasia
  - No ulceration, nodularity, or mucosal irregularities
  - No stricture
- DRE[1]
  - Smooth, flat scar
  - No nodularity
- Diffusion-weighted MRI[2]
  - Fibrotic, linear scar with low signal intensity on T2-weighted images
  - No diffusion restriction
  - No suspicious lymph nodes
- All of the criteria must be satisfied in order to define a complete clinical response
- Biopsy offers no added diagnostic value if the criteria are met[3,4]
- Circulating tumor DNA (ctDNA) has no proven role in the NOM of patients

Timing of Assessment for Complete Clinical Response

- For patients treated with chemotherapy first followed by radiation (induction chemotherapy), assessment should be performed no earlier than 8 weeks after completion of radiotherapy to allow time for delayed response to radiation.[5]
- For patients treated with radiation first followed by chemotherapy (consolidation chemotherapy), assessment should be completed within a month of completion of chemotherapy.

Near Complete Response[6,7]

- If the patient has had a near complete response and wishes to avoid surgery, then an additional 8 weeks of observation followed by reassessment can be considered.
  - An nCR is defined by:
    - ◊ Smooth induration or superficial minor mucosal irregularity on DRE
    - ◊ Endoscopic appearance with irregular small mucosal nodules, superficial ulceration, or mild persistent erythema
    - ◊ T2-weighted MRI with downstaging with or without residual fibrosis, small area of residual signal, and complete or partial regression of lymph nodes
    - ◊ Diffusion-weighted MRI with small area of residual high signal intensity

Indications for Surgery

- Radical surgery is indicated for patients who do not ultimately achieve a complete clinical response based on the above criteria or patients who have tumor regrowth after a clinical response.
- If residual tumor or regrowth is suspected at the time of assessment, it is not necessary to perform biopsies. False-negative biopsies are common in this scenario and a high degree of suspicion for tumor is sufficient as an indication for surgery.[8]

References on REC-H (2 of 2)

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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. (This category is not assigned by pathologists)
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 Rectal 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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ABBREVIATIONS

ASCO	American Society of Clinical Oncology
C/A/P	chest/abdomen/pelvis
CAP	College of American Pathologists
CBC	complete blood count
cCR	clinical complete response
CEA	carcinoembryonic antigen
CLIA	Clinical Laboratory Improvement Amendments
CLIA-88	clinical laboratory improvement amendments of 1988
CRC	colorectal cancer
CRM	circumferential resection margin
ctDNA	circulating tumor DNA
CTV	clinical target volume
DCE	dynamic contrast-enhanced
dMMR	mismatch repair deficient
DRE	digital rectal examination
DWI	diffusion-weighted imaging
EBRT	external beam radiation therapy
ED	exonuclease domain
EMVI	extramural vascular invasion
ESD	endoscopic submucosal dissection
EUS	endoscopic ultrasound
FAP	familial adenomatous polyposis
FISH	fluorescence in situ hybridization
GBCA	gadolinium-based contrast agent
GFR	glomerular filtration rate
GTV	gross tumor volume
HAI	hepatic arterial infusion
H&E	hematoxylin and eosin
ICRU	International Commission on Radiation Units and Measurements
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
IORT	intraoperative radiation therapy
LS	Lynch syndrome
LST	laterally spreading tumor
MMR	mismatch repair
MRF	mesorectal fascia
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
nCR	near complete response
NGS	next-generation sequencing
NOM	nonoperative management
PCR	polymerase chain reaction
pMMR	proficient mismatch repair
PNI	perineural invasion
PPAP	polymerase proofreading-associated polyposis
PV	pathogenic variant
SBRT	stereotactic body radiation therapy
SNV	single nucleotide variant
TAMIS	transanal minimally invasive surgery
TEM	transanal endoscopic microsurgery
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
TME	total mesorectal excision
ULN	upper limit of normal
3D-CRT	three-dimensional conformal radiation therapy

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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Discussion

This discussion corresponds to the NCCN Guidelines for Rectal Cancer. Last updated January 25, 2023

Table of Contents

Overview **MS-2**

Guidelines Update Methodology **MS-2**

Literature Search Criteria **MS-2**

Sensitive/Inclusive Language Usage **MS-3**

Risk Assessment **MS-3**

- Lynch Syndrome MS-3
- The Role of Vitamin D in CRC MS-4
- Other Risk Factors for CRC MS-5

TNM Staging **MS-6**

Pathology **MS-6**

Clinical Presentation and Treatment of Nonmetastatic Disease **MS-9**

- Management of Malignant Polyps MS-9
- Management of Localized Rectal Cancer MS-10
- NCCN Recommendations for Nonmetastatic Rectal Cancer MS-30

Management of Metastatic Disease **MS-32**

- Surgical Management of Colorectal Metastases MS-32
- Local Therapies for Metastases MS-33
- Peritoneal Carcinomatosis MS-37
- Determining Resectability MS-37
- Neoadjuvant Therapy and Conversion to Resectability MS-38
- Perioperative Therapy for Resectable Metachronous Metastatic Disease MS-42
- Systemic Therapy for Advanced or Metastatic Disease MS-43
- Recommendations for Treatment of Resectable Synchronous Metastases MS-44
- Recommendations for Treatment of Unresectable Synchronous Metastases MS-45
- Recommendations for Treatment of Metachronous Metastases MS-46

Endpoints for Advanced CRC Clinical Trials **MS-47**

Post-Treatment Surveillance **MS-47**

- Managing an Increasing CEA Level MS-50

Treatment of Locally Recurrent Disease **MS-50**

Survivorship **MS-51**

- Healthy Lifestyles for Survivors of CRC MS-52
- Secondary Chemoprevention for CRC Survivors MS-53

Summary **MS-53**

Figure 1. Definition of Rectum **MS-55**

References **MS-56**

Discussion update in progress

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Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2022, an estimated 44,850 new cases of rectal cancer will occur in the United States (26,650 cases in males; 18,200 cases in females). During the same year, it is estimated that 52,580 people will die from rectal and colon cancer combined.[1] Despite these high numbers, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005 and, more recently, 38.7 in 2016.[2,3] In addition, mortality from CRC has been decreasing for decades (since 1947 in females and since 1980 in males) and is currently down by more than 50% from peak mortality rates.[1,3] These improvements in incidence of and mortality from CRC are thought to be a result of cancer prevention and earlier diagnoses through screening and of better treatment modalities. Recent data show continued rapid declines in incidence among those aged ≥65 years, with a decrease of 3.3% annually between 2011 and 2016.[3] CRC incidence and mortality rates vary by race and ethnicity with the highest rates in non-Hispanic Black individuals and lowest in Asian Americans/Pacific Islanders.[3] The magnitude of disparity in mortality rates is double that of incidence rates. Reasons for these racial disparities include differences in risk factor prevalence, access to health care and other social determinants of health, comorbidities, and tumor characteristics.

Conversely, incidence has increased among those younger than 65 years, with a 1% annual increase in those aged 50 to 64 years and 2% annual increase in those younger than 50 years. CRC death rates also showed age-dependent trends, declining by 3% annually for those ≥65 years of age, compared to a 0.6% annual decline for individuals aged 50 to 64 years and a 1.3% annual increase for individuals younger than 50 years.[3] A retrospective cohort study of the SEER CRC registry also found that the incidence of CRC in patients younger than 50 years has been increasing.[4] 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. One review suggests that CRC that occurs in young adult patients may be clinicopathologically and genetically different from CRC in older adults, although this has not been confirmed broadly. If cancer in this population is different, there would be a need to develop specific treatment strategies for this population.[5]

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) 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 CRC who are receiving combined modality treatment.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the update of the NCCN Guidelines for Rectal Cancer, an electronic search of the PubMed database was performed to obtain key literature in colorectal cancer published since the previous Guidelines update, using the search terms: “colon cancer, colorectal cancer, rectal

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cancer." The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[6]

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; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-fat-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Risk Assessment

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

CRC is a heterogeneous disease. An international consortium recently reported a molecular classification, defining four different subtypes: CMS1 (MSI Immune), hypermutated, microsatellite unstable (see *Lynch Syndrome* and *Microsatellite Instability*, below), with strong immune activation; CMS2 (Canonical), epithelial, chromosomally unstable, with marked WNT and MYC signaling activation; CMS3 (Metabolic), epithelial, with evident metabolic dysregulation; and CMS4 (Mesenchymal), prominent transforming growth factor β activation, stromal invasion, and angiogenesis.[16] However, this classification is not yet recommended in clinical practice.

Lynch Syndrome

Lynch syndrome is the most common form of genetically determined CRC predisposition, accounting for 2% to 4% of all CRC cases.[12,13,17,18] This

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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 CRC specimens to identify individuals who might have Lynch syndrome: 1) immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation; or 2) 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.[19] 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.[19]

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.[20-23] The cost-effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for CRC, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the Centers for Disease Control and Prevention (CDC)[24-26] and by the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and ASCO in a guideline on molecular biomarkers for CRC.[27] The U.S. Multi-Society Task Force on Colorectal Cancer also recommends universal genetic testing of tumors of all patients with newly diagnosed CRC, as does the American Gastroenterological Association.[28,29] The Cleveland Clinic recently reported on its experiences implementing such a screening approach.[30]

The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with newly diagnosed colon or rectal cancer to identify individuals with Lynch syndrome. This testing is also relevant for treatment selection in stage IV disease (see *Systemic Therapy for Advanced or Metastatic Disease*, below). 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 CRC

Prospective studies have suggested that vitamin D deficiency may contribute to CRC incidence and/or that vitamin D supplementation may decrease CRC risk.[31-37] Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with CRC.[38-41] In fact, a systematic review and meta-analysis of five studies totaling 2330 patients with CRC 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.[42] Another meta-analysis determined that the relationship between vitamin D levels and mortality is linear.[43]

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.[44] 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

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specific vitamin D receptor alleles may benefit from vitamin D supplementation for prevention of advanced adenomas.[45]

Furthermore, no study has yet definitively shown that vitamin D supplementation improves outcomes in patients with CRC. Several studies have reported that supplementation did not improve survival.[46-48] In addition, while the randomized, double-blind, phase II SUNSHINE trial reported a longer progression-free survival (PFS) for patients with previously untreated metastatic CRC (mCRC) randomized to standard treatment plus high-dose vitamin D supplementation compared to those randomized to standard treatment plus low-dose vitamin D supplementation (13.0 vs. 11.0 months), this difference was not significant (HR, 0.64; 95% CI, 0–0.90; $P = .02$).[49] There was also no significant difference between high- and standard-dose vitamin D supplementation for overall response rate (ORR) or OS. In a 2010 report, the Institute of Medicine (now known as the National Academy of Medicine) concluded that data supporting a role for vitamin D were only conclusive in bone health, and not in cancer and other diseases.[50] 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 CRC.

Other Risk Factors for CRC

It is well-recognized that individuals with inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease) are at an increased risk for CRC.[51-53] Other possible risk factors for the development of CRC 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).[52,54-70] In fact, in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort of almost 350,000 individuals, those who adhered to five healthy lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, and healthy diet) had an HR for the development of CRC of 0.63 (95% CI, 0.54–0.74) compared with those who adhered to less than or equal to one of the factors.[71] Other large studies support the conclusion that adherence to healthy lifestyle factors can reduce the risk of CRC.[72,73]

Some data suggest that consumption of dairy may lower risk for the development of CRC.[69,74,75] However, a recent systematic review and meta-analysis of 15 cohort studies (>900,000 subjects; >5200 cases of CRC) only found an association between risk for colon cancer in males and the consumption of nonfermented milk.[76] No association was seen for rectal cancer in males or for colon or rectal cancer in females, and no association was seen 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 CRC, including the consumption of fish and legumes.[77-79] Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may also decrease the risk for CRC,[80-85] although evidence supporting this association is limited and variable.[86] The updated U.S. Preventive Services Task Force (USPSTF) guidance concluded that there was insufficient evidence that aspirin use reduces CRC incidence and, therefore, recommends that the decision to initiate low-dose aspirin for primary prevention of cardiovascular disease in adults aged 40 to 59 years with a 10-year cardiovascular disease risk greater than or equal to 10% should be individualized as the net benefit of aspirin use in this group is small.[87]

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption are associated with a poor prognosis.[60,88-92] Conversely, post-diagnosis fish consumption may be associated with a better prognosis.[93] A family history of CRC increases risk while improving prognosis.[94] Data on the effect of dairy consumption on prognosis after diagnosis of CRC are conflicting.[95,96]

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The relationship between diabetes and CRC is complex. Whereas diabetes and insulin use may increase the risk of developing CRC, treatment with metformin appears to decrease risk, at least in females.[97-106] Results of a small randomized study suggest that 1 year of low-dose metformin in patients who are non-diabetic with previously resected colorectal adenomas or polyps may reduce the likelihood of subsequent adenomas or polyps.[107] In addition, although patients with CRC and diabetes appear to have a worse prognosis than those without diabetes,[108,109] patients with CRC and diabetes treated with metformin seem to have a survival benefit over those not treated with metformin.[103,110,111] The data regarding the effects of metformin on CRC incidence and mortality, however, are not completely consistent, with some studies seeing no effect.[112,113]

TNM Staging

The NCCN Guidelines for Rectal Cancer adhere to the current TNM (tumor, node, metastases) staging system of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual (Table 1 of the guidelines).[114] 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.[114]

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).[114]

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.[115]

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.[114] Patients with peritoneal metastases have a shorter PFS and OS than those without peritoneal involvement.[116]

The prefixes “p” and “yp” used in TNM staging denote pathologic staging and pathologic staging following neoadjuvant therapy, respectively.[114]

Pathology

Pathologic staging information is provided by examination of the surgical specimen. Some of the information that should be detailed in the report of the pathologic evaluation of rectal cancer includes: 1) gross description of the tumor and specimen; 2) grade of the cancer; 3) depth of penetration and extension to adjacent structures (T); 4) number of regional lymph nodes evaluated; 5) number of positive regional lymph nodes (N); 6) the presence of distant metastases to other organs or sites including non-regional lymph nodes (M); 7) the status of proximal, distal, circumferential (radial), and mesenteric margins[117-121]; 8) neoadjuvant treatment effect[122,123]; 9) lymphovascular invasion (LVI)[124]; 10) perineural invasion (PNI)[125-127]; and 11) the number of tumor deposits.[128-132]

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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.[114]

The circumferential margin or circumferential resection margin (CRM) is an important pathologic staging parameter in rectal cancer.[133] 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.[133] The CRM is the closest radial margin between the deepest penetration of the tumor and the edge of resected soft tissue around the rectum (ie, the retroperitoneal or subperitoneal aspect of the tumor) or from the edge of a lymph node and should be measured in millimeters. Identification of the CRM is determined through evaluation of the outer circumference of the rectal and mesorectal specimen that often requires inking of the outer surfaces and "bread-loaf" slicing of the specimen.[134] The panel defines an involved or threatened CRM as tumor within 1 mm from the resected margin.[119,121,135,136] This definition differs slightly from the recommendations of the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting in that ESGAR defined the mesorectal fascia as "involved" when the distance between the mesorectal fascia and the tumor is less than or equal to 1 mm, while in their template, "threatened/involved" is listed as less than or equal to 2 mm.[137]

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,[133,135,138,139] including in patients undergoing neoadjuvant therapy,[120,140] and is an important consideration when postoperative treatment decisions are made. Furthermore, in a retrospective study of more than 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.[120] 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 CRCs.[114,133,141] The number of lymph nodes that can be retrieved varies with age and gender of the patient and on tumor grade or site.[142] The literature lacks consensus regarding the minimal number of lymph nodes needed to accurately identify early-stage rectal cancer.[143] 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 greater than 10 lymph nodes as the minimal number to accurately identify stage II rectal cancer.[144,145] 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.[146] 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, $P \leq .0001$).[147-149] In fact, retrieval of fewer lymph nodes may be a marker of a higher tumor response and better prognosis following neoadjuvant treatment.[150-152]

Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify

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small foci of tumor cells and the identification of particular tumor antigens through immunohistochemical analysis have been reported.[153,154] 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.[154,155] In addition, results of one study demonstrated that, following neoadjuvant radiotherapy for rectal cancer, the sensitivity for the sentinel node procedure was only 40%.[156] Furthermore, in a recent study involving 156 patients with colon cancer and 44 patients with rectal cancer, this "ultrastaging" of lymph nodes only changed the staging for 1% of patients.[157] Others have noted that micrometastasis found in node-negative patients did not predict outcome.[158] 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.[159]

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.[160] 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 reached 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.[161] 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 greater than or equal to 0.2 mm in diameter and recommends that these micrometastases be considered as standard positive nodes.[114]

Response to Treatment

The most recent CAP Guidelines require that the pathology report comment on treatment effects of neoadjuvant therapy.[162] 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).[122,123,162,163]

Perineural Invasion

Several studies have demonstrated that the presence of PNI is associated with a significantly worse prognosis.[125-127,164-166] 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.[126] 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).[127] Similar results were seen for patients with stage III disease.[125] 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).[165] 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.[128-132,166] Multivariate survival analysis in one study showed that patients with pN0 tumors without

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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).[132] Another retrospective study found a similar difference in 5-year OS rates (80.3% vs. 34.9%, respectively; P < .001).[167] The association of tumor deposits with decreased survival also holds in patients with rectal cancer who had neoadjuvant chemoradiation (chemoRT).[168-170] Tumor deposits are classified as pN1c.[114]

Tumor Budding

Tumor budding is defined as the presence of a single cell or a cluster of four or fewer neoplastic cells as detected by H&E staining at the advancing edge of an invasive carcinoma. As specified by the 2016 International Tumor Budding Consensus Conference (ITBCC), the total number of buds should be reported from a selected hot spot measuring 0.785 mm^2.[171] Budding is separated into three tiers: low (0–4 buds), intermediate (5–9 buds), and high (≥10 buds).

Several studies have shown that high-grade tumor budding in pT1 colorectal cancer or malignant polyps is associated with an increased risk of lymph node metastasis, although the methodologies for assessing tumor budding were not uniform.[172-176] Studies have also supported tumor budding as an independent prognostic factor for stage II colon cancer. A retrospective study that assessed tumor budding in 135 stage II colon cancer specimens according to ITBCC criteria found that tumor budding correlated with survival outcomes.[177] Disease-specific survival (DSS) was 89% for low-tier tumor budding, 73% for intermediate-tier, and 52% for high-tier (P = .001). Another retrospective study evaluated 174 stage II colon cancer specimens for tumor budding.[178] This study also used the ITBCC criteria and found tumor budding to be independently associated with DSS (P = .01); specifically, 5-year DSS was 96% for low-tier tumor budding compared to 92% for high-tier for all patients. The difference was even more dramatic for those patients who received no adjuvant chemotherapy. For these patients, 5-year DSS was 98% for low-tier tumor budding versus 80% for high-tier (P = .008). Tumor budding is therefore included as a high-risk factor for recurrence and may inform decisions related to adjuvant therapy.

Clinical Presentation and Treatment of Nonmetastatic Disease

Management of Malignant Polyps

A malignant rectal polyp is defined as an adenoma that harbors a focus of cancer invading through the muscularis mucosae and into the submucosa (pT1).[179] Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated into the submucosa and are therefore incapable of regional nodal metastasis.[133] Before making a decision about formal surgical resection for an endoscopically resected pedunculated or sessile malignant polyp, physicians should review the pathology[180] and consult with the patient. The panel recommends marking the malignant polyp site at the time of colonoscopy or within 2 weeks if deemed necessary by the surgeon. All patients with a malignant polyp should undergo MMR or MSI testing at diagnosis.

In patients with pedunculated polyps (adenomas), no additional surgery is required if the polyp has been completely removed endoscopically with favorable histologic features.[180,181] Favorable histologic features include lesions of grade 1 or 2 without angiolymphatic invasion and with a negative resection margin.[180] 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 outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than do pedunculated malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable

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for adverse outcome, and endoscopically removed malignant sessile polyps with grade I or II histology, negative margins, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy alone. 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 malignant polyps with unfavorable histologic features or when the specimen is fragmented or margins cannot be assessed. A complete workup is recommended prior to surgery for patients with malignant polyps showing these characteristics since more extensive disease is more likely in this situation (see section on *Clinical Evaluation/Staging* under *Management of Localized Rectal Cancer*). Unfavorable histologic features for adenomas are grade 3 or 4, angiolymphatic invasion, or a positive/unassessable 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.[180,182-184] 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.[185-188]

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.[189] 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.[190-192] 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.[193]

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 total neoadjuvant therapy (TNT), the implications of either clinically understaging or overstaging rectal cancer can be substantial. Based on this, a multidisciplinary team evaluation is recommended, including a formal surgical evaluation. A discussion of infertility risks and

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counseling on fertility preservation, if appropriate, should be carried out prior to the start of treatment.

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. Proctoscopy can be useful in determining the distance of the cancer from the anal verge and length and, therefore, is a consideration. 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. All patients with rectal cancer should undergo MMR or MSI testing at diagnosis to aid in the diagnosis of Lynch syndrome and for clinical trial availability, especially related to checkpoint inhibitors as neoadjuvant therapy (see section on dostarlimab-gxly in *Preoperative Systemic Therapy Without Chemoradiation*, below). Those with loss of MMR proteins and/or MSI should be referred for genetic counseling and testing.

Imaging also plays a critical role in preoperative evaluation, for evaluation of the primary tumor, regional adenopathy, 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.[194,195] 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 circumferential resection margin (CRM) prior to radical surgery.[196-201] The CRM by MRI is measured at the closest distance of the tumor to the mesorectal fascia. The panel defines a clear CRM as greater than 1 mm from mesorectal fascia and levator muscles and not invading into the intersphincteric plane. An involved or threatened CRM, in contrast, is within 1 mm of mesorectal fascia; or, for lower third rectal tumors, within 1 mm from levator muscle.[136] 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- and high-risk disease.[202] 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.[203] ESGAR has developed consensus guidelines for standardized imaging of rectal cancer by MRI.[137]

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.[196,199,204] In addition, CT has poor sensitivity for the prediction of CRM status.[205] Furthermore, CT has lower sensitivity and specificity for the prediction of lymph node involvement than MRI (CT, 55% and 74%; MRI, 66% and 76%).[204] Therefore, pelvic CT is not recommended for rectal staging.

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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%).[204] However, newer data suggest that EUS is not very accurate for rectal cancer staging.[206] 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).[196] Another disadvantage of EUS is a high degree of operator dependence.[204] At this time, the panel recommends that EUS may be used to evaluate the pelvis if MRI is contraindicated (eg, because of a pacemaker), or it may be considered as an alternative for superficial lesions.

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,[207-209] and studies have shown that 20% to 34% of patients with CRC present with synchronous liver metastases.[210,211]

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 Systemic Therapy 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.[212-220] 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%) of patients.[221] In this study, the use of restaging abdominal/pelvic CT was at the physician's discretion, and no difference was seen in relapse-free survival (RFS) 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.[219,222-224] FDG PET/CT is also being investigated for its ability to accurately determine response to neoadjuvant treatment.[223,225]

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.[226,227] 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]).[226,227]

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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.[228] 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.[229] A small prospective, single-blind, randomized trial compared laparoscopic surgery with laparoscopy combined with TEM in 60 patients with rectal cancer.[230] 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),[231,232] 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 high-risk T1 or T2 tumors.[233] A meta-analysis reported a substantial risk of local recurrence in patients with high-risk pT1 and pT2 rectal cancer who receive no additional therapy following local excision.[234] Completion TME or adjuvant chemoRT (for pT1) were found to mitigate that risk. 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.[235] 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.[236] 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.[189,233] 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.[237] These observations may underlie the findings that patients undergoing local excision have a higher local recurrence rate than those undergoing radical resection.[233,238,239] 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 two groups (P = .001).[239] 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).[233] More recently, an analysis of greater than 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%

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in T1/T2 combined; $P < .001$).[240] In the T1, N0 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,[238,241] although not all studies have seen such results.[242]

Thus, careful patient selection for local excision of T1, N0 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 or TNT 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.[189,227,243] 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.[244] The TME approach is designed to radically remove lymphatic drainage regions of tumors located above the level of the levator muscles.[245] 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.[246] 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.[247] 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.[248,249]

Pathologists play a key role in evaluating the surgical specimen, including a macroscopic assessment of both its external appearance/completeness and the CRM.[250,251] The panel defines an involved or threatened CRM as tumor within 1 mm from the resected margin (see *Pathology*, above).[119,121,135,136] Detailed descriptions of how the quality of the mesorectal specimens should be scored were provided in the Dutch

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Rectal Cancer Trial, and these guidelines are endorsed by the NCCN Panel.[119]

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.[252,253] 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 five large European trials suggest that there is an association between the APR procedure itself and the increased risks of recurrence and death.[252] Importantly, quality of life between patients with or without a permanent colostomy appears to be fairly comparable.[254,255]

Laparoscopic Resection

Data from randomized studies evaluating use of laparoscopic surgery in the treatment of patients with rectal cancer have matured in recent years.[256-259] One large prospective multicenter 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.[260] 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.[261] 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 two groups, at 5.0%, and no statistically significant differences were seen in DFS or OS.[256]

In the CLASICC trial comparing laparoscopically assisted resection to open resection, nearly half of the 794 patients were diagnosed with rectal cancer.[262] No significant differences in local recurrence, DFS, or OS were observed between the two 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; $P = .132$).[263]

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 with the laparoscopic approach.[264] The primary endpoint, 3-year DFS, did not differ between the two 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.[257] Factors that may confound conclusions drawn from randomized studies comparing open surgery to laparoscopically assisted surgery for CRC have been described,[265] and longer-term outcomes from laparoscopic rectal surgery have not been reported.

Two other trials, ACOSOG Z6051 and ALaCaRT, have reported pathologic outcomes.[258,259] In Z6051, the primary endpoint was a composite of CRM greater than 1 mm, negative distal margin, and TME completeness.[258] No significant differences were observed between the arms in these three 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 to 1.5; $P = .20$). However, the criteria for non-inferiority of the laparoscopic approach were not met in these initial results. Follow-up results of Z6051 reported similar 2-year DFS rates between laparoscopic (79.5%) and open resection (83.2%).[266] Locoregional and distant

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recurrence rates were also found to be similar between laparoscopic and open resection (4.6% vs. 4.5% for locoregional recurrences and 14.6% vs. 16.7% for distant recurrences). In ALaCaRT, the primary endpoint was also a composite of resection quality measures.[259] 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% to 0.1%; *P* = .06). Follow-up results for ALaCaRT showed similar recurrence, DFS, and OS rates for laparoscopic versus open resection after 2 years.[267] Two-year locoregional recurrence rates were 5.4% and 3.1%, 2-year DFS rates were 80% and 82%, and 2-year OS rates were 94% and 93% for laparoscopic resection and open resection, respectively. As in Z6051, the criteria for non-inferiority of the laparoscopic approach were not met in the initial ALaCaRT report, but the techniques were found to not differ significantly after longer follow-up with oncologic outcomes.

An analysis of results from greater than 18,000 individuals in the NCDB undergoing LAR for rectal cancer found short-term oncologic outcomes to be similar between the open and laparoscopic approaches.[268] In addition, older reviews and meta-analyses consistently found the laparoscopic approach to be safe and feasible,[257,269-282] 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.[283] Several studies have also compared outcomes of robotic-assisted resection to conventional laparoscopic resection.[284-288] 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,[256,257] whereas other studies have shown the laparoscopic approach to be associated with higher rates of CRM positivity and incomplete TME.[258,259] 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.[289]

Neoadjuvant and Adjuvant Therapy for Resectable Nonmetastatic Disease

Neoadjuvant/adjuvant therapy for 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.[134,290,291] 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.[134,292,293] 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

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retrospective multicenter study,[294] suggesting that many patients are under-staged and would benefit from chemoRT. Therefore, the guidelines recommend preoperative treatment 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 Neoadjuvant Therapy Approach

A treatment approach for stage II or III rectal cancer, including courses of both chemoRT and chemotherapy given as neoadjuvant therapy before transabdominal resection, has been gaining prominence. This approach, called TNT, was first tested in several small, phase II trials, but more recently has been supported by phase III trial data.[295-300]

In the Spanish GCR-3 randomized phase II trial, patients were randomized to receive CAPEOX either before chemoRT or after surgery.[297,301] Similar pathologic complete response rates and 5-year DFS and OS were seen, and induction chemotherapy appeared to be less toxic and better tolerated. The GCR-3 trial provided the rationale for RAPIDO and demonstrated that the TNT approach increased compliance, lowered acute toxicity, and yielded similar outcomes compared to the traditional approach. A pooled analysis of two phase II trials, EXPERT and EXPERT-C, assessed the safety and efficacy of neoadjuvant chemotherapy followed by chemoRT and surgery.[302] Of the 269 patients who were included, 91.1% completed chemotherapy, 88.1% completed chemoRT, and 89.2% underwent curative surgery. Five-year PFS and OS rates were 66.4% and 73.3%, respectively. Another phase II trial comparing response rates in patients with stage II–III rectal cancer treated with chemoRT alone or chemoRT followed by increasing durations of FOLFOX prior to resection found that delivery of FOLFOX was independently associated with higher rates of pathologic complete response, with the highest complete response rate (38%) following six cycles of neoadjuvant FOLFOX and the lowest (18%) in the group that received chemoRT alone.[303] However, it is difficult to determine if the higher pathologic complete response rate with FOLFOX was due to the increased duration of FOLFOX, the longer duration of time between chemoRT and surgery, or some combination of the two.

More recently, the TNT approach has been tested in phase III trials. RAPIDO, a randomized phase III trial, compared a standard treatment approach (chemoRT, followed by TME, then optional adjuvant chemotherapy with CAPEOX or FOLFOX) to an experimental TNT approach (short-course RT, followed by chemotherapy before TME) in 912 patients with locally advanced rectal cancer.[304] At 3 years after randomization, the rate of disease-related treatment failure was 23.7% with TNT compared to 30.4% with standard treatment (HR, 0.75; 95% CI, 0.60–0.95; $P = .019$). No differences were found in the secondary endpoint of OS. Serious adverse events occurred in 38% of the TNT group and 34% in the standard treatment group. Another randomized phase III trial, UNICANCER-PRODIGE 23, compared a neoadjuvant therapy approach including both FOLFIRINOX and chemoRT prior to TME to a standard approach of neoadjuvant chemoRT alone followed by TME for 461 patients with locally advanced rectal cancer.[305] Both arms followed TME by adjuvant FOLFOX, although the duration of adjuvant treatment was shorter in the group that had received neoadjuvant chemotherapy. After a median follow-up of 46.5 months, 3-year DFS was 76% in the group that received neoadjuvant chemotherapy, compared to 69% in the standard treatment group (HR, 0.69; 95% CI, 0.49–0.97; $P = .034$). During the whole treatment period, serious adverse events occurred in 11% of

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patients in the neoadjuvant chemotherapy group and 23% in the standard-of-care group (*P* = .0049). No postoperative deaths occurred within 30 days in the neoadjuvant group, while five deaths occurred in the standard treatment group (4 from cardiac or vascular events, 1 from suicide).

These results have also been supported by systemic review and meta-analyses showing a higher pathologic complete response rate with TNT.[306,307] In a single-institution retrospective cohort analysis of patients with T3/4 or node-positive rectal cancer, patients in the TNT group received a greater percentage of the planned chemotherapy dose than those in the adjuvant chemotherapy group.[308] The complete response rates were 36% and 21% in the TNT and adjuvant chemotherapy groups, respectively.

It is not established whether it is better to start with chemotherapy, then follow with chemoRT, or vice versa when following a TNT approach. Results from the phase II Organ Preservation in Rectal Adenocarcinoma (OPRA) trial suggest that initiating treatment with chemoRT may improve TME-free survival.[309,310] The randomized phase II CAO/ARO/AIO-12 study also looked at this question, comparing TNT approaches using either induction chemotherapy with FOLFOX followed by 5-FU/oxaliplatin chemoRT or chemoRT followed by consolidation chemotherapy.[311] This trial reported that upfront chemoRT led to higher completion rates for chemoRT, but lower completion rates for chemotherapy compared to upfront chemotherapy. Pathologic complete response was observed in 17% of those who received upfront chemotherapy and 25% of those who received upfront chemoRT. A secondary analysis reporting long-term (median, 43 months) results from the CAO/ARO/AIO-12 study showed similar long-term outcomes between the two groups, including 3-year DFS (73% for both groups; HR, 0.95; 95% CI, 0.63–1.45), 3-year incidence of local recurrence (6% vs. 5%), and distant metastases (18% vs. 16%).[312] Chronic toxicity of grade 3 or higher occurred in 11.8% of patients who received chemotherapy first compared to 9.9% who received chemoRT first. Collectively, these data suggest that the TNT approach of chemoRT followed by chemotherapy results in a higher rate of pathologic complete response while showing no significant differences in DFS, locoregional recurrence, distant metastases, or toxicities.

A few trials have investigated the use of FOLFIRINOX or FOLFOXIRI as neoadjuvant chemotherapy for locally advanced rectal cancer. One of these trials was the randomized, phase III UNICANCER-PRODIGE 23 study, which was described above.[305] The prospective, single-arm phase II FORTUNE study investigated the use of FOLFOXIRI as initial therapy for patients with stage II or III rectal cancer.[313] After initial chemotherapy, patients were either treated with surgery or RT/chemoRT followed by surgery, depending on the response to initial FOLFOXIRI. Of 103 patients who completed neoadjuvant therapy, pathologic complete response and tumor downstaging rates were 20.4% and 42.7%, respectively. Another phase II trial of patients with node-positive, cT4, or high-risk T3 rectal cancer investigated the use of induction FOLFOXIRI plus bevacizumab followed by capecitabine-based chemoRT with bevacizumab.[314] Surgery was performed 8 weeks after completion of the chemoRT. Of 49 enrolled patients, 44 completed surgery and 2-year DFS was 80%. While the NCCN Panel recommends induction chemotherapy with FOLFIRINOX as an option for T4, node-positive rectal cancer, the addition of targeted agents (such as bevacizumab) is not currently recommended in this setting. While UNICANCER-PRODIGE 23 enrolled patients with cT3 and cT4, node-negative tumors,[305] the NCCN Panel only recommends the use of FOLFIRINOX for the cT4, N+ tumors due to the higher toxicity of FOLFIRINOX compared to FOLFOX or CAPEOX and the results observed with CAPEOX or FOLFOX in RAPIDO, which enrolled patients at higher risk of recurrence.[304] It is important to note that the trials evaluating TNT with FOLFIRINOX or FOLFOXIRI compared the TNT regimen to a standard preoperative chemoRT approach, not to a TNT strategy using

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FOLFOX; therefore, there is insufficient data to compare FOLFOX to FOLFIRINOX in this setting.

The TNT approach has demonstrated benefits including the early prevention or eradication of micrometastases, higher rates of pathologic complete response and longer PFS,[303-308] minimizing the length of time patients need an ileostomy,[308] facilitating resection, and improving the tolerance and completion rates of chemotherapy.[297,303-305] For some patients, surgery may be avoided if a complete response is achieved as a result of neoadjuvant therapy (see *Watch-and-Wait Nonoperative Approach for Clinical Complete Responders*, below). Based on this, the NCCN Panel recommends TNT as the preferred approach for stage II–III rectal cancer.

Preoperative Chemoradiation

When not using a TNT approach, preoperative chemoRT is recommended 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.

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.[315] 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 two groups. Long-term follow-up of this trial was later published.[316] 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.

Putative advantages to preoperative radiation, as opposed to radiation given postoperatively, are related to both tumor response and preservation of normal tissue. First, 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,[315,317] this conclusion is not supported by two meta-analyses of randomized trials involving preoperative chemoRT in the treatment of rectal cancer.[318,319] 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).

Regimens for Concurrent ChemoRT

A number of randomized trials have established the benefit of adding chemotherapy (most often 5-FU/leucovorin or capecitabine) to RT for treatment of localized rectal cancer. Putative benefits of the addition of chemotherapy concurrent with 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 two groups, although patients receiving chemoRT were significantly more likely to exhibit a pathologic complete response (11.4% vs. 3.6%; $P < .05$)

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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%; $P < .05$).[320]

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/leucovorin (LV) chemotherapy enhanced the tumoricidal effect of RT when the two approaches were used concurrently.[321] Significant reductions in tumor size, pTN stage, lymphatic invasion, vascular invasion, and PNI rates were observed.[321] More mature results from this trial reported that no significant differences in OS were associated with adding 5-FU–based chemotherapy preoperatively or postoperatively.[322]

The conclusions of these trials have been supported in a 2009 systematic review that included four RCTs.[323] In addition, a recent Cochrane review of six 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.[324] 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.[325] Another recent meta-analysis of five RCTs comparing neoadjuvant chemoRT with neoadjuvant radiotherapy reached similar conclusions.[291]

With respect to the type of chemotherapy administered concurrently with RT,[293] 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 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.[326] However, 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.[327] 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.

Recent studies have shown that capecitabine is equivalent to 5-FU in perioperative chemoRT therapy.[328,329] 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.[329,330] 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 ($P = .053$).[328] Furthermore, in this trial capecitabine demonstrated a significant improvement in 3-year DFS (75.2% vs. 66.6%; $P = .034$).[328] 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, FOWARC, and PETACC 6) 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

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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).[331] 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.[329,330]

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.[332] 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 term follow-up.[333] The PETACC 6 trial also investigated whether the addition of oxaliplatin to pre- and postoperative capecitabine would improve DFS for locally advanced rectal cancer.[334] Similar to other trials, oxaliplatin was found to impair tolerability without improving efficacy.

Results of the German CAO/ARO/AIO-04 trial have been published.[335,336] 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%, $P = .038$),[336] but this result could be because of differences in the fluorouracil schedule between the arms.[337] 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 ($P = .03$).[335] 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, early results from 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.[338] However, final results from FOWARC showed no significant improvement in 3-year DFS, local recurrence rates, or OS for FOLFOX with or without RT compared to 5-FU/LV-RT.[339]

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.[340] 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.[341] 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

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cetuximab in this setting.[342,343] 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.[344] 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, cT3, N0 or cT2–3, N1–2, mid to low rectal cancer with a predicted negative CRM.[345] 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.[346] 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. Other randomized trials have also investigated the use of targeted therapies (eg, bevacizumab, ziv-aflibercept) within neoadjuvant therapy for localized rectal cancer with mixed conclusions.[314,347-351]

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

Preoperative Systemic Therapy 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.[352] 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 eight institutions, assessed the R0 resection rate after FOLFOX plus either bevacizumab or cetuximab.[353] 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).[338] 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). However, final results from FOWARC showed no significant improvement in DFS, local recurrence rates, or OS for FOLFOX with or without RT compared to 5-FU/LV-RT.[339] Three-year DFS was 72.9%, 77.2%, and 73.5% (P = .709); 3-year local recurrence rate after resection was 8.0%, 7.0%, and 8.3% (P = .873); and 3-year OS was 91.3%, 89.1%, and 90.7% (P = .971) for 5-FU/LV-RT, FOLFOX-RT, and FOLFOX without RT, respectively.

A 2015 systematic review identified one randomized phase III trial, six single-arm phase II trials, and one retrospective case series study that

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addressed the effectiveness of neoadjuvant chemotherapy (without chemoRT) and surgery in patients with locally advanced rectal cancer.[354] The ranges of R0 resection and pathologic complete response rates were 90% to 100% and 4% to 33%, respectively.

The 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). Accrual for this trial has been closed and results are awaited.

This approach could spare patients the morbidities associated with radiation, but the panel considers it investigational at this time for most patients with stage II/III rectal cancer. One exception is the panel's recommendation of adjuvant FOLFOX or CAPEOX alone as an option for pT3, N0, M0, margin-negative tumors, high in the rectum or at the rectosigmoid junction. However, this approach is only appropriate in this small subset of tumors that behave more like colon tumors, and therefore may be treated as such.

The checkpoint inhibitor, dostarlimab-gxly, has also been investigated as neoadjuvant therapy in a small phase II study of patients with dMMR/MSI-H stage II or III rectal cancer.[355] In this study, patients were initially treated with dostarlimab-gxly for 6 months, with chemoRT and surgery planned for those with residual disease. Remarkably, all 12 patients in this trial showed a complete clinical response to dostarlimab-gxly and no patients at the date of publication had required chemoRT or surgery. No cases of progression or recurrence were reported during follow-up (range, 6–25 months). While this data is encouraging, it has not yet been added as a recommended treatment approach in the guidelines.

Technical Aspects of Radiation Therapy

Multiple RT 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; 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 three or four 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 (available online at https://seor.es/wp-content/uploads/2014/03/RTOGAnorectalContouringGuidelines-1.pdf).[356] Intensity-modulated RT (IMRT) should be considered for clinical situations such as re-irradiation of previously treated recurrent disease, patients treated postoperatively due to increased acute or late toxicity, T4 primary tumors given the more anterior field changes with coverage of the external iliac nodes, which includes more small bowel, or unique anatomical situations where IMRT facilitates the delivery of recommended target volumes while respecting accepted normal tissue dose-volume constraints.[357] Ablative stereotactic body radiotherapy (SBRT) should only be used in the setting of a clinical trial or in the setting of oligometastasis to the lung, liver, or an abdominopelvic node when other modalities are not appropriate.

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,[358-363] it is unclear whether such longer intervals are associated with clinical benefit. Results of one NCDB analysis suggest that an interval of greater than 8 weeks is associated with increased odds of pathologic complete response,[364] whereas other similar analyses concluded that an interval greater than 56 or 60 days (8–8.5 weeks) is associated with higher

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rates of positive margins, lower rates of sphincter preservation, and/or shorter survival.[365,366] A pooled analysis of seven randomized trials concluded that the best time to achieve pathologic complete response was at 10 weeks following neoadjuvant chemoRT, with 95% of pathologic complete response events occurring within that time period.[367]

The GRECCAR-6 phase III, multicenter, randomized, open-label, parallel-group controlled trial randomized patients with stage II/III rectal cancer treated with chemoRT to a 7- or 11-week interval before surgery.[368] 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. Three-year survival results from the GRECCAR-6 trial showed no difference in 3-year OS (*P* = .8868), DFS (*P* = .9409), distant recurrence (*P* = .7432), or local recurrence (*P* = .3944) between the 7- or 11-week interval groups.[369]

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.[370] 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.[371] 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.[372-374] 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.[375] 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.[375,376]

Long-term (12 years) follow-up of one of the short-course RT trials (the Dutch TME trial[373]) was reported.[377] The analysis showed that 10-year survival was significantly improved in patients with stage III disease and a negative CRM in the RT plus surgery group compared to the group that received surgery alone (50% vs. 40%; *P* = .032).[377] However, this long follow-up showed that secondary malignancies and other non-rectal cancer causes of death were more frequent in the RT 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.[378] 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.[379] 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* =

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.003), whereas patients in the short-course arm were more likely to have a permanent stoma (38.0% vs. 29.8%; *P* = .13).[380] However, no overall difference was seen in health-related quality of life between the groups.[381] Finally, a trial compared short-course RT with long-course chemoRT with delayed surgery in both groups.[382] 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.[383]

The randomized phase III Polish II study randomized patients with cT3/cT4 rectal cancer to either preoperative short-course radiation followed by FOLFOX4 or preoperative long-course chemoRT with bolus 5-FU/LV and oxaliplatin.[384] Of 515 patients eligible for analysis, preoperative acute treatment toxicity was lower with short-course RT (*P* = .006). No differences in local efficacy or 3-year DFS were observed between the groups, although 3-year OS was higher for the short-course group (73% vs. 65%, *P* = .046). However, long-term results of this trial showed no difference in 8-year OS (49% for both groups).[385] The rate of late complications was also similar between the two groups.

The randomized RAPIDO trial assessed the use of preoperative short-course (5 x 5 Gy) RT followed by 6 cycles of CAPEOX or 9 cycles of FOLFOX4 compared to long-course (25–28 x 2.0–1.8 Gy) capecitabine-based chemoRT before resection in patients with clinical stage T3 or T4 rectal cancer. Early results of 901 evaluable patients showed a high percentage of patients who completed at least 75% of their prescribed chemotherapy (84% for the short-course arm compared to 57% in the long-course arm).[386] While considerable toxicity did occur during preoperative therapy, there were no significant differences noted in the surgical procedures performed or postoperative complications between the two arms. A more mature analysis of the RAPIDO trial reported that in 920 randomized patients, pathologic complete response rates were 28% for the short-course arm compared to 14% for the long-course arm (OR, 2.37; 95% CI, 1.67–3.37; *P* < .0001).[304] The primary outcome of 3-year disease-related treatment failure was lower in the short-course arm compared to the long-course arm (23.7% vs. 30.4%; HR, 0.75 [0.60–0.95]; *P* = .019). Probability of distant metastasis and locoregional disease progression was also lower for the short-course RT arm compared to the long-course RT arm. Overall health, quality of life, and LAR syndrome score were comparable between the two treatment arms.[304,387] Subsequently, an abstract reporting patterns of locoregional disease progression and distant metastases in the RAPIDO trial reported an increase in locoregional disease progression at 5 years for the short-course RT arm compared to long-course (7% vs. 10%; HR, 1.60).[388] Therefore, caution should be exercised in the use of short-course RT for high-risk rectal cancer.

Stockholm III was another randomized, phase III study that compared short-course RT to long-course RT in 840 patients with resectable rectal cancer.[389,390] This trial included two randomizations, a two-arm randomization that compared short-course RT with immediate surgery to short-course RT with delayed surgery (described below), and a three-arm randomization that compared short-course RT with immediate surgery, short-course RT with delayed surgery, and long-course RT with delayed surgery. For the 385 patients in the three-arm randomization, the incidence of local recurrence was 2.3% for short-course with immediate surgery, 3.1% for short-course with delayed surgery, and 5.4% for long-course RT with a median follow-up of 5.7 years.[389] Median OS was 8.1, 10.3, and 10.5 years for short-course RT with immediate surgery, short-course with delayed surgery, and long-course RT respectively. No comparisons showed statistically significant differences and long-term health-related quality of life was also similar between the groups.

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STELLAR is a randomized, phase III trial that compared short-course RT followed by CAPEOX to capecitabine-based long-course chemoRT as neoadjuvant therapy in 599 patients with stage 2–3 rectal cancer.[391] Both groups received TME 6 to 8 weeks after preoperative treatment and adjuvant chemotherapy was given based on preoperative treatment. Three-year DFS was 64.5% for short-course RT and 62.3% for long-course chemoRT. There was also no significant difference in metastasis-free survival or locoregional recurrence between the two groups. Three-year OS was higher in the short-course RT group (86.5% vs. 75.1%; P = .033), but the prevalence of acute grade ≥3 toxicities during preoperative treatment was higher with short-course RT (26.5% vs. 12.6%; P < .001).

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.[392] 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 pathologic complete response rates were significantly higher in the delayed-surgery group, with no differences in sphincter preservation and R0 resection rates. The Stockholm III trial also investigated the optimal interval between short-course radiotherapy and surgery in 455 patients within the two-arm randomization.[389,390] This trial showed similar oncologic outcomes and long-term health-related quality of life between the immediate surgery versus 4 to 8 weeks delay following short-course RT groups,[389] but a lower rate of postoperative complications in the group that delayed surgery following short-course RT (53% vs. 41%; OR, 0.61; 95% CI, 0.45–0.83; P = .001).[390]

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 locally advanced 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.

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.[393-399] 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.[400] 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%.[401] A recent retrospective review of 725 patients with rectal cancer found similar results.[397] In this study, pathologically determined response to neoadjuvant treatment correlated with long-term outcomes. Five-year RFS 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.[402,403]

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

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ypT3–4 staging.[393] Similar results were seen from another retrospective review.[404]

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 al[405] 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.[406]

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.[407] Only one 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.[408-410] 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 RFS of 69%, which rose to 94% after resections were performed.[409] A retrospective case series analysis compared patients who agreed to a watch-and-wait strategy after having a clinical complete response on neoadjuvant therapy with those who underwent surgery following neoadjuvant therapy and were found to have a pathologic complete response at resection.[411] This study found that the watch-and-wait strategy resulted in excellent rectal preservation and pelvic tumor control. However, worse survival and a higher incidence of distant tumor progression were noted in patients in the watch-and-wait group with local regrowth versus those without. Several systematic reviews have been published on the nonoperative approach.[412-414] 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.

The International Watch & Wait Database (IWWD) aims to collect data to expand knowledge on the benefits, risks, and safety of organ preservation in rectal cancer using a large-scale registry of pooled individual patient data from multiple institutions. A 2018 analysis included data from 880 patients in the IWWD with disease that had a complete clinical response following neoadjuvant therapy and were managed by watch-and-wait.[415] In this analysis, the 2-year incidence of local recurrence was 25.2% and 88% of local recurrences occurred in the first 2 years. Distant metastases occurred in 8% of patients, 5-year OS was 85%, and 5-year disease-specific survival was 94%. A 2021 analysis of the IWWD showed similar results.[416] This analysis included 793 patients with clinical complete response who were managed using the watch-and-wait strategy. With a median follow-up of 55.2 months, the probability of remaining free of local

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recurrence for an additional 2 years was 88.1% after 1 year of DFS, 97.3% after 3 years of DFS, and 98.6% after 5 years of DFS. These same measures for distant metastasis free survival was 93.8% for 1 year, 97.8% for 3 years, and 96.6% for 5 years. Together, current data from the IWWD suggests that disease recurrence occurs most frequently in the first 2 to 3 years following complete response and a more intense surveillance schedule is recommended for that time period.[415,416]

The OPRA trial is a randomized, phase II trial of the watch-and-wait approach.[310] OPRA assessed the outcomes of 324 patients with stage II or III rectal cancer treated with TNT using either an induction chemotherapy followed by chemoRT approach or an approach using chemoRT followed by consolidation chemotherapy. Following neoadjuvant treatment, patients received either TME or observation (watch-and-wait) based on tumor response. Organ preservation was achievable in about half of patients treated with TNT on OPRA with 3-year TME-free survival of 41% in the induction chemotherapy group and 53% in the consolidation chemotherapy group. The primary endpoint of DFS was 76% for both groups, which is in line with the 75% 3-year DFS rate observed historically. No differences were observed between the groups for RFS, distant metastasis-free survival, or OS.

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.[417] 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.[212-220,418] In addition, lymph node metastases are still seen in a subset of patients with pathologic complete response.[419] 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 about their risk tolerance.

Careful surveillance is essential for those considering a watch-and-wait approach in order

to treat tumor regrowth in a timely manner. The OPRA trial included the following surveillance protocol for watch-and-wait: DRE, flexible sigmoidoscopy, and CEA every 4 months for the first 2 years, then every 6 months for years 3 to 5; MRI every 6 months for the first 2 years, then every 12 months for years 3 to 5; CT chest/abdomen/pelvis once a year for 5 years; and colonoscopy once at year 1 and again at year 5.[310] Watch-and-wait surveillance protocols are an area of active investigation and other protocols have been suggested.[415,416,420] The watch-and-wait surveillance schedule recommended by the NCCN Panel based on clinical and institutional experiences is similar to the OPRA protocol and includes DRE and proctoscopy every 3 to 4 months for 2 years, then every 6 months for the next 3 years, and MRI of the rectum every 6 months for at least 3 years.

The use of nonoperative management of rectal cancer has been increasing in the United States, likely representing some early adoption of the approach described herein as well as disparities in the receipt of appropriate rectal cancer resection.[421]

Adjuvant Chemotherapy

Adjuvant chemotherapy is recommended for 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.[422,423] The addition of 5-FU adjuvant chemotherapy to preoperative chemoRT provided no benefit to the rate of local recurrence in the EORTC

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Radiotherapy Group Trial 22921.[322] However, this study showed 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).[322] 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).[424] Limitations of this trial include the fact that only 43% of participants received the full course of adjuvant chemotherapy. Other trials have shown no improvement in OS or DFS with adjuvant therapy with a fluoropyrimidine alone in this setting.[425,426]

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.[427] The open-label phase II ADORE trial randomized 321 patients with resected rectal cancer and neoadjuvant therapy to adjuvant 5-FU/LV or FOLFOX.[428] The FOLFOX arm had higher 3-year DFS, at 71.6% versus 62.9% (HR, 0.66; 95% CI, 043–0.99; *P* = .047). A long-term analysis confirmed these results with a 6-year DFS of 68.2% in the FOLFOX arm compared to 56.8% in the 5-FU/LV arm (HR, 0.63; 95% CI, 0.43–0.93; *P* = .018).[429] 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).[335]

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.[430] In addition, a meta-analysis of four 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.[431] 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 reached the opposite conclusion.[432,433] A systematic review published in 2017 identified eight phase III trials and one randomized phase II trial comparing adjuvant chemotherapy with observation in patients with nonmetastatic rectal cancer treated with neoadjuvant chemoRT.[434] 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.[435-437] However, two 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.[438,439] Another analysis of the NCDB from the same time period reported that while oxaliplatin-based adjuvant therapy was associated with improved OS in patients with pathologic stage III disease, this association was not seen in patients with pathologic stage 0 or 1 disease.[440] Therefore, the authors of this study conclude that oxaliplatin may be omitted from adjuvant therapy for tumors that exhibit a pathologic complete response.

A randomized, phase III study of the ECOG-ACRIN Research Group (E5204) compared FOLFOX alone to FOLFOX in combination with bevacizumab as adjuvant treatment for patients with stage II or III rectal cancer who had already undergone neoadjuvant chemoRT and complete resection.[441] While the trial was terminated due to poor accrual, in the 355

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registered patients, no difference was seen in 5-year OS or 5-year DFS between the two arms. However, the bevacizumab-containing arm had higher rates of early therapy discontinuation and patient withdrawal from the trial.

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.[442] 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.[443] The optimal duration of adjuvant treatment in rectal cancer is still unclear.[444,445] In the MOSAIC trial, patients with stage II/III colon cancer were treated with 6 months of adjuvant FOLFOX.[446] The use of a shorter course of adjuvant FOLFOX in rectal cancer (ie, 4 months) is justified when preoperative chemoRT is administered.

Although conclusive data on the benefits of adjuvant therapy in patients with stage II/III rectal cancer are lacking, the panel recommends adjuvant treatment with FOLFOX or CAPEOX following resection when not following the TNT approach.

NCCN Recommendations for Nonmetastatic Rectal Cancer

Recommendations for Patients with T1 and T2 Lesions

Node-negative T1 lesions are treated with transabdominal resection or transanal local excision, as appropriate. 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) 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 depend on whether there is evidence of residual disease. If there is no evidence of disease, observation or chemotherapy without resection may be considered. If there is evidence of disease, transabdominal resection should be performed, with or without adjuvant chemotherapy. 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.[447] 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.[189,448,449] 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).

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. Patients with tumors staged as pT1–2, N0, M0 require no further treatment. If pathology review reveals pT3, N0, M0, chemoRT, given either before or after 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.[450] Finally, chemotherapy with FOLFOX or CAPEOX alone is an option for margin-negative proximal tumors.

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For resected patients with positive nodes and/or pT4 disease, chemotherapy and chemoRT can be given sequentially with chemotherapy followed by concurrent chemoRT or vice-versa.[293,326,327] The panel recommends perioperative therapy for a total duration of up to 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 with T3 disease, 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*). Two potential treatment courses are recommended for this group of patients, either TNT, followed by transabdominal resection or a more traditional perioperative therapy approach, including both neoadjuvant and adjuvant therapy.

Of these two options, the preferred approach is TNT, consisting of chemotherapy with FOLFOX or CAPEOX given either before or after chemoRT. Alternatively, short-course RT may be used in place of long-course chemoRT when following a TNT approach. If short-course RT is considered, its feasibility should be evaluated in a multidisciplinary setting with discussion of the need for downstaging and the possibility of long-term toxicity. Following neoadjuvant therapy, the tumor should be restaged prior to transabdominal resection. The second option for the sequence of treatment in this population is chemoRT or short-course RT followed by restaging, transabdominal resection, and then adjuvant chemotherapy.

In those patients who achieve a complete clinical response to neoadjuvant therapy 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 disease progression 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 their risk tolerance and a careful surveillance schedule must be followed. The data supporting this approach are discussed in *Watch-and-Wait Nonoperative Approach for Clinical Complete Responders*, above.

When a TNT approach is followed, resection should be performed unless there is a clear contraindication or a watch-and-wait nonoperative approach is being pursued. 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). FOLFIRINOX is not recommended in this setting.

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

For patients with higher-risk stage II or III rectal cancer, including cT3 lesions with involved or threatened CRM by MRI, cT4 lesions, and locally unresectable or medically inoperable disease, TNT is the only recommended approach. This is because a pathologic complete response is less likely following an initial course of only chemoRT or short-course RT and the full course of neoadjuvant chemoRT/short-course RT and chemotherapy is warranted prior to resection. In the TNT approach, 12 to 16 weeks of chemotherapy are followed by chemoRT or short-course RT, restaging, and transabdominal resection. Alternatively, a TNT approach may start with chemoRT or short-course RT, followed by 12 to 16 weeks of chemotherapy, then restaging and transabdominal resection. FOLFOX or CAPEOX are generally used for chemotherapy, although FOLFIRINOX is also an option for T4, N+ disease (see *The Total Neoadjuvant Therapy Approach*, above).

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In those patients with a complete clinical response to neoadjuvant therapy 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 disease progression 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 their risk tolerance and a careful surveillance schedule must be followed. The data supporting this approach are discussed in *Watch-and-Wait Nonoperative Approach for Clinical Complete Responders*, above.

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).

For unresectable cancers, doses higher than 54 Gy may be required; the dose of RT to the small bowel should be limited to 50 Gy. For patients with T4 tumors or recurrent cancers or if margins are very close or positive, intraoperative RT (IORT),[451-455] 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.

Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with CRC will develop colorectal metastases,[456-458] and 80% to 90% of these patients have unresectable metastatic liver disease.[211,457,459-461] Metastatic disease most frequently develops metachronously after treatment for locoregional CRC, with the liver as the most common site of involvement.[462] However, 20% to 34% of patients with CRC present with synchronous liver metastases.[210,211] 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.[463]

It has been estimated that more than half of patients who die of CRC have liver metastases at autopsy, with metastatic liver disease as the cause of death in most patients.[464] Reviews of autopsy reports of patients who died from CRC showed that the liver was the only site of metastatic disease in one-third of patients.[461] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[457,465] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than three tumors, and a disease-free interval of fewer than 12 months, have been associated with a poor prognosis in patients with CRC.[210,466-470]

Other groups, including European Society for Medical Oncology (ESMO), have established guidelines for the treatment of mCRC.[471] 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.[457,472] Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,[467,470] and a recent meta-analysis reported a median 5-year survival of 38%.[473] 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.[474-

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[476] Therefore, decisions relating to patient suitability, or potential suitability, and subsequent selection for metastatic colorectal surgery are critical junctures in the management of metastatic colorectal liver disease[477] (discussed further in *Determining Resectability*).

Colorectal metastatic disease sometimes occurs in the lung.[456] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.[478-480] A series of 378 patients found that resection of pulmonary metastases resulted in a 3-year RFS rate of 28% and a 3-year OS rate of 78%.[480] Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases[479,481-485] and an analysis of patients who underwent hepatic resection followed by subsequent pulmonary resection showed positive outcomes.[486]

Evidence supporting resection of extrahepatic metastases in patients with mCRC 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.[487,488] 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).[485] A recent systematic review concluded similarly that carefully selected patients might benefit from this approach.[489]

Recent data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.[490] 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.[491-494] In a more recent retrospective analysis of 43 patients who underwent repeat hepatectomy for recurrent disease, 5-year OS and PFS rates were reported to be 73% and 22%, respectively.[491] A recent meta-analysis of 27 studies including greater than 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.[495] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[479,496,497]

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*).[498]

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. Image-guided ablation has historically been used for patients who are not candidates for surgery.[499-501] but is also indicated for small metastases that can be treated with margins, in combination with surgery or alone, as long as all visible disease is treated.[502] SBRT (also called stereotactic ablative radiotherapy [SABR]) is a reasonable option for patients who cannot be resected or ablated, as discussed in subsequent paragraphs.[460,503,504] Many patients, however, are not surgical candidates

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and/or have disease that cannot be ablated with clear margins[500] 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.[505-507]

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 colorectal hepatic metastases.[508] Local therapies are described in more detail below. The exact role and timing of using non-extirpative local therapies in the treatment of colorectal metastases remains controversial.

Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, 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.[461,509] 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.[461,510] Several other clinical trials have shown significant improvement in response or time to hepatic disease progression when HAIC was compared with systemic chemotherapy, although most have not shown a survival benefit of HAIC.[461,511] Results of some studies also suggest that HAIC may be useful in the conversion of disease from an unresectable to a resectable status.[512-514]

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAIC.[472] Limitations on the use of HAIC include the potential for biliary toxicity[461] 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.[506] A randomized trial compared the arterial delivery of irinotecan-loaded drug-eluting beads (DEBIRI) and reported an OS benefit (22 vs. 15 months; $P = .031$) of DEBIRI when compared to systemic FOLFIRI.[515] A 2013 meta-analysis identified five observational studies and one randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.[516] A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.[517] 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.[518-523] A 2013 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.[524]

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 mCRC following progression on

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initial therapy (2.1 vs. 4.5 months; *P* = .03).[525] 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.[526] In the refractory setting, a CEA level greater than or equal to 90 and LVI at the time of primary resection were negative prognostic factors for OS.[527] Additional risk factors include tumor volume and liver replacement by disease as well as albumin and bilirubin levels, performance status, and the presence of extrahepatic disease for both glass[528] and resin[529] microspheres. 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.[528,530,531] Median survival after radioembolization in the chemorefractory setting has been reported from 9 to 15.1 months.[526-531] Survival at 1 year from radioembolization of patients with heavily pretreated disease varies considerably based on the accumulation of risk factors such as extrahepatic disease, large tumor size, poor differentiation, higher CEA and alanine transaminase (ALT), and lower albumin levels.[529]

The randomized, phase III EPOCH trial studied the effect of yttrium-90 radioembolization in 428 patients who had previously experienced disease progression on first-line therapy and were randomized to receive second-line therapy with or without yttrium-90 radioembolization.[532] The primary endpoints of median PFS and hepatic PFS were longer with radioembolization (PFS, 8.0 vs. 7.2 months; HR, 0.69; 95% CI, 0.54–0.88; *P* = .0013) and (hepatic PFS, 9.1 vs. 7.2 months; HR, 0.59; 95% CI, 0.46–0.77; *P* < .0001). Overall survival was similar between the two groups (14.0 and 14.4 months) and grade 3 adverse events were reported more frequently with radioembolization (68.5% vs. 49.3%).

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX +/- bevacizumab vs. FOLFOX +/- bevacizumab) were reported.[533] 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/yttrium-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/yttrium-90 arm vs. 12.6 months for the chemotherapy only arm; HR, 0.69; 95% CI, 0.55–0.90; *P* = .002). Additionally, the SIRFLOX trial reported a higher proportion of patients with disease that became technically resectable on the yttrium-90 arm compared to control (38.1% vs. 28.9%; *P* < .001).[534]

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.[535] Pooled data from 1103 patients in these three 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 finding of a median OS benefit with radioembolization plus chemotherapy compared to chemotherapy alone in the subgroup of patients with right-sided primary origin (22.0 vs. 17.1 months; HR, 0.641; *P* = .008).[536] Based on these data, further investigation is needed to identify the 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.[533,537-539] 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

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patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

Tumor Ablation

Resection is the standard approach for the local treatment of resectable metastatic disease. However, patients with liver or lung oligometastases can also be considered for tumor ablation therapy, particularly in cases that may not be optimal for resection.[540,541] Ablative techniques include radiofrequency ablation (RFA),[500,542] microwave (MW) ablation, cryoablation, and electrocoagulation (irreversible electroporation).[543] There is extensive evidence on the use of RFA as a reasonable treatment option for non-surgical candidates and for recurrent disease after hepatectomy with small liver metastases that can be treated with clear margins.[500,542,544-546]

A small number of older retrospective studies have compared RFA and resection in the treatment of liver or lung metastases.[475,547-550] Most of these studies have shown RFA to be relatively inferior to resection in terms of rates of local recurrence and 5-year OS.[540,547] 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, technologic limitations of RFA, or a combination of these factors remains unclear.[549]

A 2012 phase II trial randomized 119 patients to receive systemic treatment alone (FOLFOX with or without bevacizumab) or systemic treatment plus RFA, with or without resection.[551] 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; $P = .025$). A subsequent analysis following prolonged follow-up of the same population in this phase II randomized, controlled trial 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.[502] This study documented a long-term survival benefit for patients receiving RFA in addition to chemotherapy compared to those treated by chemotherapy only.

Data on ablative techniques other than RFA are growing.[541,552-559] However, in a comparison of RFA with MW ablation, outcomes were similar with no local tumor progression for metastases ablated with margins greater than 10 mm (A0) and a relatively better control of perivascular tumors with the use of MW ($P = .021$).[559] Similarly, two recent studies and a position paper by a panel of experts indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins.[499-501] In the same way, a 2018 systematic review confirmed that MW provides oncologic outcomes similar to resection.[560] Recent publications indicated that the significance of margin creation is particularly important for *RAS*-mutant metastases.[561-563]

Regarding pulmonary ablation, a large prospective database of two French cancer centers enrolled 566 consecutive patients with 1037 lung metastases (the majority colorectal in origin) who received initial treatment with RFA and 136 patients (24%) underwent repeat RFA.[564] PFS rates at years 1 through 4 were 40.2%, 23.3%, 16.4%, and 13.1%, respectively. Five-year OS after RFA in CRC pulmonary ablation ranged from 40.7% to 67.5% depending on risk factors. Microwave ablation has been used increasingly within the latest years with a recent report indicating no local progression for small tumors ablated with margins of at least 5 mm.[565]

A recent multicenter, prospective phase II study (SOLSTICE) included 128 patients with 224 metastatic lung tumors that were targeted by pulmonary cryoablation.[566] In this trial, investigators demonstrated a local response of the ablated tumor at 1 and 2 years of 85.1% and 77.2%, respectively. With the use of a second cryoablation for recurrent tumor, 1- and 2-year local

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tumor control reached 91.1% and 84.4%, respectively. In this study, 1- and 2-year survival rates were 97.6% and 86.6%, respectively. The grade 3 and grade 4 complication rates were low, at 4.7% and 0.6%.

An emergent indication for ablation is the discontinuation of chemotherapy while controlling oligometastatic pulmonary disease.[565,567] The median chemotherapy-free survival (time interval between ablation and resuming chemotherapy or death without chemotherapy) was 12.2 months. Patients with no extra-pulmonary metastases had a longer median chemotherapy-free survival compared to those without (20.9 vs. 9.2 months).[567]

Resection or ablation (either alone or in combination with resection) should be reserved for patients with metastatic disease that is entirely amenable to local therapy with adequate margins. Use of surgery, ablation, or the combination of both modalities, with the goal of less-than-complete eradication of all known sites of disease, is not recommended other than in the scope of a clinical trial.

Liver- or Lung-Directed External Beam Radiation

EBRT to the metastatic site can be considered in highly selected cases in which the patient has a limited number of metastases, including the liver or lung; or the patient is symptomatic; or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include three-dimensional conformal RT (CRT), SBRT,[460,503,504,568] and IMRT, which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to healthy tissue.[569-573]

While colorectal cancer has been shown to be a relatively radioresistant histology,[574,575] multiple studies have demonstrated effective local control with minimal toxicity using SBRT in the treatment of liver,[569,576] and lung[577,578] metastases. In addition, data on the benefit of using SBRT to treat multiple metastatic lesions are emerging. A recent randomized phase II trial with multiple cancer types, including a small number of CRC origin, and up to five metastatic lesions in different organs demonstrated an improvement in OS with the addition of SBRT to standard of care treatment.[579] In patients with liver- or lung-limited disease that is not amenable to complete resection or ablation, SBRT may be considered as local therapy in centers with expertise. SBRT for the treatment of extrahepatic disease can be considered in select cases, or as part of a clinical trial.

Peritoneal Carcinomatosis

Approximately 17% of patients with mCRC have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of metastasis. Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.[116,580] 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.[581-583] A prospective randomized trial of 46 patients with stage IV rectal cancer and subacute large bowel obstruction found that patients who were randomized to placement of a self-expandable metal stunt had a significantly lower 1-year OS rate compared with those who were randomized to primary tumor resection.[584] 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.[585,586]

Determining Resectability

The consensus of the panel is that patients diagnosed with potentially resectable mCRC should undergo an upfront evaluation by a multidisciplinary team, including surgical consultation (ie, with an experienced hepatic surgeon in cases involving liver metastases) to

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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.[587-590] 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.[591] 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.[592] 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.[458,587]

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

Neoadjuvant Therapy and 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 systemic therapy can be converted from unresectable to resectable status.[540]

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.[593-597] 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.[593,594,597,598] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the disease becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed below.

In a study by 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.[589] 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,[459] 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.[466] The 5-year DFS rate for these 138 patients was 22%. In addition, results from a

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retrospective analysis of 795 previously untreated patients with mCRC 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.[599] 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 two randomized clinical trials in patients with unresectable disease.[600,601] In both studies, FOLFOXIRI led to an increase in R0 secondary resection rates: 6% versus 15%, $P = .033$ in the Gruppo Oncologico Nord Ovest (GONO) trial[600]; and 4% versus 10%, $P = .08$ in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.[601] 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 versus 16.7 months ($P = .026$).[602]

Chemotherapy regimens may be combined with bevacizumab or with cetuximab or panitumumab for *KRAS/NRAS/BRAF* wild-type unresectable synchronous disease. In addition, checkpoint inhibitors may be considered for microsatellite instability-high (MSI-H)/deficient mismatch repair (dMMR) disease as an alternative to chemotherapy-containing regimens. See the following sections for data supporting these treatment approaches.

When chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation be planned 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical re-evaluation every 2 months thereafter.[597,603-605] Reported risks associated with chemotherapy include the potential for development of liver sinusoidal dilatation, steatosis, or steatohepatitis.[593,598,606] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable.

It is important to note that some of the treatment approaches for patients diagnosed with rectal cancer and 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 recurrence 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.

Neoadjuvant Bevacizumab for 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 preoperatively in combination with 5-FU–based regimens has not been adequately evaluated. A retrospective evaluation of data from two randomized clinical trials of 1132 patients receiving chemotherapy with or without bevacizumab as initial therapy for mCRC 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.

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3.4%, respectively; *P* = .28).[607] 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.[608]

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.[609] Venous thromboembolisms, however, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[610] 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.[611] 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 CRC.[607,612] Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to gastrointestinal perforation. The U.S. Food and Drug Administration (FDA) 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.[613]

The role of bevacizumab in the patient with unresectable mCRC, 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.[614] 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. The data on use of bevacizumab with oxaliplatin-based therapy in the conversion to resectability are mixed. On one 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.[615] On the other hand, the randomized BECOME trial of 241 patients with initially unresectable *RAS* mutant CRC liver metastases showed improvement in the resectability of liver metastases as well as response rates and survival with mFOLFOX6 plus bevacizumab compared to mFOLFOX6 alone.[616] R0 resection rates were 22.3% in the bevacizumab combo versus 5.8% with mFOLFOX6 alone (*P* < .01). 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.

A pooled analysis of the phase III TRIBE and TRIBE2 studies compared upfront FOLFOXIRI plus bevacizumab to chemotherapy doublets (FOLFOX or FOLFIRI) plus bevacizumab for oligometastatic mCRC.[617] In agreement with the primary outcomes from these studies, the benefits of using the chemotherapy triplet compared to the doublet were retained in the patient population that had oligometastatic disease, with interaction *P* scores above significance for PFS, OS, and ORR outcome measures. Therefore, the authors of this study conclude that FOLFOXIRI provides a benefit for oligometastatic CRC, including when used as upfront treatment in conjunction with locoregional treatments, such as resection.

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Furthermore, an analysis of individual patient data from five trials that compared upfront FOLFOXIRI plus bevacizumab to doublet chemotherapy plus bevacizumab reported a higher R0 resection rate in the FOLFOXIRI arm.[618]

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 two half-lives of the drug[613]) between the last dose of bevacizumab and surgery. Re-initiation of bevacizumab should be delayed at least 6 to 8 weeks postoperatively.

Neoadjuvant Cetuximab and Panitumumab for Metastatic Disease

More recent favorable results of randomized clinical trials evaluating FOLFIRI, FOLFOX, or FOLFOXIRI in combination with anti-epidermal growth factor receptor (EGFR) inhibitors for the purpose of conversion of unresectable disease to resectable disease have been reported. For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.[619] 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 with the addition of cetuximab ($P < .0001$). Final analysis of this trial showed that the median OS of the entire cohort was 35.7 months (95% CI, 27.2–44.2 months), with no difference between the arms.[620] Another recent RCT compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable CRC metastatic to the liver.[621] 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).

The randomized, phase II VOLFI trial compared the efficacy and safety of mFOLFOXIRI in combination with panitumumab to FOLFOXIRI alone in patients with *RAS* wild-type, primarily non-resectable mCRC.[622] Of the cohort with unresectable, potentially convertible metastases, 75% were ultimately converted to resectable with FOLFOXIRI + panitumumab compared to 36.4% with FOLFOXIRI alone. ORR was also improved in the combination compared to FOLFOXIRI alone while PFS was similar between the two treatments and OS showed a trend in favor of the combination. A recent meta-analysis of four 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.[623]

The randomized, phase III TRIPLETE study compared mFOLFOXIRI plus panitumumab to mFOLFOX6 plus panitumumab as initial therapy for 435 patients with unresectable *RAS* and *BRAF* wild-type mCRC.[624,625] This trial found that intensification of the chemotherapy regimen did not provide additional benefit when combined with panitumumab and led to higher rates of gastrointestinal (GI) toxicity. Response rates (73% vs. 76%), early tumor shrinkage (57% vs. 58%), depth of response (48% vs. 47%), R0 resection rate (25% vs. 29%), and median PFS (12.7 vs. 12.3 months) were similar between mFOLFOXIRI plus panitumumab and mFOLFOX plus panitumumab, respectively. Reflecting this data, the combination of FOLFIRINOX with cetuximab or panitumumab is a category 2B recommendation for unresectable synchronous liver or lung only

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metastases, while the FOLFIRI or FOLFOX combinations are category 2A recommendations within the same setting.

Neoadjuvant Checkpoint Inhibitors for Metastatic Disease

While there are a lack of data in this setting, the panel considers pembrolizumab or nivolumab, as a monotherapy or in combination with ipilimumab, as options for neoadjuvant therapy of dMMR/MSI-H mCRC. While there are no clinical trial data supporting this approach, a few case studies have reported notable responses to pembrolizumab and nivolumab when used as a neoadjuvant therapy for dMMR advanced or mCRC.[626-628] The panel notes that special caution should be taken to monitor for signs of progression, which could potentially cause a previously resectable tumor to become unresectable. While this is a concern for any regimen being used as neoadjuvant therapy in the resectable mCRC setting, the risk is possibly higher with immunotherapy compared to traditional chemotherapy options.

Perioperative Therapy for Resectable Metachronous Metastatic Disease

Perioperative administration of chemotherapy is recommended for most patients undergoing liver or lung resection for metachronous metastases with the goal of increasing the likelihood that residual microscopic disease will be eradicated. A meta-analysis identified three randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.[629] 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.[630] Additional recent meta-analyses have also shown no statistically significant OS benefit with the addition of adjuvant chemotherapy in resectable mCRC.[631-633]

The choice of chemotherapy regimen in the perioperative setting depends on several factors, including the chemotherapy history of the patient and the response rates and safety/toxicity issues associated with the regimens, as outlined in the guidelines. Biologics are not recommended in the perioperative setting for metachronous metastases, with the exception of initial therapy in patients with unresectable metastatic disease that 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, the EORTC phase III study (EORTC 40983) evaluating use of perioperative FOLFOX (six cycles before and six 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.[634] 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.[635] 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.[636] Three-year OS and PFS rates were 81.9% and 47.4%, respectively.

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

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FOLFOX or CAPEOX; patients with prior oxaliplatin received FOLFIRI).[637,638] 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; $P < .048$) and longer-term follow-up confirmed these results with shorter median PFS (15.5 vs. 22.2 months) and median OS (55.4 vs. 81.0 months) with addition of cetuximab to chemotherapy. The panel thus recommends against panitumumab and cetuximab as perioperative treatment for resectable metachronous metastatic disease. The panel also notes that cetuximab and panitumumab should be used with caution in patients with unresectable disease that could potentially be converted to a resectable status.

The optimal sequencing of systemic therapy and resection remains unclear. Patients with resectable disease may undergo resection first, followed by postoperative adjuvant chemotherapy. Alternatively, perioperative (neoadjuvant plus postoperative) systemic therapy can be used.[631,639]

Potential advantages of preoperative therapy include: earlier treatment of micrometastatic disease, determination of responsiveness to therapy (which can be prognostic and help in planning postoperative therapy), and avoidance of local therapy for those patients with early disease progression. 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.[461,640,641] In fact, results from recent studies of patients with CRC receiving preoperative therapy 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.[641-643] Therefore, during treatment with preoperative systemic therapy, frequent evaluations must be undertaken and close communication must be maintained among 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.[593]

Other reported risks associated with the preoperative therapy approach include the potential for development of liver steatohepatitis and sinusoidal liver injury when irinotecan- and oxaliplatin-based chemotherapeutic regimens are administered, respectively.[593-597] 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.

Discussion update in progress

Systemic Therapy for Advanced or Metastatic Disease

The current management of disseminated mCRC involves various active drugs, either in combination or as single agents. 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 toxicity profiles of the constituent drugs. Although the specific regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[644] For example, if oxaliplatin is administered as 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: 1) preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive; and 2) plans for adjusting therapy for patients who experience certain toxicities. For example,

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decisions related to therapeutic choices after first progression of disease should be based, in part, 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 a patient must consider not only the component drugs, but also the doses, schedules, and methods of administration of these agents, and the potential for surgical cure as well as the patient's quality of life.

The continuum of care approach to the management of metastatic rectal cancer is the same as described for 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 biomarkers for treatment selection in the advanced and metastatic disease setting are also discussed.

Biomarkers for Systemic Therapy

As the role of targeted therapy for treatment of advanced CRC or mCRC has become increasingly prominent, the NCCN Panel has expanded its recommendations regarding biomarker testing. Currently, determination of tumor gene status for *KRAS/NRAS* and *BRAF* mutations, as well as HER2 amplifications and MSI/MMR status (if not previously done), are recommended for patients with mCRC. Testing may be carried out for individual genes or as part of a tissue- or blood-based next-generation sequencing (NGS) panel, although no specific methodology is recommended. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (*NTRK*) fusions. Discussion about each of these biomarkers may be found in the *Biomarkers for Systemic Therapy* section of the NCCN Guidelines for Colon Cancer.

Recommendations for Treatment of Resectable Synchronous Metastases

When patients present with rectal cancer and synchronous liver- 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 systemic therapy as described in the guidelines followed by short-course RT (preferred) or long-course chemoRT. Those with a CRM predicted to be involved can receive 1) systemic therapy followed by long-course chemoRT; or 2) short-course RT or long-course chemoRT followed by systemic therapy. 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 progression is deemed to be the greater concern, resection would be the next course of treatment. If local progression 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.[645-652] 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.[653-655] In addition, neoadjuvant short-course radiation

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of T1–T3 primary rectal tumors is an option in this setting.[656] 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.

The panel acknowledges that some patients may not be candidates for systemic therapy or radiation; clinical judgment should be used in such cases.

Recommendations for Treatment of Unresectable Synchronous Metastases

Patients with unresectable synchronous liver- 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 disease resection (see *Determining Resectability* and *Neoadjuvant Therapy and Conversion to Resectability*, above). Chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[657] 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 with disease that remains unresectable after initial systemic therapy should proceed to second-line systemic therapy for advanced or metastatic disease and local therapy may be considered for select patients. Palliative RT or chemoRT can be given prior to second-line therapy if progression of the primary tumor occurred during first-line treatment.

Results from one study suggest that there may be some benefit in both OS and PFS from resection of the primary tumor in the setting of unresectable colorectal metastases.[658] Other systematic reviews and retrospective analyses have also shown a potential benefit.[658-664] Separate analyses of the SEER database and the National Cancer Database also identified a survival benefit of primary tumor resection in this setting.[665,666]

However, a different analysis of the National Cancer Database came to the opposite conclusion.[667] The randomized phase III JCOG1007 study also concluded that primary tumor resection followed by chemotherapy in patients with synchronous unresectable metastases conferred no survival benefit over chemotherapy alone.[668] For the 165 patients enrolled in this study, median OS was 25.9 months with primary tumor resection plus chemotherapy compared to 26.7 months for chemotherapy alone. Median PFS was 10.4 and 12.1 months, respectively. Three patients in this study died following primary tumor resection due to postoperative complications. Furthermore, 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.[669] The median OS was 19.9 months. Notably, symptomatic improvement in the primary is often seen with systemic chemotherapy even within the first 1 to 2 weeks.

Complications from the intact primary lesion are uncommon in this setting,[498] and its removal delays initiation of systemic therapy. In fact, a systematic review concluded that resection of the primary tumor does not reduce complications and does not improve OS.[670] Another systematic review and meta-analysis identified five studies that compared open to laparoscopic palliative colectomies in this setting.[671] 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 resection of asymptomatic primary tumors in the setting of

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unresectable colorectal metastases. Routine palliative resection of a synchronous primary lesion should therefore only be considered if the patient has an unequivocal imminent risk of obstruction, acute significant bleeding, perforation, or other significant tumor-related symptoms.

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, because 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.[672] Resection of liver- 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.[673,674] Specifically, Joyce et al reported that the preoperative PET changed or precluded curative-intent liver resection in 25% of patients.[673] 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.[675] 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, and 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.[676]

As with other conditions in which stage IV disease is diagnosed, a tumor analysis (metastases or original primary) for *KRAS/NRAS* and *BRAF* mutations and HER2 amplifications, as well as MSI/MMR testing if not previously done, should be performed (see *Neoadjuvant Cetuximab and Panitumumab for Metastatic Disease*, 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 up to 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 or lung 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

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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 (category 2B for the use of biologic agents in these settings). Observation is preferred if oxaliplatin-based therapy was previously administered.

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 *Second-line or Subsequent Systemic Therapy* 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 systemic therapy should be monitored with CT or MRI scans approximately every 2 to 3 months.

Endpoints for Advanced CRC Clinical Trials

In the past few years, there has been much debate over what endpoints are most appropriate for clinical trials in advanced CRC.[677] Quality of life is an outcome that is rarely measured but is of unquestioned clinical relevance.[678] 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.[678] PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.[678-680] In 2011, the GRUPO Español Multidisciplinar en Cáncer Digestivo (GEMCAD) proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.[681]

A study, in which individual patient data from three 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).[679] 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.[682,683] 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 CRC 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,[684] and a recent study found that 95% of recurrences occurred in the first 5 years.[685]

Advantages of more intensive follow-up of patients after treatment of stage II and/or stage III disease have been demonstrated prospectively in several older studies[686-688] and in multiple meta-analyses of RCTs designed to compare low-intensity and high-intensity programs of surveillance.[689-693] 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.[293] 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.[694]

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Results from the randomized controlled FACS trial of 1202 patients with resected stage I to III disease showed that intensive surveillance imaging or CEA screening resulted in an increased rate of curative-intent surgical treatment compared with a minimum follow-up group that only received testing if symptoms occurred, but no advantage was seen in the CEA and CT combination arm (2.3% in the minimum follow-up group, 6.7% in the CEA group, 8% in the CT group, and 6.6% in the CEA plus CT group).[695] 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% to 7.1%). The authors concluded that any strategy of surveillance is unlikely to provide a large survival advantage over a symptom-based approach.[695] The randomized COLOFOL trial of 2509 patients with stage II or III CRC looked at follow-up testing with CT of the thorax and abdomen and CEA screening, comparing a high-frequency surveillance approach (CT and CEA at 6, 12, 18, 24, and 36 months post-surgery) to a low-frequency approach (CT and CEA at 12 and 36 months post-surgery).[696] This trial reported no significant difference in 5-year overall mortality or CRC-specific mortality between the two screening approaches.

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-mCRC at 11 hospitals in the Netherlands.[697] 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.[698] 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.[699]

The randomized phase III PRODIGE 13 trial is comparing 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.[700] An abstract reporting results from 1995 patients on this trial concluded that the more intensive surveillance program did not provide any benefit in 5-year OS, but did result in more curative intent secondary surgeries for colon cancer. Surgical treatment of recurrence was performed in 40.9% of patients receiving minimal surveillance (no CT, no CEA), 66.3% of patients receiving lower intensity imaging plus CEA, 50.7% of patients receiving no CEA but higher intensity imaging, and 59.5% in the maximum surveillance group with both CEA and CT (P = .0035).[701]

Meta-analyses support the conclusion that more intensive surveillance of patients with resected CRC results in earlier detection of recurrences, without any effect on survival.[690,691]

Patients who had resection of mCRC 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 greater than or equal to 36 months.[702]

Controversies remain regarding selection of optimal strategies for following patients after potentially curative CRC 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.

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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–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.[703] More frequent colonoscopies may be indicated in patients who present with CRC before age 50.[703] Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps since data show that patients with a history of CRC have an increased risk of developing second cancers,[704] 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 CRC.[703]

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.[705] 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,[706] 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.[689,706,707] 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.[689,708] 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.[709] Those scanned once per year survived a median of 54 months versus 43 months for those scanned three to four 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.[708,710] The CT that accompanies a PET/CT is usually a noncontrast CT, and therefore is not of ideal quality for routine surveillance.

The American Society of Clinical Oncology (ASCO) Clinical Practice Guidelines Committee has endorsed the Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer, from Cancer Care Ontario (CCO).[711,712] 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

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annual scanning). The panel bases its recommendation on the fact that approximately 10% of disease recurrences occur after 3 years.[685,713] The American Society of Colon and Rectal Surgeons also released surveillance guidelines, which are also very similar to NCCN surveillance recommendations.[714] 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

Management of 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 CRC were false positives, with most being single high readings or repeat readings in the range of 5 to 15 ng/mL.[715] In this study, false-positive results greater than 15 ng/mL were rare, and all results greater than 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.[716,717] 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.[718] 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 CRC 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.[719]

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,[720] 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.[721] 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 of 24.7 months.[672]

The panel recommends that patients with unresectable lesions be treated with systemic therapy, chemoRT, or short-course RT according to their ability to tolerate therapy. Debulking that results in gross residual cancer is not recommended. Potentially resectable isolated pelvic/anastomotic

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recurrence may be managed with neoadjuvant therapy, including chemotherapy before or after chemoRT or short-course RT, followed by resection. When following this approach, starting neoadjuvant therapy with chemotherapy is preferred. IORT or brachytherapy should be considered with resection if it can be safely delivered.[453,722-724] Alternatively, resection may be done first, followed by adjuvant chemoRT.

A 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; $P = .353$).[672] 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.[725,726] In a study of 43 consecutive patients with advanced pelvic recurrence of CRC 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.[726] Studies of patients who previously received pelvic radiation show that re-irradiation can be effective, with acceptable rates of toxicity.[727-730] In one such study of 48 patients with recurrent rectal cancer and a history of pelvic radiation, the 3-year rate of grade 3–4 late toxicity was 35%, and 36% of patients treated were able to undergo surgery following radiation.[727] 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.[731] 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.[732]

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).[733-738] Urogenital dysfunction following resection and/or pelvic irradiation is common.[733,739-741] 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 CRC survivors include oxaliplatin-induced peripheral neuropathy, fatigue, insomnia, cognitive dysfunction, and emotional or social distress.[742-747] Specific management interventions to address side effects of CRC have been described,[748] and a survivorship care plan for patients with CRC has been published.[749]

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. These guidelines include many topics with potential relevance to survivors of CRC, including anxiety, depression, and distress; cognitive dysfunction; fatigue; pain; sexual dysfunction; healthy lifestyles; and immunizations.

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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 CRC, 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.[732]

Healthy Lifestyles for Survivors of CRC

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 CRC. 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.[750] In addition, a recent study of a large cohort of men treated for stage I–III CRC showed an association between increased physical activity and lower rates of CRC-specific mortality and overall mortality.[751] More recent data support the conclusion that physical activity improves outcomes. In a cohort of greater than 2000 survivors of non-mCRC, those who spent more time in recreational activity had a lower mortality than those who spent more leisure time sitting.[752] In addition, recent evidence suggests that both pre- and post-diagnosis physical activity decrease CRC mortality. Those enrolled in the Women's Health Initiative study who subsequently developed CRC had lower CRC-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.[753] Similar results were seen in other studies and in recent meta-analyses of prospective studies.[754-757]

A retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[758] Recent analyses confirm the increased risk for recurrence and death in patients affected by obesity.[89] Data from the ACCENT database also found that pre-diagnosis BMI has a prognostic impact on outcomes in patients with stage II/III CRC undergoing adjuvant therapy.[759] However, a recent analysis of participants in the Cancer Prevention Study II Nutrition Cohort who subsequently developed non-mCRC found that pre-diagnosis obesity but not post-diagnosis obesity was associated with higher all-cause and CRC-specific mortality.[760] A meta-analysis of prospective cohort studies found that pre-diagnosis obesity was associated with increased CRC-specific and all-cause mortality.[761] Other analyses confirm the increased risk for recurrence and death in patients affected by obesity.[89,762-765]

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.[766] In addition, results of one retrospective observational study of a cohort of 3408 patients with resected stage I–III CRC suggest that the relationship between mortality and BMI might be U shaped, with the lowest mortality for those with a BMI 28 kg/m^2.[767] However, several possible explanations for this so-called “obesity paradox” have been suggested.[768] Overall the panel believes that survivors of CRC 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.[769] 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 CRC.[95] Recent analysis of the CALGB 89803 trial found that higher dietary glycemic load was also

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associated with an increased risk of recurrence and mortality in patients with stage III disease.[770] 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.[771] The link between red and processed meats and mortality in survivors of non-mCRC 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 CRC-specific mortality than those with low intake (RR, 1.79; 95% CI, 1.11–2.89).[91]

A discussion of lifestyle characteristics that may be associated with a decreased risk of CRC recurrence, such as those recommended by the ACS,[772] 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 CRC, suggesting that survivors may be open to health behavior change.[773]

Therefore, survivors of CRC 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; and quit smoking.[774] 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.[775]

Secondary Chemoprevention for CRC Survivors

Limited data suggest a link between post-colorectal-cancer-diagnosis statin use and increased survival.[112,776,777] A meta-analysis that included four 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; $P < .001$).[776]

Abundant data show that low-dose aspirin therapy after a diagnosis of CRC decreases the risk of recurrence and death.[778-784] For example, a population-based, observational, retrospective cohort study of 23,162 patients with CRC in Norway found that post-diagnosis aspirin use was associated with improved CRC-specific survival (HR, 0.85; 95% CI, 0.79–0.92) and OS (HR, 0.95; 95% CI, 0.90–1.01).[778] Some evidence suggests that tumor mutations in *PIK3CA* may be predictive of response to aspirin, although the data are somewhat inconsistent and other predictive markers have also been suggested.[780,785-790] 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.[791]

Based on these data, the panel believes that survivors of CRC 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 CRC survivors.[792]

Summary

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

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consisting of chemoRT/short-course RT and chemotherapy is 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 systemic therapy, chemoRT, or RT alone may be given.

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. Preoperative systemic therapy, and sometimes chemoRT or short-course RT, 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 systemic therapy options for advanced or metastatic disease depend on whether the patient is appropriate for intensive therapy; the biomarker status of the tumor; and for patients with progressive disease, the choice of initial therapy.

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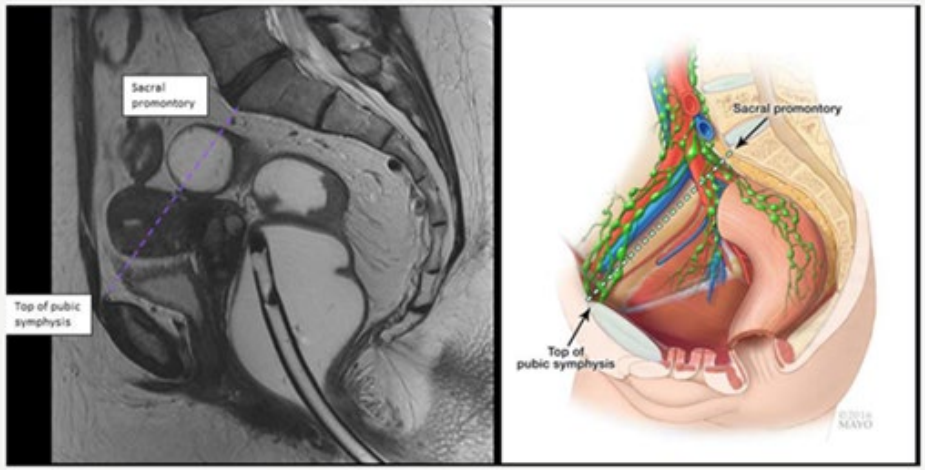
Figure 1. Definition of Rectum



"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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