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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

Version 3.2025 — April 24, 2025

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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NCCN Guidelines Version 3.2025
Colon Cancer

NCCN Guidelines Index
Table of Contents
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Continue

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Þ Internal medicine
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§ Radiotherapy/Radiation oncology
¶ Surgery/Surgical oncology
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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion

NCCN Colon Cancer Panel Members
Summary of the Guidelines Updates

Clinical Presentations and Primary Treatment:
- Pedunculated or Sessile Polyp (Adenoma) with Invasive Cancer (COL-1)
- Workup for Colon Cancer Appropriate for Resection (Non-metastatic)/Suspected or Proven Metastatic Adenocarcinoma (COL-2)

Treatment for pMMR/MSS Colon Cancer
- pMMR/MSS: Findings and Primary Treatment for Colon Cancer Appropriate for Resection (Non-metastatic) (COL-3)
- pMMR/MSS: Pathologic Stage, Adjuvant Treatment (COL-4)
- pMMR/MSS: Findings and Treatment for Suspected or Proven Metastatic Synchronous Adenocarcinoma (COL-5)

Surveillance and Recurrence
- Surveillance (COL-8)
- Recurrence and Workup (COL-9)
- pMMR/MSS: Metachronous Metastases (COL-10)

Treatment for dMMR/MSI-H Colon Cancer
- dMMR/MSI-H or *POLE/POLD1* Mutation: Deficient MMR (dMMR)/MSI-High (MSI-H) Colon Cancer (Non-metastatic) (COL-12)
- dMMR/MSI-H: Pathologic Stage, Adjuvant Treatment (COL-13)
- dMMR/MSI-H or *POLE/POLD1* Mutation: Findings and Treatment for Suspected or Proven Metastatic Synchronous Adenocarcinoma (COL-14)
- dMMR/MSI-H or *POLE/POLD1* Mutation: Resectable Metachronous Metastases (COL-15)

Principles of Imaging (COL-A)
Principles of Pathologic and Molecular Review (COL-B)
Principles of Surgery and Locoregional Therapies (COL-C)
Systemic Therapy for Advanced or Metastatic Disease (COL-D)
Principles of Radiation and Chemoradiation Therapy (COL-E)
Principles of Risk Assessment for Stage II Disease (COL-F)
Principles of Adjuvant Therapy (COL-G)
Principles of Survivorship (COL-H)
Principles of Appendiceal Adenocarcinoma (COL-I)
Principles of Pharmacogenetics (COL-J)
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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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Colon Cancer

NCCN Guidelines Index
Table of Contents
Discussion

Updates in Version 3.2025 of the NCCN Guidelines for Colon Cancer from Version 2.2025 include:

COL-2
- Colon cancer appropriate for resection (non-metastatic)
  - Workup recommendation removed: Enterostomal therapist as indicated for preoperative marking of site, teaching
- Footnote i modified: 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 *Principles of Pharmacogenetics (COL-J) and* DPYD Testing and Fluoropyrimidine-Associated Toxicity Discussion section for more information.

COL-J
- New section added: Principles of Pharmacogenetics

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

COL-2
- Workup
  - Colon cancer appropriate for resection (non-metastatic)
    - ◊ Bullet 3 added: Consider PIK3CA testing for stage II-III
- Footnote i revised: ~~Routine DPYD testing prior to fluoropyrimidine therapy is not recommended at this time. See Discussion for more information.~~ *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 for more information.*

COL-4
- pMMR/MSS Adjuvant Treatment
  - Branch added: If PIK3CA mutation, add aspirin 100-162 mg PO daily for 3 years

COL-12
- Footnote qq modified: Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, cemiplimab-rwlc, dostarlimab-gxly, 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 COL-14, COL-15)

COL-13
- dMMR/MSI-H Adjuvant Treatment
  - Branch added: If PIK3CA mutation, add aspirin 100-162 mg PO daily for 3 years for stage II-III disease

COL-D 4 of 12
- Footnote x 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.

MS-1
- The Discussion section titled ' DPYD Testing and Fluoropyrimidine-Associated Toxicity' has been updated.

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Updates in Version 1.2025 of the NCCN Guidelines for Colon Cancer from Version 6.2024 include:

TOC
- Reorganized and updated section headers

COL-2
- Colon cancer appropriate for resection (non-metastatic)
  - Qualifier modified: dMMR/MSI-H *or POLE/POLD1 mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb]* (Also for COL-12, COL-13)
- Suspected or proven metastatic adenocarcinoma
  - Qualifier modified: dMMR/MSI-H or POLE/POLD1 mutation *with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb]* (Also for COL-9, COL-14, COL-15, COL-D)

COL-4
- pMMR/MSS Adjuvant Treatment
  - T3, N0, M0 (no high-risk features)
    - ◊ Pathway preference modified: Observation *(preferred)*
  - Footnote o revised: *Historical* high-risk factors for recurrence (exclusive of those cancers that are MSI-H): poorly differentiated/undifferentiated histology; lymphatic/vascular invasion; bowel obstruction; <12 lymph nodes examined; perineural invasion (PNI); localized perforation; close, indeterminate, positive margins; or high-tier tumor budding. In patients with high-risk, stage II disease, there are no data that correlate risk features and selection of chemotherapy. *ctDNA is prognostic, but not predictive.*
  - Footnote r revised: Circulating tumor (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.
  - Footnote removed: A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged ≥70 years has not been proven. (Also for COL-13)

COL-6
- Footnote w revised: 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 COL-7, COL-10, COL-11, COL-14, COL-15)
- Footnote x revised: 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 (COL-C and COL-E). *For small lesions (≤3 cm), thermal ablation is equivalent to resection.* (Also for COL-7, COL-10, COL-11, COL-14, COL-15)

COL-7
- Footnote y revised: ~~An FDA-approved biosimilar is an appropriate substitute for bevacizumab.~~ *An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.*

COL-8
- Surveillance
  - Stage II, III
    - ◊ 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

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Updates in Version 1.2025 of the NCCN Guidelines for Colon Cancer from Version 6.2024 include:

COL-8
- Surveillance
  - Stage 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
    - ◊ Text added: FDG-PET/CT is not indicated
  - 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.~~

COL-9
- 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.

COL-10
- pMMR/MSS Resectable Metachronous Metastases
  - Pathways modified: Resection ~~(preferred)~~ and/or Local therapy (Also for COL-15)

COL-11
- pMMR/MSS Unresectable Metachronous Metastases
  - Initial Treatment
    - ◊ Qualifier modified: (FOLFIRI or irinotecan) ± (cetuximab or panitumumab) (KRAS/NRAS/BRAF WT *and left-sided tumors only*)
  - Footnote y added: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
  - Footnotes removed (Also for COL-D):
    - ◊ An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
    - ◊ An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

COL-12
- Deficient MMR (dMMR)/MSI-high (MSI-H) or POLE/POLD1 mutation with ultra-hypermutated phenotype [eg, TMB>50 mut/Mb] colon cancer (non-metastatic)
  - Findings, option modified: Clinical T4b *or bulky nodal disease*
  - Footnote ll modified: Patients ~~with dMMR/MSI-H disease~~ who are not candidates for immunotherapy should be treated as recommended for pMMR/MSS disease. (Also for COL-14, COL-15)
  - Checkpoint inhibitor immunotherapy options added to footnote qq: Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, ~~or~~ pembrolizumab, *cemiplimab-rwlc, dostarlimab-gxly, retifanlimab-dlwr, toripalimab-tpzi, or tislelizumab-jsgr.* (Also for COL-14, COL-15)

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Updates in Version 1.2025 of the NCCN Guidelines for Colon Cancer from Version 6.2024 include:

COL-13
- dMMR/MSI-H; Adjuvant Treatment
  - T1–3, N1 (low-risk stage III) and T4, N1–2; T Any, N2 (high-risk stage III)
    - ◊ Capecitabine and 5-FU changed from category 2A to category 2B recommendations

COL-15
- 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

COL-A 1 of 2
- Principles of Imaging
  - Monitoring
    - ◊ Bullet 2 modified: FDG-PET/CT*, FDG-PET/MRI, or contrast-enhanced MRI* can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, thermal ablation, radioembolization).

COL-A 2 of 2
- Surveillance
  - Bullet 3, sub-bullet 2 modified: FDG-PET/CT*, FDG-PET/MRI, or contrast-enhanced MRI* can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, thermal ablation, radioembolization) or serial CEA elevation during follow-up.
- Reference added: Görgec B, Hansen IS, Kemmerich G, et al. MRI in addition to CT in patients scheduled for local therapy of colorectal liver metastases (CAMINO): an international, multicentre, prospective, diagnostic accuracy trial. Lancet Oncol 2024;25:137-146.

COL-B 5 of 10
- 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.~~

COL-B 6 of 10
- POLE/POLD1
  - Bullet 4 revised: 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~~).

COL-C 1 of 6
- Principles of Surgery and Locoregional Therapies
  - Colectomy
    - ◊ Bullet 2, sub-bullet 2 revised: ~~Consider~~ *Preoperative localization is performed (eg, radiographic identification,* preoperative endoscopic marking, *endoscopic landmarks)* ~~of lesion(s)~~.
    - ◊ Bullet 2, sub-bullet 4 revised: Minimally invasive approaches are generally not indicated for locally advanced cancer *(eg, invasion into adjacent structure)* or acute bowel obstruction....

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Updates in Version 1.2025 of the NCCN Guidelines for Colon Cancer from Version 6.2024 include:

COL-C 3 of 6
- 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*

COL-D 1 of 12
- 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

COL-D 2 of 12
- 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

COL-D 3 of 12
- 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)

COL-D 4 of 12
- Footnotes
  - Footnote c added: An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. (Also for COL-D 5 through 9 of 12)
  - Footnote t 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.

COL-D 8 of 12 and **COL-D 9 of 12**
- Regimen and dosing updated.

COL-D 10 of 12 through **COL-D 12 of 12**
- References updated.

Continued

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Updates in Version 1.2025 of the NCCN Guidelines for Colon Cancer from Version 6.2024 include:

COL-E 1 of 2

- Principles of Radiation and Chemoradiation 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 2 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.~~
    - ◊ Bullet 6: 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.

COL-E 2 of 2

- 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.

COL-G 2 of 2

- Principles of Adjuvant Therapy - Chemotherapy Regimens and References
  - Duration removed for the following:
    - ◊ Capecitabine 1000–1250 mg/m^2 PO twice daily for 14 days every 3 weeks ~~x 24 weeks.~~
    - ◊ Capecitabine 1000 mg/m^2 PO twice daily for 14 days every 3 weeks ~~x 24 weeks.~~

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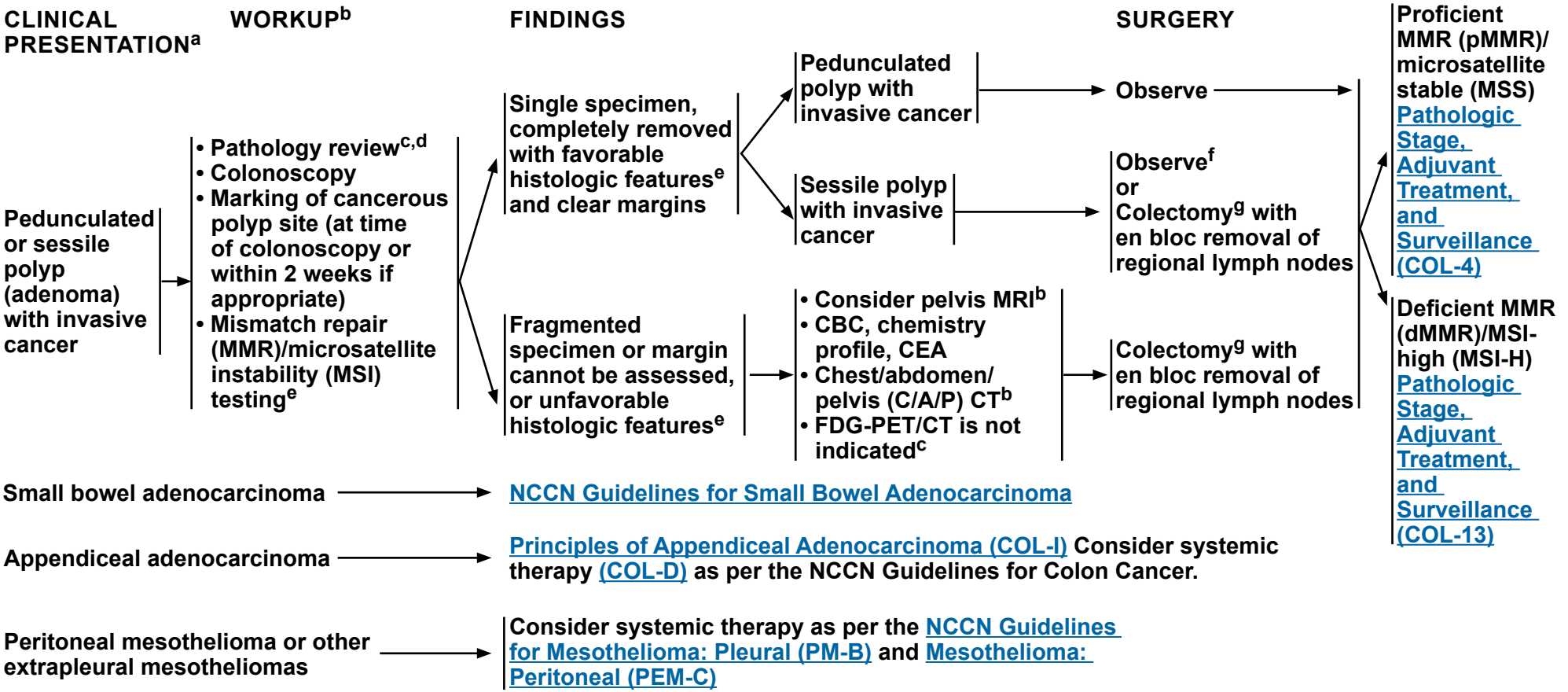
NCCN Guidelines Version 3.2025
Colon Cancer



[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For 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] Principles of Imaging (COL-A).

[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 (COL-B).

[f] Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than pedunculated malignant polyps. See Principles of Pathologic Review (COL-B) - Endoscopically removed malignant polyp.

[g] Principles of Surgery and Locoregional Therapies (COL-C).

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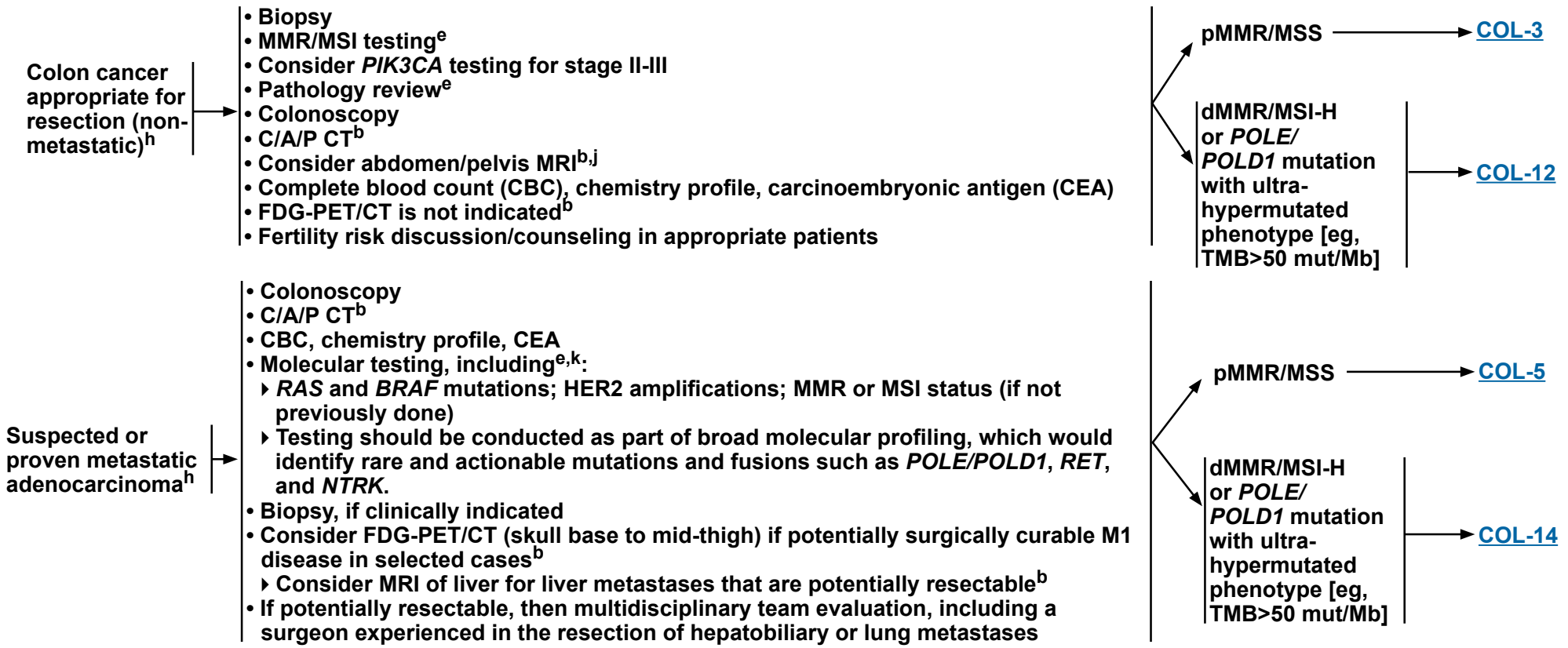

[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected LS, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.

[b] Principles of Imaging (COL-A).

[e] Principles of Pathologic Review (COL-B).

[h] For tools to aid in optimal assessment and care of older adults with cancer, see the NCCN Guidelines for Older Adult Oncology.

[i] 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 Principles of Pharmacogenetics (COL-J) and *DPYD* Testing and Fluoropyrimidine-Associated Toxicity Discussion section for more information.

[j] Consider an MRI to assist with the diagnosis of rectal cancer versus colon cancer (eg, low-lying sigmoid tumor). The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.

[k] Tissue- or blood-based next-generation sequencing (NGS) panels have the ability to pick up rare and actionable mutations and fusions.

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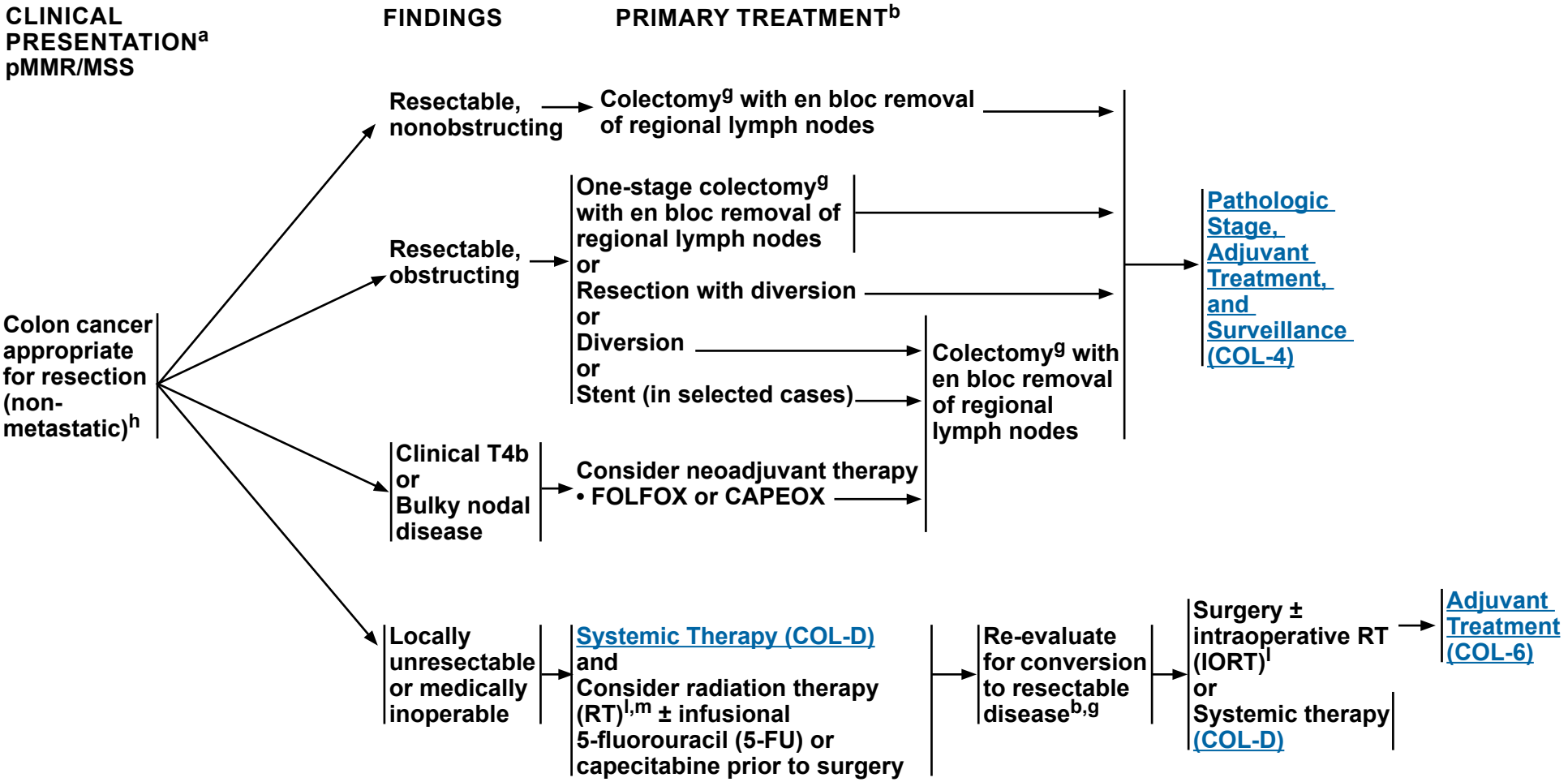

[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected LS, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.

[b] Principles of Imaging (COL-A).

[g] Principles of Surgery and Locoregional Therapies (COL-C).

[h] For tools to aid in optimal assessment and care of older adults with cancer, see the NCCN Guidelines for Older Adult Oncology.

[l] Principles of Radiation and Chemoradiation Therapy (COL-E).

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

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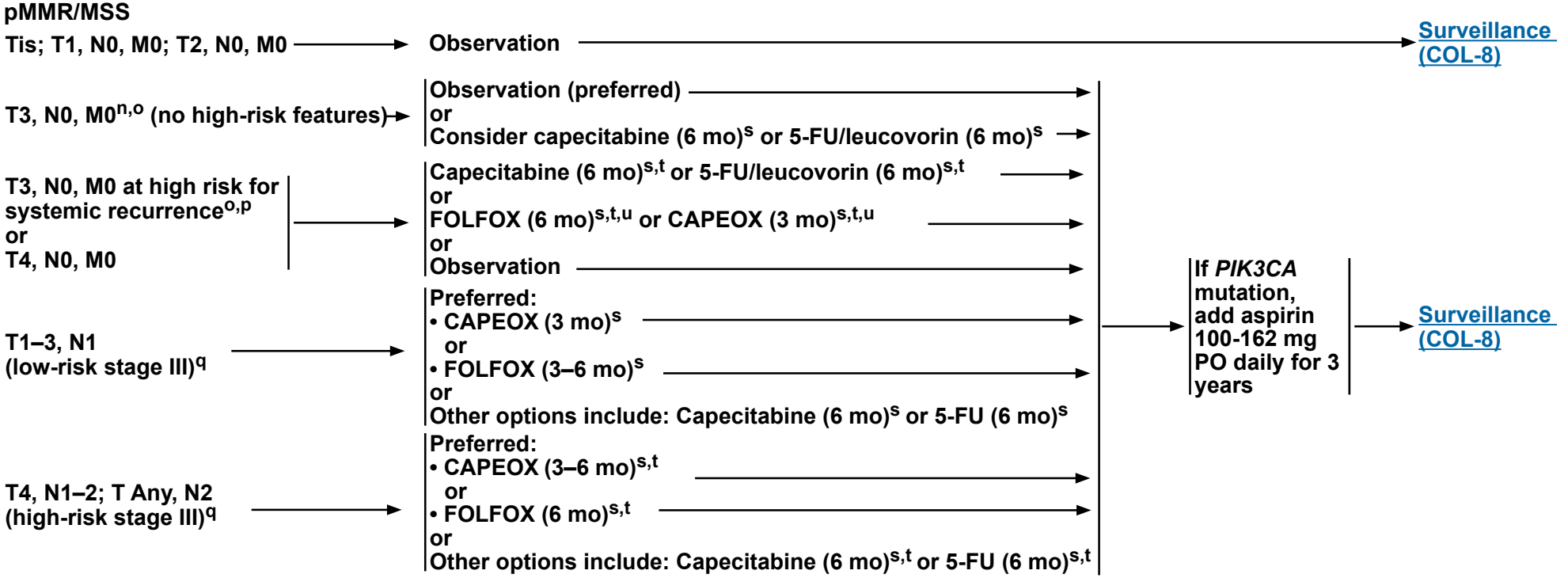

[b] Principles of Imaging (COL-A).
[e] Principles of Pathologic Review (COL-B).
[n] Principles of Risk Assessment for Stage II Disease (COL-F).
[o] Historical high-risk factors for recurrence (exclusive of those cancers that are MSI-H): poorly differentiated/undifferentiated histology; lymphatic/vascular invasion; bowel obstruction; <12 lymph nodes examined; perineural invasion (PNI); localized perforation; close, indeterminate, positive margins; or high-tier tumor budding. In patients with high-risk, stage II disease, there are no data that correlate risk features and selection of chemotherapy. ctDNA is prognostic, but not predictive.
[p] There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.
[q] While nonnferiority of 3 mo vs. 6 mo of CAPEOX has not been proven, 3 mo of CAPEOX numerically appeared similar to 6 mo of CAPEOX for 5-year overall survival (82.1% vs. 81.2%; hazard ratio [HR], 0.96), with considerably less toxicity (Andre T, et al. Lancet Oncol 2020;21:1620-1629). These results support the use of 3 mo of adjuvant CAPEOX over 6 mo in the vast majority of patients with stage III colon cancer. In patients with colon cancer, staged as T1–3, N1 (low-risk stage III), 3 mo of CAPEOX is noninferior to 6 mo for disease-free survival (DFS); noninferiority of 3 mo vs. 6 mo of FOLFOX has not been proven. In patients with colon cancer staged as T4, N1–2 or T any, N2 (high-risk stage III), 3 mo of FOLFOX is inferior to 6 mo for DFS, whereas noninferiority of 3 mo vs. 6 mo of CAPEOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 mo vs. 6 mo of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX). Grothey A, et al. N Engl J Med 2018;378:1177-1188.
[r] Circulating tumor (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.
[s] Principles of Adjuvant Therapy (COL-G).
[t] Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation and Chemoradiation Therapy (COL-E).
[u] A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer. Tournigand C, et al. J Clin Oncol 2012;30:3353-3360.

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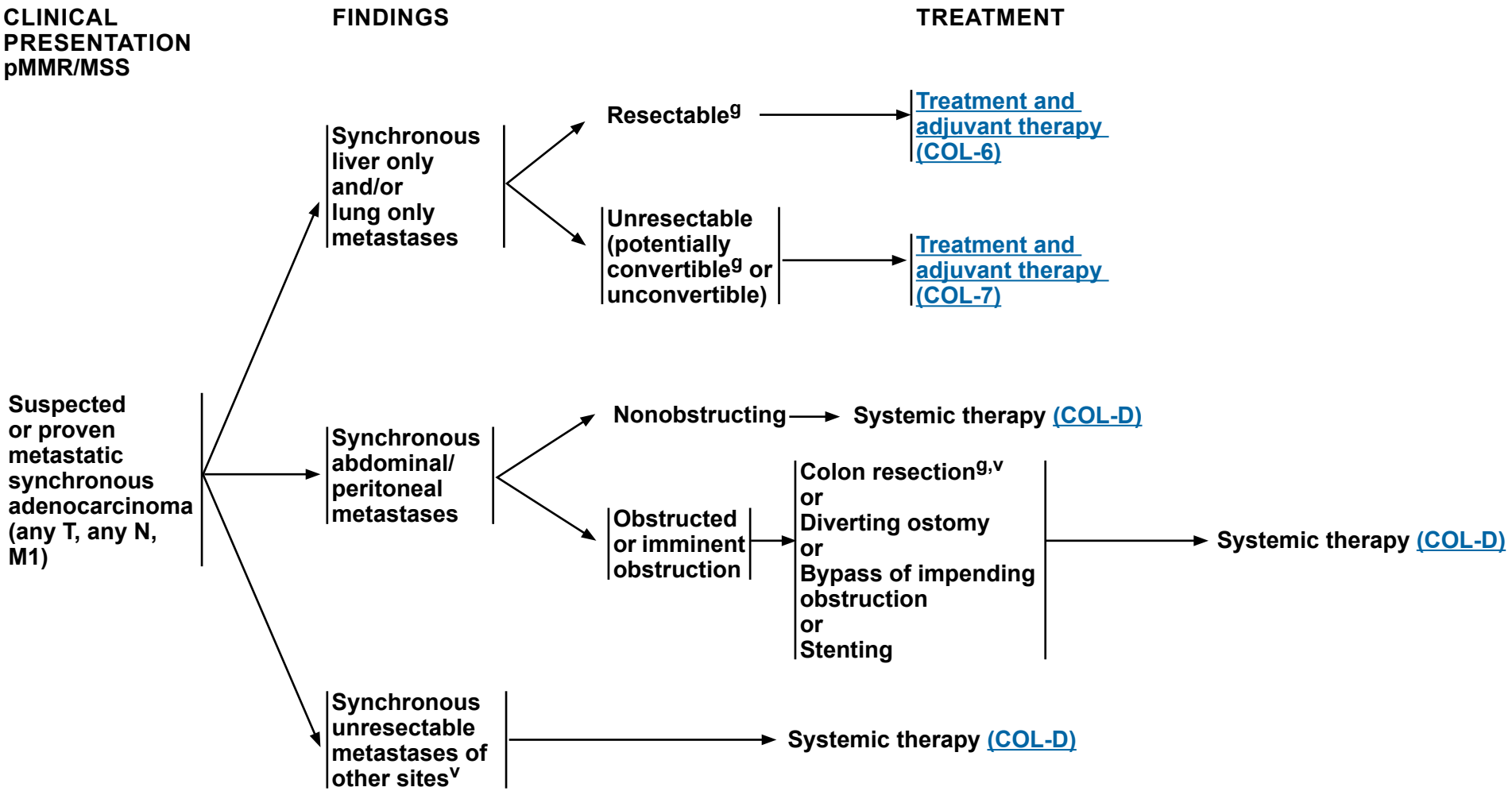

[g] Principles of Surgery and Locoregional Therapies (COL-C).
[v] Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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TREATMENT
Resectable[g] synchronous liver and/or lung metastases only
pMMR/MSS

ADJUVANT TREATMENT[b] (UP TO 6 MO PERIOPERATIVE TREATMENT) (resected metastatic disease)

Synchronous or staged colectomy[w] with liver or lung resection (preferred) and/or local therapy[x]
or
Neoadjuvant therapy (for 2–3 mo) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFIRINOX (category 2B) followed by synchronous or staged colectomy[w] and resection (preferred) and/or local therapy[x] of metastatic disease
or
Colectomy,[w] followed by chemotherapy (for 2–3 mo) FOLFOX (preferred) or CAPEOX (preferred) or FOLFIRI (category 2B) or FOLFIRINOX (category 2B) and staged resection (preferred) and/or local therapy[x] of metastatic disease

→ **FOLFOX (preferred)**
or
CAPEOX (preferred)
or
Capecitabine or 5-FU/leucovorin

→ **Surveillance (COL-8)**

[b] Principles of Imaging (COL-A).
[g] Principles of Surgery and Locoregional Therapies (COL-C).
[w] 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.
[x] 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 (COL-C and COL-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.

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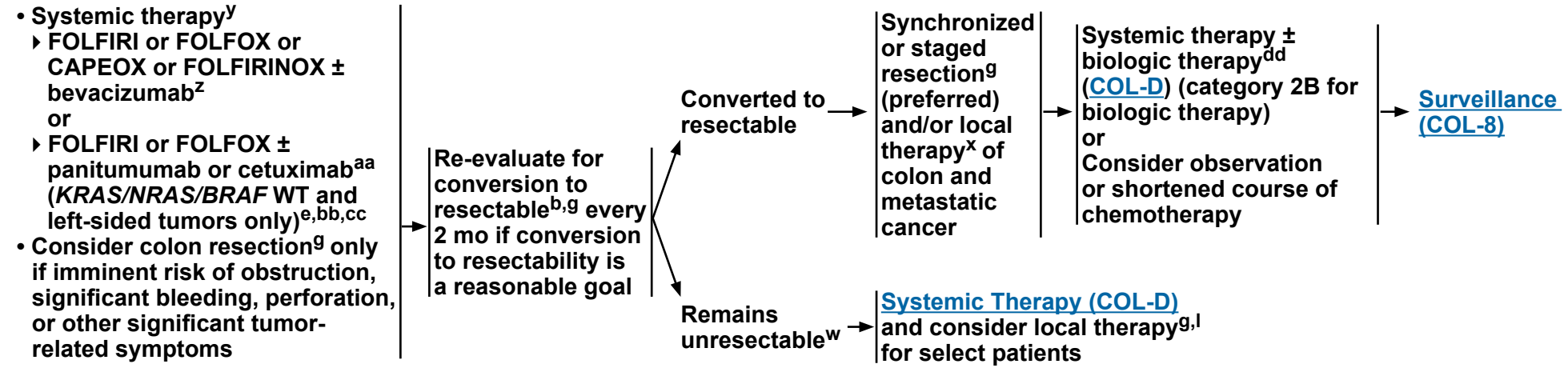
TREATMENT
Unresectable[g] synchronous liver and/or lung metastases only pMMR/MSS

ADJUVANT TREATMENT[b] (UP TO 6 MO PERIOPERATIVE TREATMENT)



[b] Principles of Imaging (COL-A).
[g] Principles of Surgery and Locoregional Therapies (COL-C).
[e] Principles of Pathologic Review (COL-B 4).
[l] Principles of Radiation and Chemoradiation Therapy (COL-E).
[w] 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.
[x] 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 (COL-C and COL-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.
[y] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[z] There should be at least a 6-week interval between the last dose of bevacizumab and elective surgery and re-initiation of bevacizumab 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.
[aa] There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.
[bb] Cetuximab or panitumumab should only be used for left-sided tumors. The Panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.
[cc] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.
[dd] Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.

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PATHOLOGIC STAGE	SURVEILLANCE[b]
Stage I	Colonoscopy[a] at 1 y after surgery • If advanced adenoma, repeat in 1 y • If no advanced adenoma,[ff] repeat in 3 y, then every 5 y[gg]
Stage II, III[ee]	• History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA[hh] every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • C/A/P CT every 6–12 mo (category 2B for frequency <12 mo) from date of surgery for a total of 5 y • Colonoscopy[a] 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,[ff] repeat in 3 y, then every 5 y[gg] • FDG-PET/CT is not indicated • Principles of Survivorship (COL-H)
Stage IV	• History and physical examination every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA[hh] every 3–6 mo x 2 y, then every 6 mo for a total of 5 y • C/A/P CT 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,ii] 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,[ff] repeat in 3 y, then every 5 y[gg] • FDG-PET/CT is not indicated • Principles of Survivorship (COL-H)

Serial CEA elevation or documented recurrence → Workup and treatment (COL-9)

[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected LS, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.
[b] Principles of Imaging (COL-A).
[ee] ctDNA is not recommended for surveillance.
[ff] Villous polyp, polyp >1 cm, or high-grade dysplasia.
[gg] Kahi CJ, et al. Gastroenterology 2016;150:758-768.
[hh] If patient is a potential candidate for further intervention.
[ii] 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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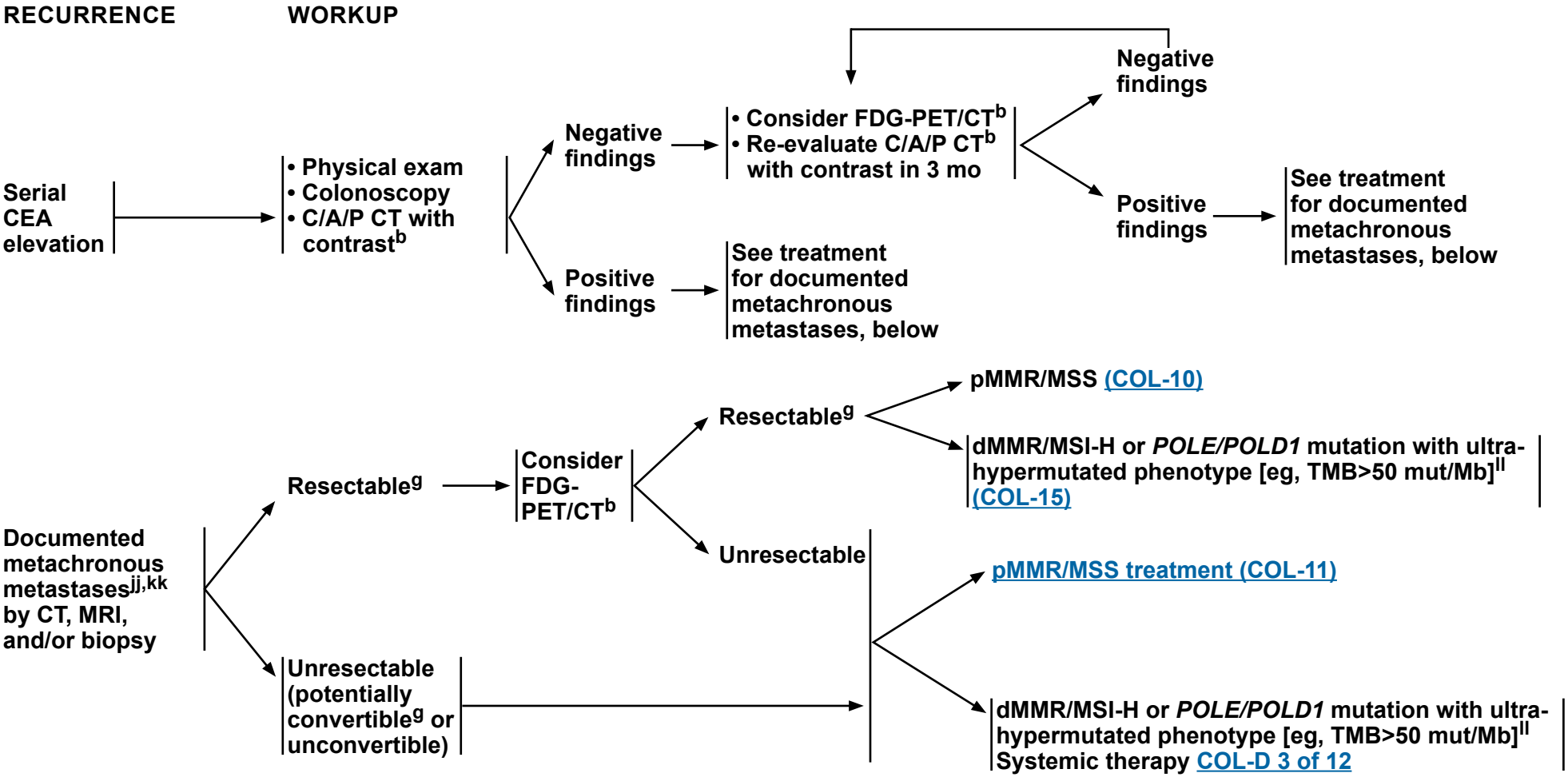

[b] Principles of Imaging (COL-A).
[g] Principles of Surgery and Locoregional Therapies (COL-C).
[jj] Determination of tumor gene status for *RAS* and *BRAF* mutations and HER2 amplifications (individually or as part of tissue- or blood-based NGS panel. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (COL-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.
[kk] Patients should be evaluated by a multidisciplinary team including surgical consultation for patients with potentially resectable disease.
[ll] 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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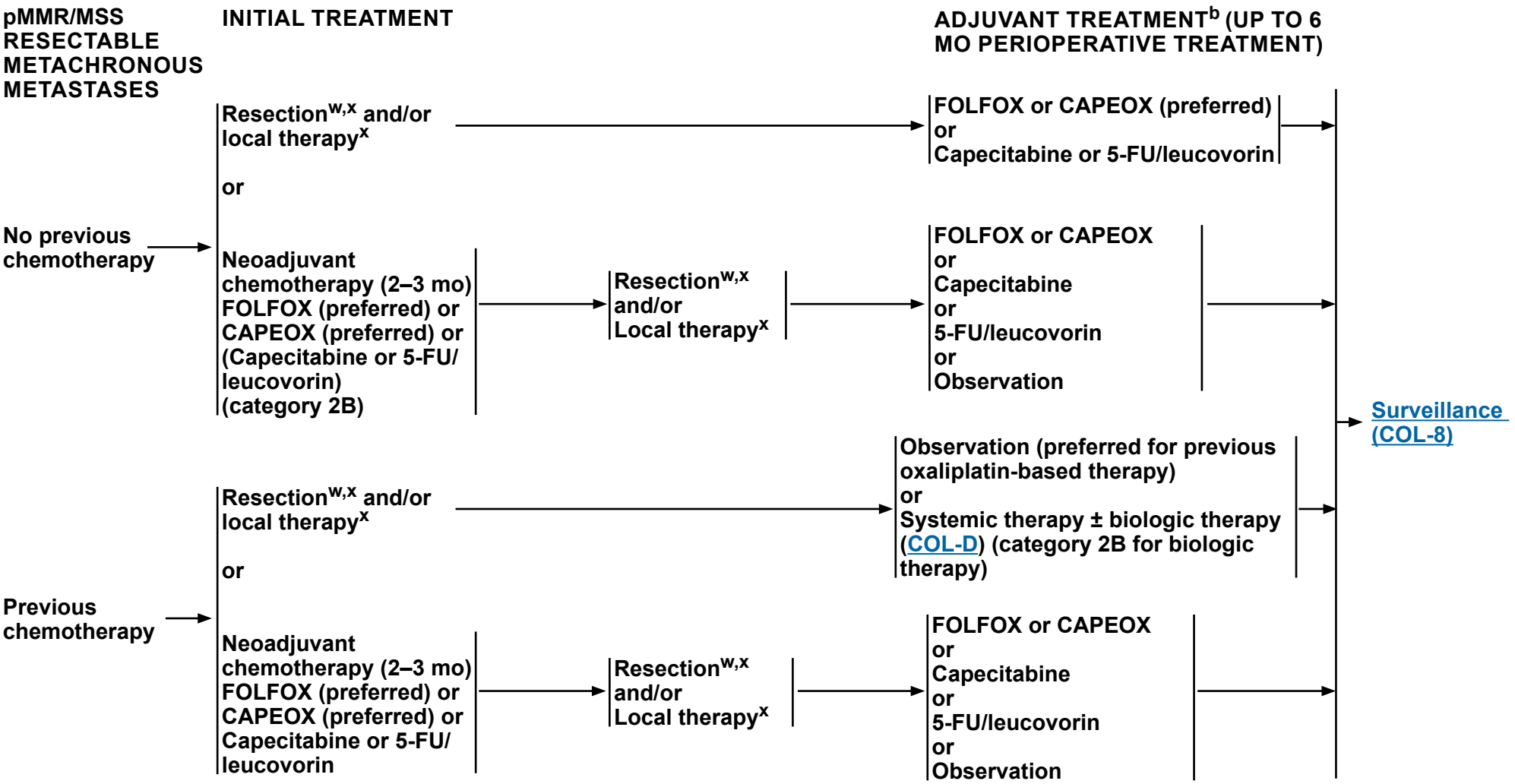

[b] Principles of Imaging (COL-A).

[w] 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.

[x] 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 (COL-C and COL-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.

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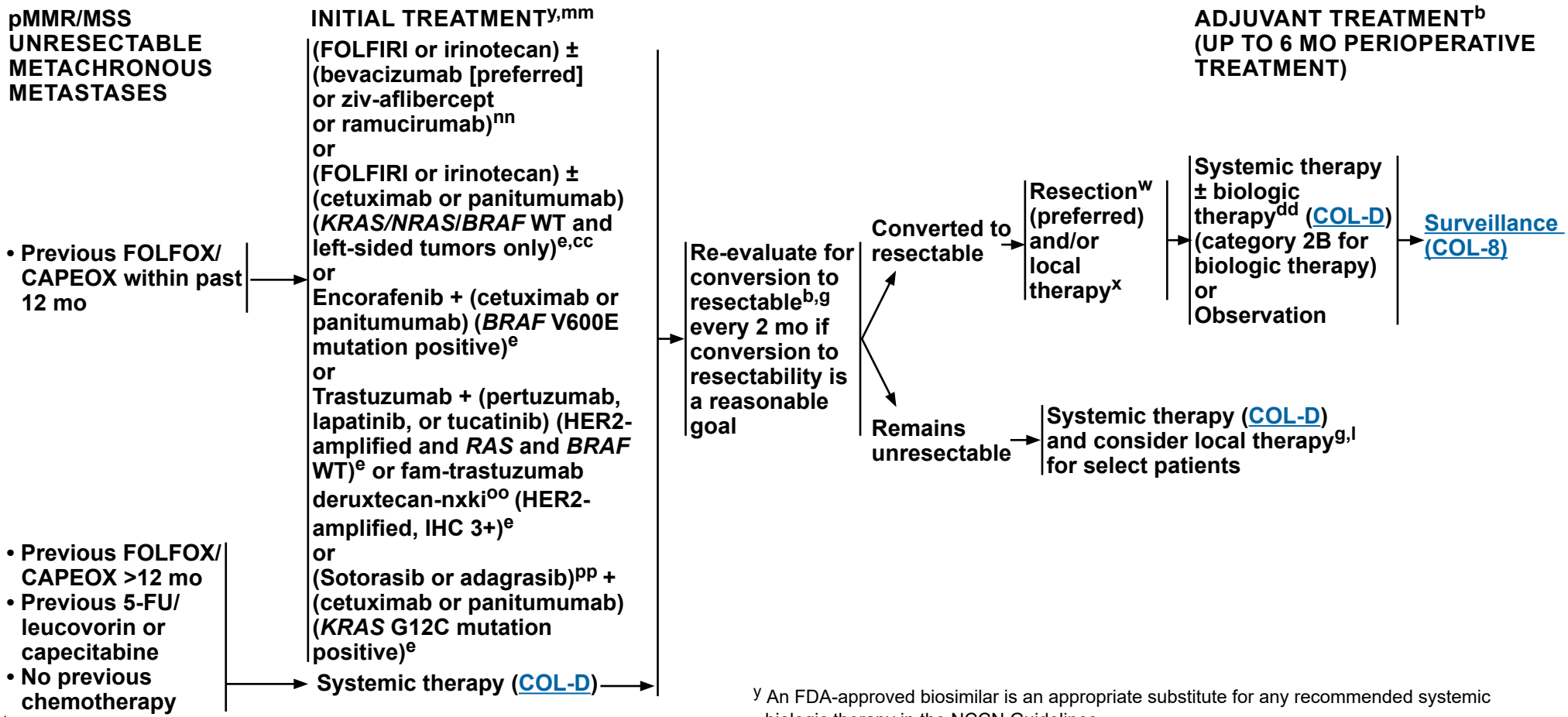

[b] Principles of Imaging (COL-A).
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[y] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[cc] Patients with *BRAF* mutations other than V600E may be considered for anti-EGFR therapy.
[dd] Biologic therapy is only appropriate for continuation of favorable response from conversion therapy.
[mm] 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.
[nn] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[oo] 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).
[pp] If patient is unable to tolerate EGFR inhibitor due to toxicity, single-agent adagrasib or sotorasib can be considered.

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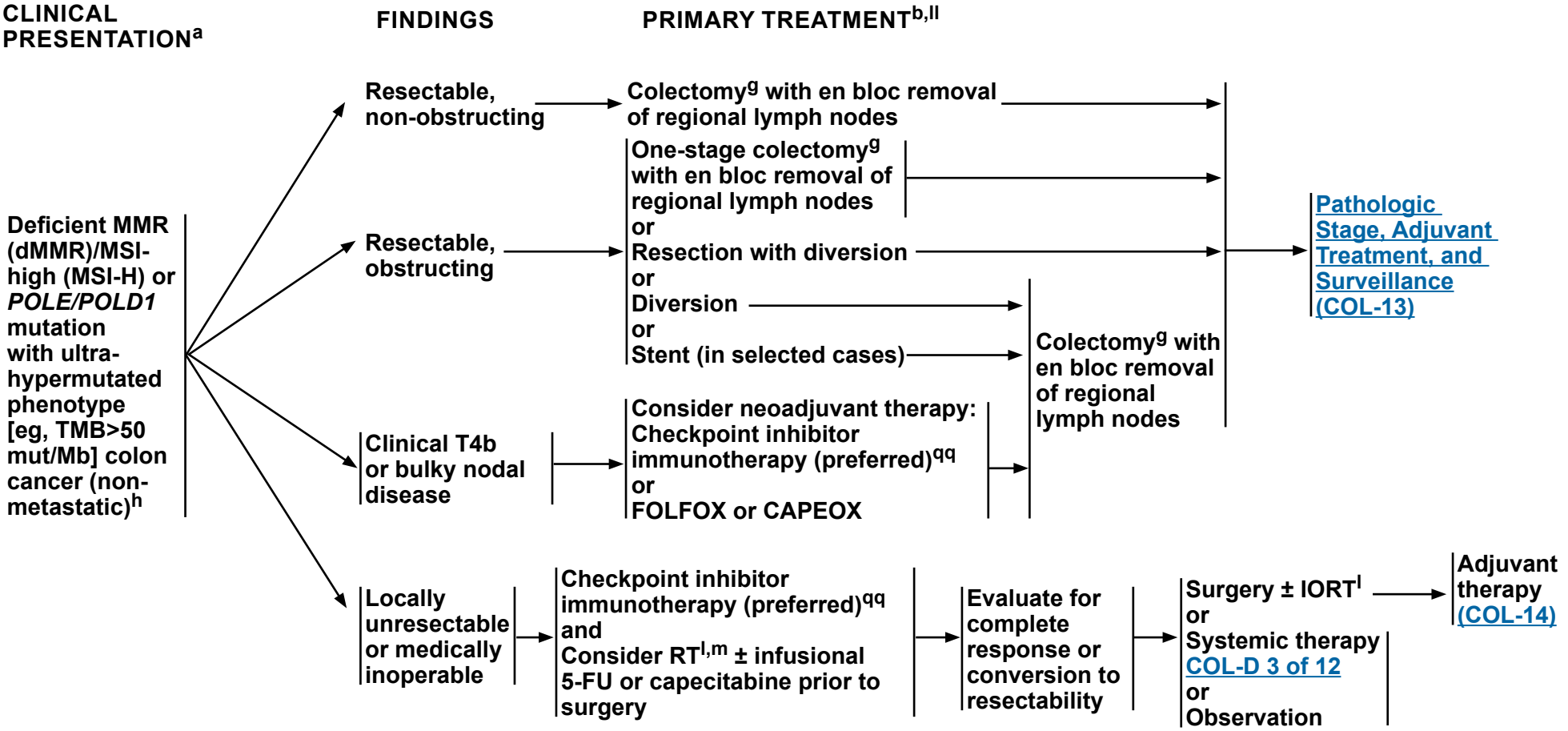

[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected LS, FAP, and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[b] Principles of Imaging (COL-A).

[g] Principles of Surgery and Locoregional Therapies (COL-C).

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[l] Principles of Radiation and Chemoradiation Therapy (COL-E).

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

[ll] 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.

[qq] Checkpoint inhibitor therapy options include: nivolumab ± ipilimumab, pembrolizumab, cemiplimab-rwlc, dostarlimab-gxly, 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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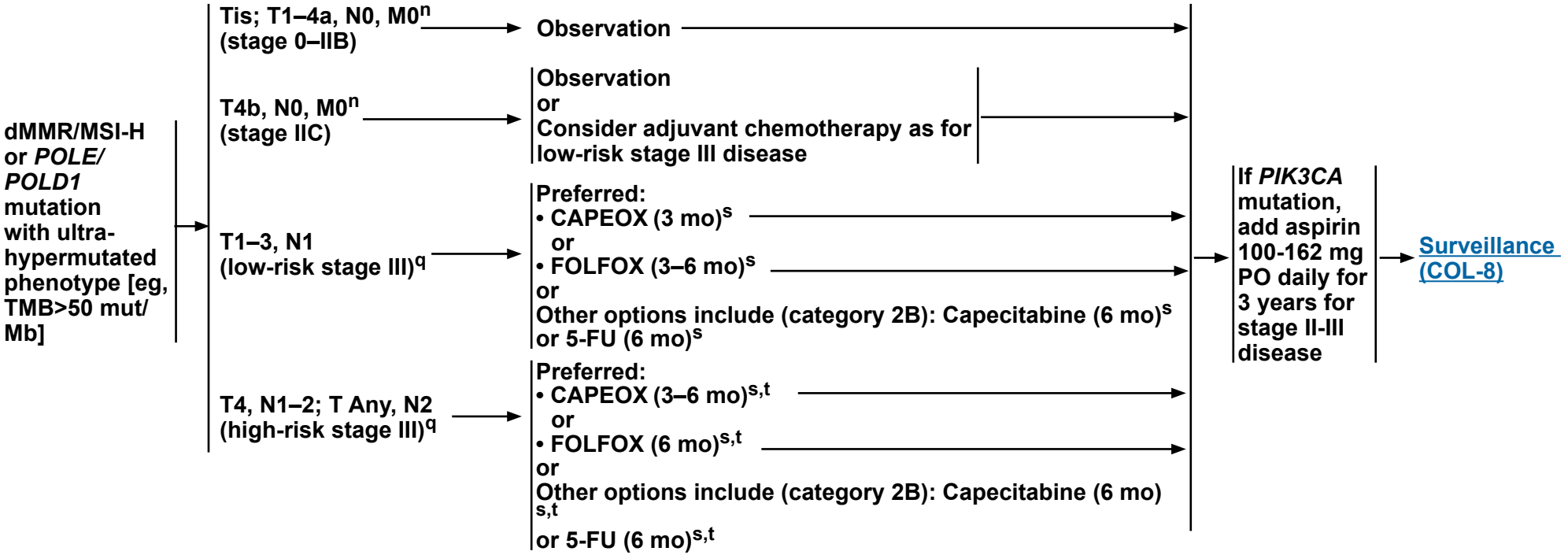

[b] Principles of Imaging (COL-A).
[e] Principles of Pathologic Review (COL-B).
[n] Principles of Risk Assessment for Stage II Disease (COL-F).
[q] While noninferiority of 3 mo vs. 6 mo of CAPEOX has not been proven, 3 mo of CAPEOX numerically appeared similar to 6 mo of CAPEOX for 5-year overall survival (82.1% vs. 81.2%; HR, 0.96), with considerably less toxicity (Andre T, et al. Lancet Oncol 2020;21:1620-1629). These results support the use of 3 mo of adjuvant CAPEOX over 6 mo in the vast majority of patients with stage III colon cancer. In patients with colon cancer, staged as T1–3, N1 (low-risk stage III), 3 mo of CAPEOX is noninferior to 6 mo for DFS; noninferiority of 3 mo vs. 6 mo of FOLFOX has not been proven. In patients with colon cancer staged as T4, N1–2 or T any, N2 (high-risk stage III), 3 mo of FOLFOX is inferior to 6 mo for DFS, whereas noninferiority of 3 mo vs. 6 mo of CAPEOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 mo vs. 6 mo of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX). Grothey A, et al. N Engl J Med 2018;378:1177-1188.
[s] Principles of Adjuvant Therapy (COL-G).
[t] Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation and Chemoradiation Therapy (COL-E).

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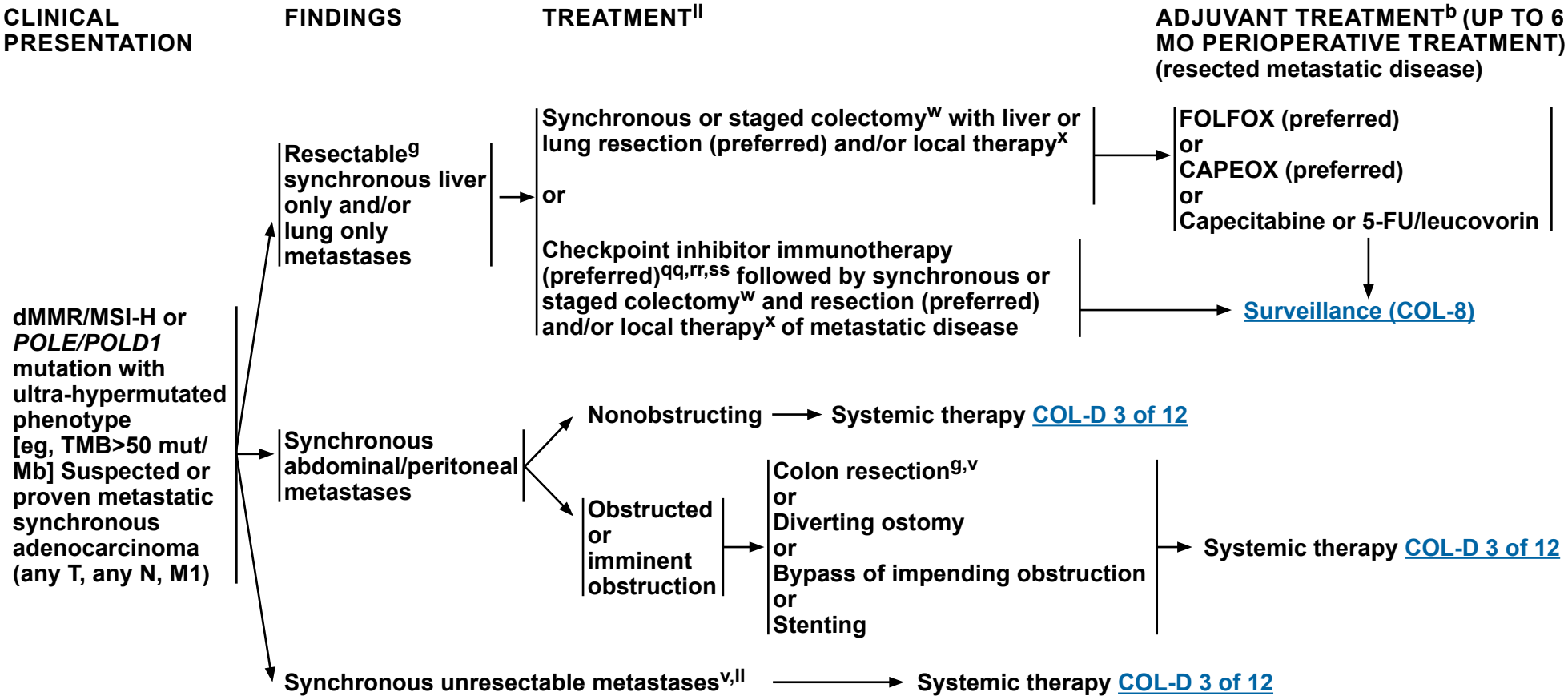

[b] Principles of Imaging (COL-A).
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[v] Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.
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[x] Resection 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 (COL-C and COL-E). For small lesions (≤3 cm), thermal ablation is equivalent to resection.
[ll] 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.
[qq] 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.
[rr] If no previous treatment with a checkpoint inhibitor.
[ss] 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.

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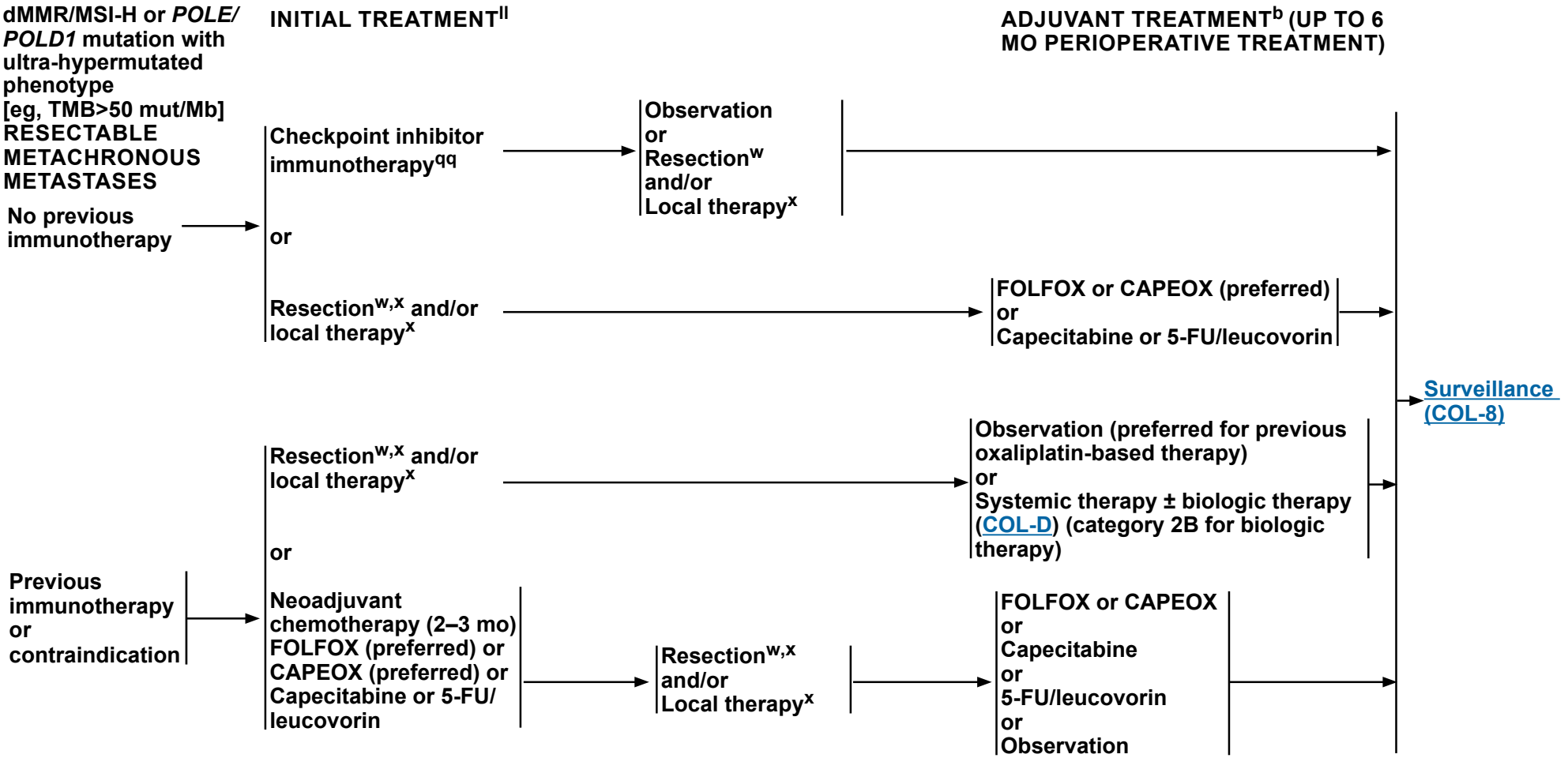

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[ll] Patients who are not candidates for immunotherapy should be treated as recommended for pMMR/MSS disease. See NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

[qq] 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

- C/A/P CT
  - 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 should be performed with intravenous iodinated contrast and oral contrast material unless contraindicated.
  - Intravenous contrast is not required for the chest CT (but usually given if performed with abdominal CT).
  - If IV iodinated contrast material is contraindicated because of significant contrast allergy, then MRI examination of the abdomen and pelvis 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.
- Consider an abdomen/pelvis MRI to assist with the diagnosis of rectal cancer versus colon cancer (eg, low-lying sigmoid tumor). The rectum lies below a virtual line from the sacral promontory to the upper edge of the symphysis as determined by MRI.
- Consider MRI of liver for liver metastases if potentially resectable.
- 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 selected patients considered for image-guided liver-directed therapies (ie, thermal ablation, radioembolization).[4-8]
- If liver-directed therapy or surgery is contemplated, a hepatic MRI with intravenous routine extracellular or hepatobiliary GBCA is preferred over CT to assess exact number and distribution of metastatic foci for local treatment planning.[9]

Monitoring

- C/A/P CT with contrast
  - Prior to adjuvant treatment to assess response to primary therapy or resection
  - During re-evaluation of conversion to resectable disease
- FDG-PET/CT, FDG-PET/MRI, or contrast-enhanced MRI can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, thermal ablation, radioembolization).

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PRINCIPLES OF IMAGING[1-3]

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.**
  - **FDG-PET/CT is not indicated.**
- **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.**
  - **FDG-PET/CT, FDG-PET/MRI, or contrast-enhanced MRI can be considered for assessment of response and liver recurrence after image-guided liver-directed therapies (ie, thermal ablation, radioembolization) or serial CEA elevation during follow-up.**

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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 mucosa and into the submucosa (pT1). pTis is not considered a "malignant polyp."
- Favorable histologic features: grade 1 or 2 (low-grade histology according to WHO 2019), 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 (high-grade histology according to WHO 2019), angiolymphatic invasion, or a "positive margin." See the positive margin definition above. In several studies, high 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 outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than do pedunculated 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 margins, and no lymphovascular invasion can be successfully treated with endoscopic polypectomy.[3-7]

Colon Cancer Appropriate for Resection

- Histologic confirmation of primary colonic malignant neoplasm

Pathologic Stage

- The following parameters should be reported:
  - Grade of the cancer
  - Depth of penetration (T)
  - Number of lymph nodes evaluated and number positive (N)
  - Status of proximal, distal, radial, and mesenteric margins[8,9]; see Staging (ST-1)
  - Lymphovascular invasion[10,11]
  - Perineural invasion (PNI)[12-14]
  - Tumor deposits[15-18]

References

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PRINCIPLES OF PATHOLOGIC AND MOLECULAR REVIEW

Pathologic Stage (continued)

- **Radial (circumferential) margin evaluation - The serosal surface (peritoneal) does not constitute a surgical margin. In colon cancer the circumferential (radial) margin represents the adventitial soft tissue closest to the deepest penetration of tumor, and is created surgically by blunt or sharp dissection of the retroperitoneal aspect. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. The circumferential resection margin corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells, and must be dissected from the retroperitoneum to remove the viscus. On pathologic examination it is difficult to appreciate the demarcation between a peritonealized surface and non-peritonealized surface. Therefore, the surgeon is encouraged to mark the area of non-peritonealized surface with a clip or suture. The mesenteric resection margin is the only relevant circumferential margin in segments completely encased by the peritoneum.[10,11]**
- **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 (DFS). For stage II carcinoma, those with PNI have a significantly worse 5-year DFS compared to those without PNI (29% vs. 82%; *P* = .0005).[12-14]**
- **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 peritumoral 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 DFS and overall survival, their number should be recorded in the surgical pathology report. This poorer outcome has also been noted in patients with stage III carcinoma.[15-18]**
- **High tumor budding - In recent years, high tumor budding has been identified as a new prognostic factor in colon cancer. Recently, there was an international consensus conference on tumor budding reporting.[19] 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[20,21] using this scoring system have shown tumor budding to be an independent prognostic factor for stage II colon cancer. An ASCO guideline for stage II colon cancer designates tumor budding as an adverse (high-risk) factor.[22] 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 tier were not uniform.[23-27]**

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Lymph Node Evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately stage colon cancers.[8,9,28] The literature lacks consensus as to what is the minimum number of lymph nodes to accurately identify stage II cancer. The minimum number of nodes has been reported as >7, >9, >13, >20, and >30.[29-37] The number of lymph nodes retrieved can vary with patient age, gender, tumor grade, and tumor site.[30] 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 pathologist should attempt to retrieve as many lymph nodes as possible. It has been shown that the number of negative lymph nodes is an independent prognostic factor for patients with stage IIIB and IIIC colon cancer.[38]

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). The 8th edition of the AJCC Cancer Staging Manual and Handbook[39] 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.[40-49] 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.[45-50] A recent meta-analysis[51] demonstrated that micrometastases (≥0.2 mm) are a significant poor prognostic factor. However, another recent multicenter prospective study of stage I or II disease (via H&E) had a 10% decrease in survival for IHC-detected isolated tumor cells, (<0.2 mm) but only in those with pT3–pT4 disease.[52]

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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 colorectal cancer (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.[53-55] *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a *BRAF* inhibitor.[56-58]
- *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.[59]

Microsatellite Instability or Mismatch Repair Testing

- Universal MMR[a] or MSI[a] testing is recommended in all newly diagnosed patients with colon 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.[60]
- Stage II (MSI-H) cancers may have a good prognosis and do not benefit from 5-FU adjuvant therapy.[61]
- 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.[60]

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

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HER2 Testing

- Diagnostic testing is via IHC, fluorescence in situ hybridization (FISH), or 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 who have a HER2 score of 2+ should be reflexed to FISH testing.[62-64] HER2 amplification by FISH is considered positive when the HER2:CEP17 ratio is ≥2 in more than 50% of the cells.[62-64] NGS is another methodology for testing for HER2 amplification.[65]
- 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.[66] 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 8 CRCs harboring *NTRK* fusions, 7 were found in the small subset that were dMMR (MLH-1)/MSI-H.[67] *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,[68] FISH, DNA-based NGS, and RNA-based NGS.[66,69] 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 1 in 5 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.[69] However, selection of the appropriate assay for *NTRK* fusion detection depends on tumor type and genes involved, as well as consideration of other factors such as available material, accessibility of various clinical assays, and whether comprehensive genomic testing is needed concurrently.[69]

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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).[70,71]
- Germline PVs within the ED of *POLE* and *POLD1* predispose patients to multiple colorectal adenomas and carcinomas, resulting in polymerase proofreading-associated polyposis (PPAP)[70,71] (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.[70,72]
- 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).[72,73]
- *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).[72-74]
- 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.[74-79]

***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.[80]
- 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.[80]
- Somatic activating alterations in *RET* include point mutations as well as gene rearrangements and have been identified in a variety of tumors.[80-82]
- 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*.[80-83]
- The *RET*-targeted inhibitor, selpercatinib, is FDA-approved for patients with solid tumors harboring activating *RET* fusions.[84]
- 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.[81-83]

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES

Colectomy

- **Lymphadenectomy**
  - **Proper technique for lymphadenectomy requires proximal ligation of the associated vascular pedicle(s) with en bloc removal of the colonic segment and its mesentery.[1]**
  - **Clinically positive lymph nodes outside the standard field of resection that are considered suspicious should be biopsied or removed, if possible.**
  - **Positive nodes left behind indicate an incomplete (R2) resection.**
  - **A minimum of 12 lymph nodes should be examined to adequately establish N stage.[2]**
  - **Resection needs to be complete to be considered curative.**
- **Minimally invasive approaches (eg, laparoscopic-, robot-assisted) may be performed with the following considerations[3]:**
  - **The surgeon has experience performing minimally invasive colorectal operations.[4,5]**
  - **Preoperative localization is performed (eg, radiographic identification, preoperative endoscopic marking, endoscopic landmarks).**
  - **Thorough abdominal exploration and assessment can be performed.[6]**
  - **Minimally invasive approaches are generally not indicated for locally advanced cancer (eg, invasion into adjacent structure) or acute bowel obstruction or perforation from cancer but may be considered with appropriate surgeon experience.**
- **Surgical considerations for patients with known or clinically suspected hereditary syndromes:**
  - **See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric.**

Locoregional Therapies

- **Image Guided Tumor Ablation[7]**
  - **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[7-9]**
  - **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 nonsurgical candidates with small tumors that can be completely ablated with margins.**

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES

- **Liver Tumor Ablation (cont.)**
  - 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.[7-9]
  - 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**[10-12]
  - 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.

- **Arterially Directed Embolic Therapy**
  - Hepatic Transarterial Radioembolization (TARE) with Yttrium-90 (Y-90) Microspheres[13,14]
    - ◊ 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 considered for small tumors non-eligible for resection or thermal ablation.
  - Transarterial Chemoembolization (TACE)[15]
    - ◊ 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.

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES

- **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 if 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 stereotactic 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.[16-21]**
    - ◊ **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 COL-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.[22]
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[23]
- There should be no unresectable extrahepatic sites of disease.[24-27]
- Partial debulking (less than an R0 resection) is not recommended.[23]
- Patients with resectable metastatic disease and a 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.[28]
  - Staged procedures can be performed as liver-first or primary-first approaches.[29]
- 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.[30]
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches using preoperative portal vein embolization,[31] staged liver resection,[32] or Y-90 radioembolization[33] can be considered.
- At the time of surgery, ablative techniques may be considered alone or in conjunction with resection. 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.[34-37]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[38-41]
- Re-resection and re-ablation can be considered in selected patients.[42]
- 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.[43-46]
- 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.[47]
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[48]

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PRINCIPLES OF SURGERY AND LOCOREGIONAL THERAPIES – REFERENCES

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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] and left-sided tumors only: ▸ FOLFOX[e] + (cetuximab or panitumumab)[j,k] ▸ CAPEOX[e] + (cetuximab or panitumumab)[j,k] ▸ FOLFIRI[f] + (cetuximab or panitumumab)[j,k] • *BRAF* V600E mutation positive[i]: ▸ Encorafenib + (cetuximab or panitumumab) + FOLFOX[e] • If disease progression, see COL-D 2 of 12	• 5-FU ± leucovorin ± bevacizumab • Capecitabine ± bevacizumab • *KRAS/NRAS/BRAF* WT[i] and left-sided tumors only: ▸ (Cetuximab or panitumumab)[j,k] (category 2B) • HER2-amplified and *RAS and* BRAF WT[j]: ▸ Trastuzumab + [pertuzumab or lapatinib or tucatinib][l] • If disease progression and improvement in functional status: ▸ Consider initial therapy in first column[m] ▸ OR if previous fluoropyrimidine, see COL-D 2 of 12 • 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 COL-D 3 of 12

Footnotes

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

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,o]

Previous oxaliplatin-based therapy without irinotecan

- FOLFIRI[f] or irinotecan[f]
- FOLFIRI[f] + (bevacizumab[p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q])
- Irinotecan[f] + (bevacizumab[p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q])

- If *KRAS/NRAS/BRAF* WT[i]:
  - FOLFIRI[f] + (cetuximab or panitumumab)[j,r]
  - (Cetuximab or panitumumab)[j,r] ± irinotecan[f]

- Biomarker-directed therapy (see Biomarker-directed therapy)

Previous therapy with oxaliplatin and irinotecan

- If *KRAS/NRAS/BRAF* WT[i]:
  - (Cetuximab or panitumumab)[j,r] ± irinotecan[j]

- 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)

Biomarker-directed therapy

- *BRAF* V600E mutation positive[j]
  - Encorafenib + (cetuximab or panitumumab)[s]
  - (Encorafenib + [cetuximab or panitumumab] + FOLFOX[e])[t] (category 2B)

- HER2-amplified and *RAS* and *BRAF* WT[j]
  - (Trastuzumab + [pertuzumab or lapatinib or tucatinib])[l]

- HER2-amplified (IHC 3+)
  - Fam-trastuzumab deruxtecan-nxki[u]

- *KRAS* G12C mutation positive[f]
  - (Sotorasib or adagrasib)[v] + (cetuximab or panitumumab)

- *NTRK* gene fusion-positive
  - Entrectinib
  - Larotrectinib
  - Repotrectinib[w]

- *RET* gene fusion-positive
  - Selpercatinib

Previous irinotecan-based therapy without oxaliplatin

- 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,r] ± irinotecan[f]

- Biomarker-directed therapy (see Biomarker-directed therapy)

Previous therapy without oxaliplatin or irinotecan

- FOLFOX[e] or CAPEOX[e]
- (FOLFOX or CAPEOX)[e] + bevacizumab
- FOLFIRI[f] or irinotecan[f]
- (FOLFIRI or irinotecan)[f] + (bevacizumab[p] [preferred] or ziv-aflibercept[p,q] or ramucirumab[p,q])
- Irinotecan[f] + oxaliplatin[e] ± bevacizumab
- FOLFIRINOX[e,h] ± bevacizumab

- If *KRAS/NRAS/BRAF* WT[i]:
  - FOLFIRI[f] + (cetuximab or panitumumab)[j,r]
  - (Cetuximab or panitumumab)[j,r] ± irinotecan[f]

- Biomarker-directed therapy (see Biomarker-directed therapy)

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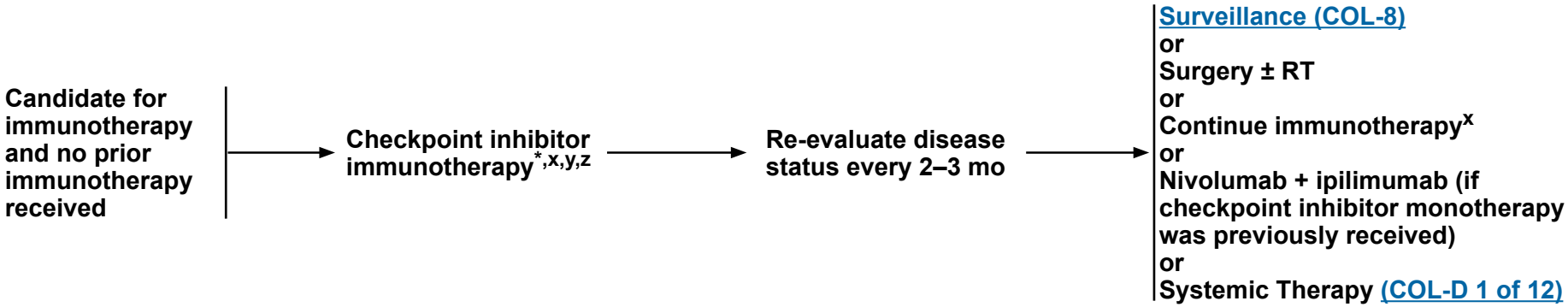
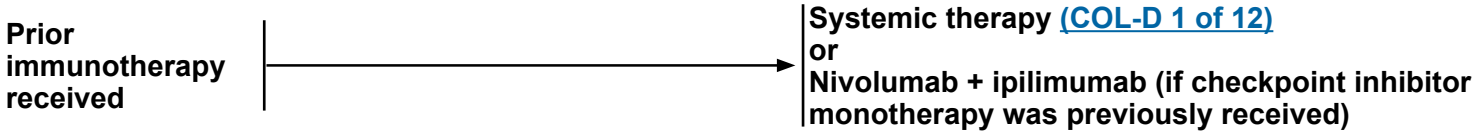
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b,c]

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





* 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 (COL-D [5 of 12]).
[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 (COL-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 (COL-B).
[k] The panel defines the left side of the colon as splenic flexure to rectum. Evidence suggests that patients with tumors originating on the right side of the colon (hepatic flexure through cecum) are unlikely to respond to cetuximab and panitumumab in first-line therapy for metastatic disease. Data on the response to cetuximab and panitumumab in patients with primary tumors originating in the transverse colon (hepatic flexure to splenic flexure) are lacking.
[l] If no previous treatment with HER2 inhibitor.
[m] The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.
[n] 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 (COL-C).
[o] 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.
[p] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[q] 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.
[r] Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
[s] In the second-line setting for *BRAF* V600E mutation-positive tumors, there is phase 3 evidence for better efficacy with targeted therapies over FOLFIRI.
[t] *BRAF* V600E regimen may be given with FOLFOX as subsequent line therapy if no previous treatment with oxaliplatin or BRAF-targeting regimen.
[u] 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).
[v] If patient is unable to tolerate EGFR inhibitor due to toxicity, single-agent adagrasib or sotorasib can be considered.
[w] On the TRIDENT-1 trial, repotrectinib showed activity in both NTRK TKI-naïve and NTRK TKI-pretreated patients.
[x] 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.
[y] NCCN Guidelines for Management of Immunotherapy-Related Toxicities.
[z] 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[aa]
Leucovorin 400 mg/m² IV day 1[bb]
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[aa]
Leucovorin 400 mg/m² IV day 1[bb]
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,cc]
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[aa]
Capecitabine 1000[dd] mg/m² twice daily PO for 14 days
Repeat every 3 weeks

CAPEOX + bevacizumab[8,cc]
Oxaliplatin 130 mg/m² IV day 1[aa]
Capecitabine 1000[dd] 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[bb] 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,cc]
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.

[aa] 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.

[bb] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².

[cc] 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).

[dd] 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.

References

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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 day 1,[aa] 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[21,22,h]
Oxaliplatin 85 mg/m² IV on day 1,[aa] 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[23,cc]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

IROX[24]
Oxaliplatin 85 mg/m² IV,[aa]
followed by irinotecan 200 mg/m² over 30–90 minutes every 3 weeks

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

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[25]
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[bb] 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[26]
or
5-FU 2600 mg/m² by 24-hour infusion plus leucovorin 500 mg/m²
Repeat every week[26]

[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.
[aa] 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.
[bb] Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
[cc] 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).

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

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

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

Capecitabine[27,dd]
Capecitabine 850–1250 mg/m² PO twice daily for 14 days
Repeat every 3 weeks

Capecitabine + bevacizumab[28,cc]
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[29,30]
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[31]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[16]
(preferred for every 2 weeks)

Irinotecan + panitumumab[17,32]
(*KRAS*/*NRAS*/*BRAF* WT)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + bevacizumab[33,cc]
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[31]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[16]
(preferred for every 2 weeks)

Panitumumab[34]
(*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[35]
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[36]
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.
[cc] 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).
[dd] 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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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS[c]

Trifluridine + tipiracil ± bevacizumab[37,38]
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[39] (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[40] (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[41] (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[42] (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[43,44] (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[45,46] (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[47-50] (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[51,52] (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[53]
(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[54]
(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[55]
(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.

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

Fam-trastuzumab deruxtecan-nxki[56] (HER2-amplified, IHC 3+)
Fam-trastuzumab deruxtecan-nxki 5.4 mg/kg IV on day 1
Repeat every 21 days

Encorafenib + cetuximab[57-59]
(*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[57-59]
(*BRAF* V600E mutation positive)
Encorafenib 300 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

Encorafenib + FOLFOX + cetuximab[60]
(*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[60]
(*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[61] (*NTRK* gene fusion-positive)
100 mg PO twice daily

Entrectinib[62] (*NTRK* gene fusion-positive)
600 mg PO once daily

Repotrectinib[63] (*NTRK* gene fusion-positive)
160 mg PO daily for first 14 days,
Then increase to 160 mg PO twice daily

Selpercatinib[64] (*RET* gene fusion-positive)
Patients ≥50 kg: 160 mg PO twice daily
Patients <50 kg: 120 mg PO twice daily

Adagrasib + cetuximab[65] (*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[66] (*KRAS* G12C mutation positive)
Sotorasib 960 mg PO daily
Panitumumab 6 mg/kg IV every 2 weeks

Fruquintinib[67]
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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PRINCIPLES OF RADIATION AND CHEMORADIATION THERAPY

General Principles

- **Neoadjuvant RT with concurrent fluoropyrimidine-based chemotherapy may be considered for initially unresectable or medically inoperable non-metastatic T4 colon cancer to aid resectability.**
  - **Infusional 5-FU + RT[1]**
    5-FU 225 mg/m² IV over 24 hours on days 1–5 or days 1–7 for 5 weeks with RT
  - **Capecitabine + RT[2,3]**
    Capecitabine 825 mg/m² PO BID, Monday–Friday on days of radiation treatment only, throughout the duration of RT (typically 28–30 treatment days)
  - **Bolus 5-FU/leucovorin + RT[1,a]**
    5-FU 400 mg/m² IV bolus + leucovorin 20 mg/m² IV bolus for 4 days during weeks 1 and 5 of 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

- **IMRT is preferred for unique clinical situations such as reirradiation of previously treated patients with recurrent disease or unique anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints.**
- **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.**
- **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.**
- **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.**
- **IORT, if available, may be considered for patients with T4 or recurrent cancers as an additional boost.**
- **Target Volumes**
  - **RT fields should include the tumor bed, which should be defined by preoperative radiologic imaging and/or surgical clips.**
  - **Radiation doses should be: 45–50 Gy in 25–28 fractions.**
    - ◊ **Consider boost for close or positive margins or unresectable cases after evaluating the cumulative dose to adjacent organs at risk.**
    - ◊ **Small bowel dose should be limited to Dmax 55 Gy, V45 Gy should be ≤150 cc, or V 50 should be ≤30 cc for individual small bowel loops, if possible.[4]**
    - ◊ **Appropriate organs at risk should be evaluated on the dose-volume histogram (DVH).**
    - ◊ **Fluoropyrimidine-based chemotherapy should be delivered concurrently with radiation.**
- **Consider radiation treatment for T4 with penetration to a fixed structure after surgery.**

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

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PRINCIPLES OF RADIATION AND CHEMORADIATION THERAPY

Supportive Care

- **Patients should be considered for vaginal dilators and instructed on the symptoms of vaginal stenosis, if applicable.**
- **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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PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE[1,2,3]

- **Patient/physician discussion should take place regarding the potential risks of therapy compared to potential benefits, including prognosis. This should include discussion of evidence supporting treatment, assumptions of benefit from indirect evidence, morbidity associated with treatment, high-risk characteristics, and patient preferences.**
- **When determining if adjuvant therapy should be administered, the following should be taken into consideration:**
  - **Number of lymph nodes analyzed after surgery (<12)**
  - **Poor prognostic features (eg, poorly differentiated histology [exclusive of those that are MSI-H]; lymphatic/vascular invasion; bowel obstruction; PNI; localized perforation; close, indeterminate, or positive margins; or high tumor budding)**
  - **Assessment of other comorbidities and anticipated life expectancy.**
- **The benefit of adjuvant chemotherapy does not improve survival by more than 5%.**
- **MSI or MMR testing (COL-B 4 of 10)**

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PRINCIPLES OF ADJUVANT THERAPY

- **CAPEOX or FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.[1,2]**
- **Capecitabine appears to be equivalent to bolus 5-FU/leucovorin in patients with stage III colon cancer.[3]**
- **A survival benefit has not been demonstrated for the addition of oxaliplatin to 5-FU/leucovorin in stage II colon cancer.[4] FOLFOX is reasonable for patients with stage II colon cancer with multiple high-risk factors and is not indicated for patients with good- or average-risk stage II colon cancer.**
- **A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged ≥70 years has not been proven.[4]**
- **While noninferiority of 3 versus 6 months of CAPEOX has not been proven, 3 months of CAPEOX numerically appeared similar to 6 months of CAPEOX for 5-year overall survival (82.1% vs. 81.2%; HR, 0.96), with considerably less toxicity.[5] These results support the use of 3 months of adjuvant CAPEOX over 6 months of adjuvant CAPEOX in the vast majority of patients with stage III colon cancer. In patients with colon cancer, staged as T1–3, N1 (low-risk stage III), 3 months of CAPEOX is noninferior to 6 months of CAPEOX for DFS; noninferiority of 3 versus 6 months of FOLFOX has not been proven. In patients with colon cancer staged as T4, N1–2 or T any, N2 (high-risk stage III), 3 months of FOLFOX is inferior to 6 months of FOLFOX for DFS, whereas noninferiority of 3 versus 6 months of CAPEOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 versus 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX).[6]**
- **A pooled analysis of patients with high-risk stage II disease in the IDEA collaboration did not show noninferiority of 3 months compared to 6 months of adjuvant treatment. Similar to stage III, the duration of therapy was associated with a small (and not statistically significant) difference in DFS between 3 and 6 months of CAPEOX. There were significantly fewer grade 3–5 toxicities with 3 versus 6 months.[7]**

Chemotherapy Regimens and References

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[2] Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trail. J Clin Oncol 2009;27:3109-3116.
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PRINCIPLES OF ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS AND REFERENCES

mFOLFOX 6
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.[1,2,3]

Capecitabine[4]
Capecitabine 1000–1250[c] mg/m² PO twice daily for 14 days every 3 weeks.

CAPEOX[5]
Oxaliplatin 130 mg/m² IV[a] day 1
Capecitabine 1000[c] mg/m² PO twice daily for 14 days every 3 weeks.

5-FU/leucovorin
- **Leucovorin 500 mg/m² given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m² given bolus 1 hour after the start of leucovorin and repeated 6 x weekly. Every 8 weeks for 4 cycles.[6]**
- **Simplified biweekly infusional 5-FU/leucovorin (sLV5FU2)[7]**
  Leucovorin 400[b] mg/m² IV 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.

Footnotes

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

Colorectal Cancer Surveillance

- Surveillance recommendations can be found on COL-8.
- Long-term surveillance should be carefully managed with routine good medical care and monitoring, including cancer screening, routine health care, and preventive care.
- Routine CEA monitoring and routine CT scanning are not recommended beyond 5 years.

Survivorship Care Planning

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

- Develop survivorship care plan that includes:
  - Overall summary of treatment, including all surgeries, radiation treatments, and chemotherapy received.
  - Description of possible expected time to resolution of acute toxicities, long-term effects of treatment, and possible late sequelae of treatment.
  - Surveillance recommendations.
  - 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.
- For chronic diarrhea or incontinence:
  - 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 (see page SPA-C 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]
  - Consider non-pharmacologic therapies such as heat or acupuncture.
  - Pregabalin or gabapentin are not recommended.

Counseling Regarding Healthy Lifestyle and Wellness[8] (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 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.
- Receive smoking cessation counseling as appropriate.

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

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PRINCIPLES OF APPENDICEAL ADENOCARCINOMA

Pathologic and Molecular Classification

- Careful pathologic definition is key.[1]
  - Infiltrative invasion is the hallmark of appendiceal adenocarcinoma (AA) and is distinct from the pushing invasion of low-grade appendiceal mucinous neoplasms (LAMN) and high-grade appendiceal mucinous neoplasms (HAMN). HAMN is a very rare diagnosis and should be labeled only by expert pathologic review as the clinical behavior is more similar to LAMN, but may be misclassified as adenocarcinoma.
  - AA is more aggressive than neuroendocrine tumors (NET) and mixed NET-adenocarcinoma.
- Mucinous (including goblet cell, a mixed adenocarcinoma-neuroendocrine [MANEC] histology) and non-mucinous adenocarcinomas are seen, which can be further classified as well-, moderate-, and poorly differentiated.
  - Non-mucinous AA behaves similarly to colon adenocarcinoma.
  - Signet ring mucinous adenocarcinoma is associated with a very poor prognosis.
- Discordance in histology may be seen between the appendiceal primary and peritoneal metastases. Survival is most closely associated with the peritoneal pathologic grade.[2]
- The molecular workup should mirror CRC. *KRAS* mutations are common, especially in non-mucinous adenocarcinoma. MSI is rare.[3,4]

Clinical Presentation

- AA may present incidentally and be diagnosed after an episode of acute appendicitis.
  - Patients whose appendicitis is managed nonoperatively should be followed closely to avoid a missed diagnosis of an occult malignancy.[5,6]
  - Recommend repeat CT within 6 months of the episode of appendicitis to ensure resolution of imaging findings.
- Initial presentation may be confused with primary right-sided colon or ovarian/gynecologic cancer.
- A screening colonoscopy should be considered in all patients diagnosed with AA.
  - A primary lesion may not be visualized by colonoscopy depending on the location of the tumor within the appendix.
  - A negative colonoscopy in a person with a suggestive history (eg, appendiceal neoplasm, peritoneal carcinomatosis) does not necessarily rule out an appendiceal cancer.
- Non-specific abdominal bloating, distention, or post-prandial discomfort may be observed with mucinous peritoneal involvement.
- CEA and CA 19-9 should be evaluated and abnormal measurements trended.[7]
  - CA-125 could be considered, especially if CEA and CA 19-9 are normal.

Systemic Therapy (COL-D)

References

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PRINCIPLES OF APPENDICEAL ADENOCARCINOMA

Localized Disease

- Screening colonoscopy is recommended in all patients diagnosed with AA prior to definitive resection to rule out synchronous large polyps or cancers.
- Right hemicolectomy with adequate lymphadenectomy is recommended.
- Appendectomy may be sufficient for patients with T1, low-grade disease and absence of lymphovascular invasion.[8]
- The use of adjuvant chemotherapy is largely extrapolated from colon cancer and should be considered for high-risk stage II and stage III cancers.[9,10]
- During surveillance, a second-look diagnostic laparoscopy to evaluate for residual/recurrent disease is not routinely recommended, but may be considered for symptomatic patients in the absence of clear imaging findings, especially in the setting of rising tumor markers.
- Surveillance imaging should occur at least annually, and may be done more frequently for patients with acellular mucinous spread at the time of surgery.

Metastatic Disease

- Prognosis is best for localized-only disease. Recurrence risk is higher for focal mucin, while widespread acellular mucin has the highest recurrence risk. The pathologic M stage distinguishes between intraperitoneal acellular mucin only (M1a), intraperitoneal mucinous epithelium (M1b), and non-intraperitoneal metastasis (M1c).
- Mucinous disease is poorly visualized by FDG-PET; MRI may be preferred for suboptimal CT candidates.[8]
- Visceral or more than limited to peritoneal disease
  - Treatment should follow metastatic colon cancer guidelines.
  - There is no clear evidence for anti-EGFR therapy, even among *RAS/RAF* wild-type cancers.
  - It is reasonable to use other targeted options (MSI-H, *BRAF* mutation, HER2) in line with CRC guidelines.

Metastatic Disease cont.

- Limited to peritoneal disease
  - Pseudomyxoma peritonei is an outdated umbrella term that encompasses both low- and high-grade disease and is not recommended.
  - Classification of peritoneal disease should be per current guidelines
    - ◊ Low-Grade Mucinous Carcinoma Peritonei (MCP-L; formerly labeled Diffuse Peritoneal Adenomatosis [DPAM])
    - ◊ High-Grade Mucinous Carcinoma Peritonei (MCP-H; formerly labeled Peritoneal Mucinous Carcinoma [PMCA])
    - ◊ MCP-H with signet ring cells (MCP-H-S; formerly labeled PMCA-S).
  - Patients deemed possible surgical candidates should be evaluated at a high-volume center for candidacy for hyperthermic intraperitoneal chemotherapy (HIPEC). These candidates are suggested to receive chemotherapy for up to 6 months, preferably in the neoadjuvant setting. Additional chemotherapy may be considered for patients who are not resectable at initial diagnosis with the possibility of converting to resectable disease.[11]
  - A peritoneal cancer index (PCI) score and completeness of cytoreduction (CC) score should be reported for cytoreductive surgery.
  - If a patient is not a candidate for surgery, treatment should follow metastatic colon cancer guidelines.
  - The extent of cytoreduction should be individualized. Surgery is discouraged for high PCI, biliary obstruction, extensive disease at the gastrohepatic ligament/porta hepatis, extensive retroperitoneal disease, intraparenchymal liver lesions requiring a major resection, diffuse small bowel serosa/mesenteric involvement, and/or multiple sites of small bowel obstruction.

Systemic Therapy (COL-D)

References

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

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PRINCIPLES OF APPENDICEAL ADENOCARCINOMA
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PRINCIPLES OF PHARMACOGENETICS

- **Pharmacogenetics (PGx) is the study of how genetic factors influence an individual's response to drugs. PGx aims to inform both the choice of drug and dosage in an effort to maximize efficacy and minimize toxicity.**
- **Drugs given at the same dose in the same schedule for the same disease may have different effects on patients due to inherent differences in drug disposition and metabolism related to genetic alterations. These differences may affect the anti-tumor efficacy of agents and/or may alter the risk and degree of toxicity.**
- **PGx testing may be considered prior to the initiation of chemotherapies known to be subject to variable metabolism that might predictably change the relative risk of severe toxicity or drug exposure.**
- **Historically, there have been a multitude of barriers to implementing global clinical PGx testing, particularly the concern of delaying the initiation of therapy while awaiting results.**
  - **It is also necessary to have consensus on an optimal testing platform, the expertise to interpret what is often highly complex data, and to offer providers guidance in applying the information to a given patient.**
- **Consider consulting a clinical pharmacist or PGx specialist if available to aid in drug dose adjustments based on interpretation and evaluation of PGx test results.**

UGT1A1: Irinotecan

- ***UGT1A1*6*** **allele represents a mutation in the coding sequence (c.211G>A) that results in decreased function.** ***UGT1A1*28*** **represents a dinucleotide repeat (TA7) in the promoter region that also results in decreased function.**
- **Individuals with wild type** ***UGT1A1*** **genotype are considered to have normal** ***UGT1A1*** **function, represented as the *1 allele. However, this designation is dependent on which regions of** ***UGT1A1*** **have been tested.[1-5]**
  - **Studies show that patients with the following diplotypes are at increased risk of severe neutropenia during treatment with irinotecan:**
    - ◊ **Homozygous** ***UGT1A1*28/*28*** **and** ***UGT1A1*6/*6***
    - ◊ **Compound heterozygous** ***UGT1A1*28/*6***
    - ◊ **See FDA website for additional information**
  - **These patients are considered** ***UGT1A1*** **poor metabolizers and have increased exposure to the active metabolite of irinotecan, SN-38, due to decreased** ***UGT1A1*** **function.**
  - **Consider dose reduction of the initial dose of irinotecan by 30% for patients with** ***UGT1A1*28/*28*** **alleles. The dose may be titrated upwards in subsequent cycles if it is well-tolerated.[6]**
  - **Patients who are heterozygous for either the** ***UGT1A1*28*** **or *6 alleles (*1/*28, *1/*6) are considered intermediate metabolizers and may also have a risk of severe neutropenia. However, current evidence does not support a preemptive dose reduction for** ***UGT1A1*** **intermediate metabolizers.[6,7]**
- **Currently, PGx testing for** ***UGT1A1*** **is commercially available.**

References

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PRINCIPLES OF PHARMACOGENETICS

Dihydropyrimidine Dehydrogenase (*DPYD*): 5-Fluorouracil, Capecitabine

- ***DPYD*** **is the gene that encodes the DPD enzyme. Genetic variants of *DPYD* are known to affect the risk of severe toxicity and drug exposure in patients receiving fluoropyrimidines.**
- **Based on race and ancestry, between 4-8% of the population has deleterious *DPYD* variants.[8,9] More than 1000 variants have been identified, most of which are extremely rare and have yet to be functionally characterized.**
- **The nomenclature of *DPYD* genetic variants is not currently universal such that a variant may be referred to by different names.**
- **Until efforts to standardize *DPYD* nomenclature succeed, variants may be designated with the Human Genomic Variation Society (HGVS) cDNA nomenclature, a star (*) allele name or by its rsID, a unique identifier referencing single nucleotide polymorphisms.**
  - **The four most common and best characterized variants in recommended HGVS nomenclature are[10] (alternative names included in parentheses):**
    - **c.1905+1G>A (DPYD*2A)(rs3918290)**
    - **c.2846 A>T (p.D949V)(rs67376798)**
    - **c.1679T>G (DPYD*13)(rs558886062)**
    - **c.1236G>A (tagging DPYD-HapB3)(rs56038477)**
  - **Please refer to the Clinical Pharmacogenetics Implementation Consortium (CPIC) website for a more comprehensive list of alternative nomenclatures.**
- **Currently, the pathogenicity of *DPYD* variants is determined based on functional studies providing evidence for loss or reduced function.**
- **In the clinical setting, phenotypes (i.e., the functional effect of a genetic variant such as intermediate and poor metabolizers) are commonly used to disseminate *DPYD* information to and between clinicians.**
- **Similar to *DPYD* genetic variants, phenotype nomenclature is inconsistent. For example, intermediate metabolizer, partial DPD deficiency, and heterozygous variant carrier can all be used to describe the same *DPYD* variant with reduced function. Furthermore, reference laboratories are adopting activity score terminology to provide more granular descriptions of DPD function.**
- **On its website, CPIC provides dosing recommendations for more than 80 of the less common *DPYD* variants. However, the data in support of these recommendations are insufficient to consider these definitive.**
- ***DPYD*** **genetic testing is complex. Focused assays that interrogate selected variants are not comprehensive and do not exclude the presence of different deleterious variants. Therefore, a 'negative' test result should be interpreted as the absence of the variants listed in the assay rather than a 'normal' test result and assumption of fluoropyrimidine tolerance. Assays that extend a larger net to cover more of the *DPYD* gene, such as next generation sequencing, can identify additional pathogenic variants but are also more likely to identify variants of unknown functional and clinical significance. Since these variants have limited evidence to determine function, dosing recommendations would not be possible.**
- **The risk:benefit of *DPYD* testing and dose reduction is a function of a patient's circumstances. In particular, there needs to be balance between the benefit of mitigating severe, and sometimes lethal, toxicities with the risk of undertreatment of individuals receiving a fluoropyrimidine as part of a curative strategy. For those who do receive an initial dose reduction to mitigate risk of toxicity, dose escalation to a higher dose for those who tolerate the initial dose reduction is recommended.**
- **The FDA recommends that consideration of PGx testing be discussed with the patient with the understanding that it recommends no specific testing platform and that the data are insufficient for informing dose adjustments for many variants.**

References

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PRINCIPLES OF PHARMACOGENETICS
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American Joint Committee on Cancer (AJCC) TNM Staging Classification for Colon 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 Colon Cancer 8th ed., 2017

Table 2. **Prognostic Groups**

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

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ABBREVIATIONS

AA	appendiceal adenocarcinoma
ASCO	American Society of Clinical Oncology
C/A/P	chest/abdomen/pelvis
CBC	complete blood count
CC	completeness of cytoreduction
CEA	carcinoembryonic antigen
CLIA-88	clinical laboratory improvement amendments of 1988
CRC	colorectal cancer
ctDNA	circulating tumor DNA
DFS	disease-free survival
dMMR	mismatch repair deficient
DPAM	diffuse peritoneal adenomatosis
DVH	dose-volume histogram
EBRT	external beam radiation therapy
ED	exonuclease domain
FAP	familial adenomatous polyposis
FISH	fluorescence in situ hybridization
GBCA	gadolinium-based contrast agent
GFR	glomerular filtration rate
H&E	hematoxylin and eosin
HAI	hepatic arterial infusion
HAMN	high-grade appendiceal mucinous neoplasms
HIPEC	hyperthermic intraperitoneal chemotherapy
HR	hazard ratio
IGRT	image-guided radiation therapy
IHC	immunohistochemistry
IMRT	intensity-modulated radiation therapy
IORT	intraoperative radiation therapy
LAMN	low-grade appendiceal mucinous neoplasms
LS	Lynch syndrome
MANEC	mixed adenocarcinoma-neuroendocrine
MCP-H	high-grade mucinous carcinoma peritonei
MCP-H-S	high-grade mucinous carcinoma peritonei with signet ring cells
MCP-L	low-grade mucinous carcinoma peritonei
MEN2	multiple endocrine neoplasia type 2
MMR	mismatch repair
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
NET	neuroendocrine tumor
NGS	next-generation sequencing
PCI	peritoneal cancer index
PCR	polymerase chain reaction
PMCA	peritoneal mucinous carcinoma
pMMR	proficient mismatch repair
PNI	perineural invasion
PPAP	polymerase proofreading-associated polyposis
PV	pathogenic variant
SBRT	stereotactic body radiation therapy
SNV	single nucleotide variant
TMB	tumor mutational burden
TMB-H	tumor mutational burden-high
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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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Colon Cancer

Discussion

This discussion corresponds to the NCCN Guidelines for Colon Cancer. A section of this discussion was updated on March 31, 2025. The last full discussion update was January 17, 2025.

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

Staging **MS-6**

Pathology **MS-6**

- Margins MS-7
- Lymph Nodes MS-7
- Tumor Deposits MS-8
- Perineural Invasion MS-8
- Tumor Budding MS-9

Appendiceal Neoplasms **MS-9**

Clinical Presentation and Treatment of Nonmetastatic Disease **MS-13**

- Workup and Management of the Malignant Polyp MS-13
- Workup and Management of Invasive Nonmetastatic Colon Cancer MS-14
- Adjuvant Chemotherapy for Resectable Colon Cancer MS-17
- Perioperative Chemoradiation MS-28

Management of Metastatic Disease **MS-28**

- Surgical Management of Colorectal Metastases MS-29
- Local Therapies for Metastases MS-30
- Peritoneal Carcinomatosis MS-36
- Determining Resectability MS-37
- Neoadjuvant Therapy and Conversion to Resectability MS-38
- Perioperative Therapy for Resectable Metachronous Metastatic Disease MS-41
- Systemic Therapy for Advanced or Metastatic Disease MS-43
- Workup and Management of Synchronous Metastatic Disease MS-79
- Workup and Management of Metachronous Metastatic Disease MS-82

Endpoints for Advanced CRC Clinical Trials **MS-83**

Post-Treatment Surveillance **MS-84**

Survivorship **MS-87**

Summary **MS-90**

References **MS-91**

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 2024, an estimated 106,590 new cases of colon cancer and 46,220 cases of rectal cancer will occur. During the same year, an estimated 53,010 people will die of colon and rectal 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 >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 diagnosis through screening and 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 inequity in mortality rates is double that of incidence rates. Reasons for these racial inequities 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 <65 years, with a 1% annual increase in those aged 50 to 64 years and 2% annual increase in those <50 years. CRC death rates also showed age-dependent trends, declining by 3% annually for those ≥65 years, compared to a 0.6% annual decline for individuals aged 50 to 64 years and a 1.3% annual increase for individuals <50 years.[3] A retrospective cohort study of the SEER CRC registry also found that the incidence of CRC in patients <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 of age by 2030. The cause of this trend is currently unknown. One review suggests that CRC that occurs in patients <45 years may be clinicopathologically and genetically different from CRC in adults ≥45 years, 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] In a cohort study of 1959 patients with metastatic CRC (mCRC), patients who developed mCRC at a younger age (<50 years) showed worse survival outcomes and unique adverse event (AE) profiles, which the authors partially attribute to distinct genetic profiles.[6]

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Colon 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, surveillance, management of recurrent and metastatic disease, and survivorship. When reviewing these guidelines, clinicians should be aware of several things. First, these guidelines adhere to the TNM (tumor, node, metastasis) staging system (see *Table 1* in the algorithm).[7] Although the guidelines are believed to represent the optimal treatment strategy, the Panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.

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 Colon Cancer, an electronic search of the PubMed database was performed to obtain key

Discussion Update in progress

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literature in the field of CRC published since the previous Guidelines update, using the following search terms: colon cancer, colorectal cancer, and rectal cancer. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[8]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice 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.[9] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-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 colon cancer cases are associated with familial clustering, and first-degree relatives of patients with colorectal adenomas or invasive CRC are at increased risk for CRC.[10-14] 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).[15-17] Therefore, it is recommended that all patients with colon cancer be queried regarding their family history and considered for risk assessment, as detailed in the NCCN Guidelines for Colorectal Cancer Screening. Results from a 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.[18]

CRC is a heterogeneous disease. An international consortium recently reported a molecular classification, defining four different subtypes: CMS1 (microsatellite instability [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.[19] However, this classification is not yet recommended in clinical practice.

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Lynch Syndrome

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases.[15,16,20,21] This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Although identifying a germline mutation in an MMR gene through sequencing is definitive for Lynch syndrome, patients usually undergo selection by considering family history and performing an initial test on tumor tissue before sequencing. One of two different initial tests can be performed on CRC specimens to identify individuals who might have Lynch syndrome: 1) immunohistochemical (IHC) analysis for MMR protein expression, which is often diminished because of mutation; or 2) analysis for MSI, which results from MMR deficiency (dMMR) and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.[22] Testing the *BRAF* gene for mutation is indicated when IHC 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.[22] Testing for *MLH1* promoter methylation may also be used to determine this.

Many NCCN Member Institutions and other comprehensive cancer centers now perform IHC 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.[23-26] 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)[27-29] and by the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and American Society of Clinical Oncology (ASCO) in a guideline on molecular biomarkers for CRC.[30] 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.[31,32] The Cleveland Clinic recently reported on its experiences implementing such a screening approach.[33]

The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome. This testing is also relevant for adjuvant therapy planning for stage II disease and treatment selection in stage IV disease (see *Microsatellite Instability* and *Checkpoint Inhibitor Immunotherapy for dMMR/MSI-H or POLE/POLD1 Mutation-Positive Disease in the First-Line and Non–First-Line Settings*, 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.[34-40] Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with CRC.[41-44] 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.[45] Another meta-analysis determined that the relationship between vitamin D levels and mortality is linear.[46]

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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.[47] A later analysis of the same study reported that the effect of vitamin D supplementation on recurrence of advanced adenomas varied significantly based on the genotype of the vitamin D receptor, indicating that only individuals with specific vitamin D receptor alleles may benefit from vitamin D supplementation for prevention of advanced adenomas.[48]

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.[49-51] In addition, while the randomized, double-blind, phase II SUNSHINE trial reported a longer progression-free survival (PFS) for patients with previously untreated 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).[52] 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.[53] 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.[54-56] 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).[55,57-73] In fact, in the 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 one or fewer of the factors.[74] Other large studies support the conclusion that adherence to healthy lifestyle factors can reduce the risk of CRC.[75,76]

Some data suggest that consumption of dairy may lower risk for the development of CRC.[72,77,78] However, a systematic review and meta-analysis of 15 cohort studies (>900,000 patients; >5200 cases of CRC) only found an association between risk for colon cancer in males and the consumption of nonfermented milk.[79] No association was seen for rectal cancer in males or for colon or rectal cancer in females, and no association was seen for either cancer in either sex 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.[80-82] Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may also decrease the risk for CRC,[83-88] although evidence supporting this association is limited and variable.[89] While the U.S. Preventive Services Task Force (USPSTF) guidance previously recommended daily low-dose aspirin for CRC prevention,[90] the 2022 update concluded that there was insufficient evidence that aspirin use reduces CRC incidence.[91]

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption are associated with a poor prognosis.[59,92-96] Conversely, post-diagnosis fish consumption may be associated with a better prognosis.[97] A family history of CRC increases

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risk while improving prognosis.[98] Data on the effect of dairy consumption on prognosis after diagnosis of CRC are conflicting.[99,100]

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 women.[101-110] Results of a small randomized study suggest that 1 year of low-dose metformin in patients without diabetes with previously resected colorectal adenomas or polyps may reduce the likelihood of subsequent adenomas or polyps.[111] In addition, although patients with CRC and diabetes appear to have a worse prognosis than those without diabetes,[112,113] patients with CRC and diabetes treated with metformin seem to have a survival benefit over those not treated with metformin.[109,114,115] The data regarding the effects of metformin on CRC incidence and mortality, however, are not completely consistent, with some studies seeing no effect.[116,117]

Staging

Staging in colon cancer is based on the TNM system. The TNM categories reflect very similar survival outcomes for rectal and colon cancer; these diseases therefore share the same staging system.[7]

In the 8th edition of the AJCC 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.[7] The T component of colon cancer staging is very important in prognostication, because analyses have shown that patients with T4,N0 tumors have a lower survival than those with T1–2,N1–2 tumors.[118-120] Furthermore, in an analysis of 109,953 patients with invasive colon cancer included in the SEER colon cancer database from 1992 to 2004, the relative 5-year survival rate (ie, 5-year survival corrected by age-related morbidity) was considerably higher (79.6%) for patients with node-negative T4a tumors compared with patients with node-negative T4b tumors (58.4%).[121]

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).[7]

Metastatic disease is classified as M1a when metastases that are limited to only one site/solid organ (including to lymph nodes outside the primary tumor regional drainage area) are positive. 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.[7] Patients with peritoneal metastases have a shorter PFS and OS than those without peritoneal involvement.[122]

Pathology

CRCs are usually staged after surgical exploration of the abdomen and pathologic examination of the surgical specimen. Some of the criteria that should be included in the report of the pathologic evaluation include the following: grade of the cancer; depth of penetration and extension to adjacent structures (T); number of regional lymph nodes evaluated; number of positive regional lymph nodes (N); an assessment of the presence of distant metastases to other organs, to the peritoneum or an abdominal structure, or in non-regional lymph nodes (M); the status of proximal, distal, radial, and mesenteric margins; lymphovascular invasion;

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perineural invasion (PNI); and tumor deposits.[7,123-131] The prefixes "p" and "yp" used in TNM staging denote "pathologic staging" and "pathologic staging after neoadjuvant therapy and surgery," respectively.[7]

Margins

In colon cancer, the radial margin (or circumferential resection margin, CRM) represents the adventitial soft tissue closest to the deepest penetration of the tumor. It is created surgically by blunt or sharp dissection of the retroperitoneal aspect, and it corresponds to any aspect of the colon that is not covered by a serosal layer of mesothelial cells.[7] It must be dissected from the retroperitoneum to remove the viscus. The serosal (peritoneal) surface does not constitute a surgical margin. The radial margins should be assessed in all colonic segments with non-peritonealized surfaces. In segments of the colon that are completely encased by peritoneum, such as the transverse colon, the mesenteric resection margin is the only relevant radial margin.[7] On pathologic examination, it is difficult to appreciate the demarcation between the peritonealized surface and the non-peritonealized surface. The surgeon is therefore encouraged to mark the area of non-peritonealized surface with a clip or suture.[7] In a study of 608 patients with rectal cancer, a positive radial margin was shown to be a negative prognostic factor for both local recurrence and OS.[132] Patients who have had CRM-positive resections had a 38.2% local recurrence rate, whereas those with CRM-negative resections had a 10.0% local recurrence rate.[132]

Lymph Nodes

The number of lymph nodes evaluated is important to note on the pathology report. A secondary analysis of patients from the Intergroup Trial INT-0089 showed that an increase in the number of lymph nodes examined was associated with increased survival for patients with both node-negative and node-positive disease.[133] In addition, results from population-based studies show an association between improvement in survival and examination of ≥12 lymph nodes.[134,135] The mechanism for this correlation is poorly understood. It has been hypothesized that the analysis of more lymph nodes would result in more accurate staging and thus better tailored treatments, but more recent results suggest that this idea is not correct.[136-138] Instead it is likely that other factors associated with lymph node harvest are important for the survival advantage. For instance, the extent and quality of surgical resection can have an impact on the node harvest.[139] The number of regional lymph nodes retrieved from a surgical specimen also varies with age of the patient, sex, and tumor grade or site.[133,134,140,141] In addition, it has been suggested that lymph nodes in patients who have a strong anti-cancer immune response are easier to find, and that such patients have an improved prognosis.[142] Another possibility is that the underlying tumor biology affects lymph node yield and prognosis in parallel. For instance, MSI and wild-type *KRAS/BRAF* have been associated with improved prognosis and increased lymph node retrieval.[143,144]

Regardless of the mechanism for the observed correlation, the Panel recommends examination of ≥12 lymph nodes. This recommendation is supported by CAP[145] and the 8th edition of the AJCC Cancer Staging Manual,[7] which also specify pathologic examination of ≥12 lymph nodes. Notably, emerging evidence suggests that a greater number of nodes may need to be examined in some situations, particularly for T4 lesions, to provide an adequate assessment of disease stage.[146] For stage II (pN0) colon cancer, it is recommended that the pathologist go back to the specimen and submit more tissue of potential lymph nodes if <12 nodes were initially identified. Patients considered to have N0 disease but for whom <12 nodes have been examined are suboptimally staged and should be considered to be at higher risk.

The ratio of positive lymph nodes to the total number of lymph nodes examined is also being evaluated for possible prognostic impact. Case

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series have suggested cutoffs of 0.1, 0.2, or 0.25 as lymph node ratios that are prognostic for OS or PFS.[147-150] A systematic review and meta-analysis of 33 studies that included >75,000 patients with node-positive CRC concluded that a higher lymph node ratio was significantly associated with shorter OS and disease-free survival (DFS).[151] Analysis of the SEER database, however, suggests that the lymph node ratio does not adequately represent the different effects of both the number of positive lymph nodes and the number of lymph nodes examined.[152]

The potential benefit of sentinel lymph node evaluation for colon cancer has mostly been associated with providing more accurate staging of nodal pathology through detection of micrometastatic disease in the sentinel node(s).[153] Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells and the identification of particular tumor antigens through IHC have been reported.[153-158]

There is also a potential benefit of assessing regional lymph nodes for micrometastases and isolated tumor cells.[156,159-162] The 8th edition of the AJCC Cancer Staging Manual considers clusters of 10 to 20 tumor cells, or clumps of tumor that measure ≥0.2 mm in diameter, but <2 mm in diameter, to be micrometastases.[7] Such micrometastases have been shown to be a poor prognostic factor. One study of 312 consecutive patients with pN0 disease found that positive cytokeratin staining was associated with a higher risk of recurrence.[163] 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 2012 systematic review and meta-analysis came to a similar conclusion, finding decreased survival in patients with pN0 tumors with IHC or reverse transcriptase polymerase chain reaction (RT-PCR) evidence of tumor cells in regional nodes.[164] A 2014 meta-analysis also found that the presence of micrometastases increases the likelihood of disease recurrence.[165]

Tumor Deposits

Tumor deposits, also called extranodal tumor deposits, peritumoral deposits, or satellite nodules, are irregular discrete tumor deposits in the pericolic or perirectal fat that show no evidence of residual lymph node tissue but 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 arise from lymphovascular invasion or, occasionally, PNI.[166,167] The number of tumor deposits should be recorded in the pathology report, because they have been shown to be associated with reductions in DFS and OS.[130,131,168,169] Multivariate survival analysis in one study showed that patients with pN0 tumors without satellite nodules had a 91.5% 5-year survival rate compared with a 37.0% 5-year survival rate for patients with pN0 tumors and the presence of satellite nodules ($P < .0001$).[131]

Perineural Invasion

Several studies have shown that the presence of PNI is associated with a significantly worse prognosis.[127-129,168,170-173] For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at one institution found a four-fold greater 5-year survival in patients with tumors without PNI versus patients whose tumors invaded nearby neural structures.[128] Multivariate analysis of patients with stage II rectal cancer showed that patients with tumors with PNI have a significantly worse 5-year DFS compared with those without PNI (29% vs. 82%; $P = .0005$).[129] Similar results were seen for patients with stage III disease.[127] 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).[171] PNI is therefore included as a high-risk factor for systemic recurrence.

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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.[174] 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 CRC or malignant polyps is associated with an increased risk of lymph node metastasis, although the methodologies for assessing tumor budding were not uniform.[175-179] 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.[180] 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.[181] 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). A post-hoc analysis of the PRODIGE-GERCOR study also reported that tumor budding is an independent prognostic factor for both DFS and OS in stage III colon cancer.[182] Tumor budding is therefore included as a high-risk factor for recurrence and may inform decisions related to adjuvant therapy.

Appendiceal Neoplasms

Pathologic and Molecular Classification

Primary appendiceal neoplasms are rare and most often found incidentally during an appendectomy following clinical presentation of acute appendicitis. Management and treatment of primary appendiceal cancers are dependent on classification, grading, and staging of these neoplasms.[183] Appendiceal neoplasms can be histopathologically classified as neuroendocrine neoplasms (NENs), mucinous neoplasms, goblet cell adenocarcinomas (GCAs), colonic-type adenocarcinomas (non-mucinous), and signet ring cell carcinomas (epithelial origin).[184,185] Mucinous neoplasms can be further subclassified into low-grade appendiceal mucinous neoplasms (LAMNs), high-grade appendiceal mucinous neoplasms (HAMNs), and mucinous adenocarcinomas with or without signet ring cells. Both colonic-type adenocarcinoma and colorectal adenocarcinoma develop from precancerous adenomas and are managed and treated similarly.[186,187] In contrast, GCAs are primarily composed of epithelial and neuroendocrine elements and characteristically contain goblet cells. Neuroendocrine cells are composed of enterochromaffin-like cells (ECLs) and often produce serotonin.[185]

Appendiceal Adenocarcinomas

Histopathologic features of LAMN present as circumferential proliferation of low-grade mucinous epithelium with a pushing pattern into the lamina propria, submucosa, muscularis propria, and into the subserosa.[188] LAMN can also present with fibrosis of the submucosa, pushing patterns resembling diverticulum, and mucin and/or cells from the neoplasm outside of the appendix.[7,189] HAMNs have similar features to LAMN but have more extensive and complex atypical cytologic features. Comparably, both LAMN- and HAMN-classified tumors lack infiltrative invasion and are both maintained within the appendix.[183]

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Data suggest that appendiceal mucinous neoplasms (AMNs) develop from the same mutational sequence as colorectal carcinomas beginning with a point mutation in *KRAS*. In addition, genetic mutations in *GNAS* and *RNF43* are found in both LAMN and HAMN, which further supports the theory that HAMN tumors progress from LAMN tumors.[190-192] In contrast, HAMN tumors have been shown to harbor additional mutations in *TP53*, *ATM*, and *APC*, which may be linked to their more aggressive phenotype.[191-193] In addition, mucinous adenocarcinomas resemble LAMNs and HAMNs but with the presence of infiltrative invasion (instead of the signature pushing pattern seen in the mucinous neoplasms). Mucinous adenocarcinomas can be further subclassified based on the presence of signet ring cells. If a tumor is composed of ≤50% signet ring cells, then it is classified as a mucinous adenocarcinoma with signet ring cells. If there is a presence of >50% signet ring cells, then the tumor is classified as a signet ring cell carcinoma.[183]

The cells that compose the mucinous adenocarcinomas produce an excess of extra- and intracellular mucin; the intracellular mucin displaces the cell's nuclei resulting in its characteristic ring-like appearance.[194] It has been well-established that the presence of signet ring cells leads to a poorer prognosis; 10% to 40% of patients with G3 (poorly differentiated) mucinous adenocarcinoma with signet ring cells have a 5-year OS.[195-197] The 8th edition of the AJCC Staging Manual now uses the following terminology to further characterize appendiceal neoplasms: well, moderately, and poorly differentiated with corresponding alphanumeric classification of G1, G2, and G3, respectively.[183]

Due to the rarity of appendiceal adenocarcinomas (AAs), treatment typically follows CRC despite AAs having distinct histologic, biological, and clinical manifestations. A recent molecular analysis was performed on patients diagnosed with mucinous AAs (MAAs) in order to guide clinical decision-making. Out of 164 MAAs tested, 24 were predominantly *RAS*-mutated with *GNAS* and *TP53* wild-type.[198] This tumor type has significantly fewer mutations and chromosomal alterations when compared to *GNAS* or *TP53* mutation predominance, and OS in this subgroup was improved when compared to *GNAS*-mutant ($P = .05$) and *TP53*-mutant ($P = .04$) tumors. In addition, *RAS*-mutant predominant tumors had reduced tumor bulk ($P = .04$) and stromal invasion ($P < .01$) and responded more to first-line chemotherapy (50%) compared to *GNAS*-mutant predominant (6%, $P = .03$) tumors.[198] The following molecular subtypes were identified in this study: *RAS*-mutant/*GNAS*-wild-type/*TP53*-wild-type, which was typically clinically indolent; *GNAS*-mutant predominance, which showed chemotherapy resistance; and *TP53*-mutant predominance, which was highly aneuploid and aggressive. This clinical behavior was observed regardless of histopathology.[198]

Goblet Cell and Neuroendocrine Carcinomas of the Appendix

Appendiceal goblet cell carcinomas (GCCs) account for approximately 14% to 19% of primary appendiceal neoplasms and consist of both glandular epithelial cells and neuroendocrine components.[186,199,200] GCCs are considered mixed adenoneuroendocrine carcinomas (MANECs) and display the IHC staining consistent with neuroendocrine markers but behave more aggressively like an adenocarcinoma. For this reason, it is recommended to clinically treat GCCs as an adenocarcinoma.[201,202] Appendiceal neuroendocrine carcinomas (ANCs) can develop in the jejunum/ileum, appendix, or cecum. They are composed of ECLs in the bowel wall and can often produce serotonin.[185] They are usually indolent tumors when found in the appendix or the rectum but progress more aggressively when found in the colon.[203] ANCs are usually asymptomatic and found incidentally if tumor development occurs at the tip of the appendix, but can cause symptomatic obstruction and appendicitis if found in the mid or proximal portions.[203] Progression and OS of the patient is dependent on the histologic subtype of the appendiceal neoplasm.[202]

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Clinical Presentation

Patients typically present with symptoms resembling appendicitis, which include but are not limited to: abdominal pain in the right lower quadrant, vomiting, change in bowel habits, intestinal obstruction, compression of the ureters, and nausea.[204-207] There should be increased suspicion of an appendiceal neoplasm if the patient is >50 years of age with a family history of inflammatory bowel disease, colon cancer, and/or unexplained anemia.[208] Additionally, if appendicitis is treated nonoperatively (typically with antibiotics), repeat interval imaging is crucial to ensure that the imaging findings resolve. Lack of resolution may suggest an appendiceal malignancy.

Diagnosing neoplasms of the appendix is challenging and symptoms may overlap with colon cancer, gynecologic cancers, or varying abdominal pathologies. Diagnostic tests to be considered at initial presentation include imaging studies such as CT/MRI, endoscopy, tumor biopsy, and in some cases surgery, in addition to a thorough medical history and physical examination.[209] An appendix >15 mm on a CT or MRI with an irregular or thickened wall is suggestive of appendiceal carcinoma.[210] Non-specific abdominal bloating/distention and/or postprandial discomfort may also be observed with mucinous peritoneal involvement. Colonoscopy is recommended if the patient has been diagnosed with mucinous adenocarcinoma of the appendix as there is an increased risk of colonic polyps and neoplasia.[210,211]

Tumor biomarkers CEA and CA 19-9 can be evaluated and used as prognostic indicators for patients receiving cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC).[212] In a recent study, a multivariate analysis was performed to establish predictors of disease progression using tumor biomarkers. This analysis concluded that when CA 19-9 was elevated preoperatively, PFS was unfavorable. Additionally, when CEA was elevated preoperatively, OS was also unfavorable.[212] CA-125 level was inconclusive in this study; however, other studies suggest normal serum levels of CA-125 and CA 19-9 correspond to an increase in survival and a decrease in recurrence.[213] Tumor differentiation and classification were the strongest predictors of both PFS and OS.

Workup and Management of Localized Appendiceal Adenocarcinoma

A screening colonoscopy is recommended in all patients diagnosed with AA to rule out synchronous large polyps or cancer. CT of the chest, abdomen, and pelvis is also recommended for evaluation of the primary tumor and any possibility of metastatic disease.[213] Tis- and T1-staged tumors may be managed with appendectomy alone if negative margins are obtained during resection and there is no evidence of angiolymphatic invasion.[185] T1 and T2 tumors with unfavorable characteristics such as angiolymphatic invasion or positive margins should be considered for a right hemicolectomy and removal of ≥12 lymph nodes for accurate resection and staging.[185]

Extrapolating from CRC, patients with stage III (nodal involvement) or stage II colonic-type AA should be considered for adjuvant systemic chemotherapy.[185] A univariate and multivariate analysis was performed on patients diagnosed with stage II and stage III GCC who received surgical resection and adjuvant chemotherapy to evaluate the impact of adjuvant chemotherapy on OS. Out of 619 patients, adjuvant chemotherapy was administered in 9.4% (N = 48) of stage II and 47.7% (N = 51) of stage III individuals.[214] For patients with stage II disease, 5-year OS was 96.9% with adjuvant chemotherapy and 89.1% without adjuvant chemotherapy (*P* = .236). Patients with stage III disease had a 5-year OS of 77.1% with adjuvant chemotherapy and 42.8% without adjuvant chemotherapy (*P* = .003). This study concluded that administration of adjuvant chemotherapy was associated with better OS in patients with stage III GCC.[214]

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In certain patients who are candidates for disease monitoring, surveillance imaging should occur at least annually and may occur more frequently in patients with acellular mucinous spread noted during surgery. If evidence of appendiceal rupture and dissemination of tumor cells were found outside of the appendix, imaging may not be a reliable source for accurate disease monitoring. If there is clinical suspicion of active disease (eg, symptoms, elevated tumor markers) despite unremarkable imaging, laparoscopy should be considered.

Workup and Management of Metastatic Appendiceal Adenocarcinoma

The heterogeneity of the appendiceal neoplasms causes a varying risk of metastasis across histologic tumor types. Distant metastasis in colonic-type adenocarcinomas has been reported in 23% to 37% of cases with the most common site being dissemination to the peritoneum, with metastasis to the liver and lung being less common.[186,215] The pathologic M stage distinguishes between intraperitoneal acellular mucin only (M1a), intraperitoneal mucinous epithelium (M1b), and non-intraperitoneal metastasis (M1c). If metastasis spreads beyond the peritoneum, then treatment should follow the NCCN Guidelines for Colon Cancer recommendations for metastatic disease.

Appendiceal neoplasms (mucinous and non-mucinous) tend to metastasize within the peritoneal cavity through various ways of dissemination. Metastasis of a mucinous adenocarcinoma can arise from the excess secretion of mucin from neoplastic epithelial cells. This results in appendiceal rupture and spread of mucin and tumor cells within the peritoneal cavity leading to neoplastic epithelial cells adhering to the peritoneal surface and causing varying sized lesions.[185,216] The clinical syndrome of mucinous ascites was once referred to as pseudomyxoma peritonei (PMP), but has since been further subclassified into multiple histologic grading systems by the World Health Organization (WHO). PMP is now used as an outdated umbrella term for the following classifications: low-grade mucinous carcinoma peritonei (MCP-L), which is also synonymous with the previous classification of DPAM (disseminated peritoneal adenomucinosis). MCP-L presents as mucin pools with <10% cellularity and non-stratified cuboidal epithelium that lack infiltrative growth.[217] High-grade mucinous carcinoma peritonei (MCP-H) is synonymous with the previous classification, peritoneal mucinous carcinomatosis (PMCA), presenting with mucin pools of high atypical cellularity, high mitotic index, cribriform growth pattern, and infiltrative invasion of underlying organs. An MCP-H classification with the presence of signet ring cells is denoted MCP-H-S and was previously classified as PMCA-S. [217]

Cytotoxic chemotherapy with efficacy against CRC is used to treat AA. It is reasonable to use other targeted therapy options for MSI-high (MSI-H), *BRAF* mutation, or HER2 status, which is consistent with recommendations within the NCCN Guidelines for Colon Cancer and NCCN Guidelines for Rectal Cancer. There is no clear evidence for anti-epidermal growth factor receptor (EGFR) therapy even if the patient's tumor is *RAS*/*RAF* wild-type. A retrospective medical record review of patients with AA was conducted to test for differentials in OS when adjuvant chemotherapy followed complete cytoreduction.[218] In total, 103 patients with AA were enrolled in the study, and 68 patients (66%) achieved a cytoreductive score of 0–1. Out of these 68 patients, 26 received adjuvant chemotherapy. The median OS was 9.03 years compared to 2.88 years in those who did not receive adjuvant chemotherapy (P = .02). This increase in OS was only observed in patients who did not have low-grade AA.[218] This study suggests that adjuvant chemotherapy does not have a benefit in patients with LAMN but does show an increase of OS in patients with other histologic tumor types. In addition, a study was conducted to identify the association of systemic chemotherapy and survival in patients with grade 1, stage IV appendiceal

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mucinous neoplasm (low-grade appendiceal neoplasm). Out of 639 patients identified, 5-year OS for patients not undergoing chemotherapy was 52.9% and for patients undergoing chemotherapy was 61.3%. No association between receiving chemotherapy and OS was observed in this cohort.[219]

In select patients diagnosed with metastatic spread to the peritoneum, CRS and HIPEC have the potential to be curative.[220,221] CRS and HIPEC are associated with morbidity and mortality, and it is imperative that a capable multidisciplinary medical team perform extensive preoperative tests to deem a patient fit for this combination therapy. The intent of CRS is to achieve maximum cytoreduction before the initiation of HIPEC. Because of this, presurgical evaluation of peritoneal involvement is recommended and can be achieved through laparoscopy and the peritoneal carcinomatosis index (PCI) scoring system.[222] The PCI quantifies the distribution of tumors throughout 13 regions of the abdomen and pelvis along with a lesion size score. Cases with higher PCI scores are associated with worse prognosis and lack of benefit from CRS.[223] The completeness of cytoreduction (CC) score is also used to determine patient prognosis after surgery. Complete cytoreduction is denoted with a CC-0 or CC-1, while incomplete cytoreduction is denoted with a CC-2 or a CC-3.[223] Complete cytoreduction is defined by the removal of all macroscopic disease found on the peritoneum or surrounding viscera. For unresected tumors, the size of each tumor cannot be >2.5 mm in size. This is because intraperitoneal chemotherapy is not effective against tumors >2.5 mm.[224] In addition, for appendiceal tumors and PMP, the grade of the tumor and its histologic features also have an impact on the outcome of complete cytoreduction.[224]

Once an individual is deemed a candidate for CRS/HIPEC they should continue chemotherapy for up to 6 months, preferably in the neoadjuvant setting. Additional chemotherapy may be considered for patients whose disease is not resectable at initial diagnosis but has the potential to convert to resectable disease.[221] In successful cases, data suggest that the combined therapeutic approach of CRS and HIPEC offered patients a 15-year survival rate of 59% and a PFS of 8.2 years.[225] Patients are discouraged from CRS if they have been diagnosed with biliary obstruction, extensive disease at the gastrohepatic ligament/porta hepatis, extensive retroperitoneal disease, intraparenchymal liver lesions (requiring major resection), diffuse small bowel serosa/mesenteric involvement, and/or multiple sites of small bowel obstruction. If a patient is not a candidate for surgery, treatment should follow metastatic colon cancer guidelines, as found in the NCCN Guidelines for Colon Cancer. Prognosis is best for patients when disease is localized only.

Clinical Presentation and Treatment of Nonmetastatic Disease

Workup and Management of the Malignant Polyp

A malignant polyp is defined as one with cancer invading the submucosa (pT1). Conversely, polyps classified as carcinoma in situ (pTis) have not penetrated the submucosa and are therefore not considered capable of regional nodal metastasis.[124] The Panel recommends marking the polyp site during colonoscopy or within 2 weeks of the polypectomy, if appropriate. Testing for MMR/MSI should be done during the initial workup to help with diagnosis of Lynch syndrome and inform treatment decision-making.

Before making a decision about surgical resection for an endoscopically resected adenomatous polyp or adenoma, physicians should review the pathology and consult with the patient.[226] In patients with invasive cancer in a pedunculated or sessile polyp (adenoma), no additional surgery is required if the polyp has been completely resected and has favorable histologic features.[227,228] Favorable histologic features include lesions of grade 1 or 2, no angiolymphatic invasion, and a negative resection margin.

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However, in addition to the option of observation, the Panel includes the option of colectomy in patients with a completely removed, single-specimen, sessile polyp with favorable histologic features and clear margins. This option is included because the literature seems to indicate that patients with sessile polyps may have a significantly greater incidence of adverse outcomes, including disease recurrence, mortality, and hematogenous metastasis compared with those with pedunculated polyps. This increased incidence likely occurs because of the high probability of a positive margin after endoscopic removal.[229-231]

If the polyp specimen is fragmented, the margins cannot be assessed; if the specimen shows unfavorable histopathology, additional workup including complete blood count (CBC), chemistry profile, carcinoembryonic antigen (CEA) determination, chest/abdomen/pelvis CT, and consideration of pelvic MRI should be performed to better assess for local staging and extent of disease (see *Workup and Management of Invasive Nonmetastatic Colon Cancer* for more details on this workup). If appropriate following workup, colectomy with en bloc removal of lymph nodes is recommended.[226,232-234] Laparoscopic surgery is an option.[235] Unfavorable histopathologic features for malignant polyps include grade 3 or 4, angiolymphatic invasion, or a positive margin of resection.[177,236] Notably, no consensus currently exists as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as the presence of tumor within 1 to 2 mm of the transected margin or the presence of tumor cells within the diathermy of the transected margin.[226,237-239] 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.[240-243]

All patients who have malignant polyps removed by transanal excision or transabdominal resection should undergo total colonoscopy to rule out other synchronous polyps and should subsequently undergo appropriate follow-up surveillance endoscopy. Adjuvant chemotherapy is not recommended for patients with stage I lesions.

Workup and Management of Invasive Nonmetastatic Colon Cancer

Patients who present with invasive colon cancer appropriate for resection require a complete staging workup, including biopsy, pathologic tissue review, total colonoscopy, CBC, chemistry profile, CEA determination, and baseline CT scans of the chest, abdomen, and pelvis.[244] Testing for MMR/MSI should be done at diagnosis to help with detection of Lynch syndrome and to inform treatment decision-making. CT should be with intravenous (IV) and oral contrast. If the CT of the abdomen and pelvis is inadequate or if CT with IV contrast is contraindicated, an abdomen/pelvis MRI with contrast plus a non-contrast chest CT should be considered. The chest CT can identify lung metastases, which occur in approximately 4% to 9% of patients with colon and rectal cancer.[245-247] One series of 378 patients found that resection of pulmonary metastases resulted in 3-year relapse-free survival (RFS) of 28% and 3-year OS of 78%.[248] Fertility risks should be discussed with appropriate patients prior to treatment and referral for and/or counseling on fertility preservation options should be done if indicated (see the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology for more information on this topic).

The consensus of the Panel is that a PET/CT scan is not indicated at baseline for preoperative workup. In fact, PET/CT scans are usually done without contrast and multiple slicing and do not obviate the need for a contrast-enhanced diagnostic CT scan. If, however, abnormalities are seen on CT or MRI scan that are considered suspicious but inconclusive for metastases, then a PET/CT scan may be considered to further delineate that abnormality, if this information will change management. A PET/CT scan is not indicated for assessing subcentimeter lesions, because these are routinely below the level of PET/CT detection.

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For resectable colon cancer that is causing overt obstruction, one-stage colectomy with en bloc removal of regional lymph nodes, resection with diversion, or diversion or stent (in selected cases) followed by colectomy are options. Stents are generally reserved for cases of distal lesions in which a stent can allow decompression of the proximal colon with later elective colostomy with primary anastomosis.[249] A meta-analysis found that oncologic outcomes were similar for surgery and for stenting followed by elective surgery.[250] This result was supported by the ESCO trial, an RCT from Europe that reported similar outcomes between colonic stenting as a bridge to surgery compared to emergency surgery for malignant colon obstruction.[251,252] Another meta-analysis of comparative studies compared colectomy to diversion followed by colectomy.[253] Although 30-day mortality and morbidity were the same between the groups, the diversion group was less likely to have a permanent colostomy (OR [odds ratio], 0.22; 95% CI, 0.11–0.46). Preoperative stoma education and marking of the site by an enterostomal therapist have been shown to improve outcomes and are therefore recommended for patients who are expected to receive a stoma following surgery.[254-256]

Bulky nodal disease or clinical T4b may benefit from neoadjuvant therapy prior to resection, oxaliplatin-based chemotherapy for MMR-proficient (pMMR)/microsatellite-stable (MSS) disease, and either chemotherapy or a checkpoint inhibitor for cT4b dMMR/MSI-H disease. If the cancer is locally unresectable or the patient is medically inoperable, systemic therapy, radiation, and/or chemoradiation is recommended, possibly with the goal of converting the lesion to a resectable state.

Neoadjuvant Therapy for Resectable Colon Cancer

For bulky nodal disease or clinical T4b, neoadjuvant treatment with FOLFOX or CAPEOX may be considered prior to surgery. The randomized phase III FOxTROT trial is assessing whether this approach improves DFS. Results from the feasibility phase of the trial were reported in 2012.[257] One hundred fifty patients with T3 (with ≥5 mm invasion beyond the muscularis propria) or T4 tumors were randomly assigned to three cycles of preoperative therapy (fluorouracil [5-FU]/leucovorin [LV]/oxaliplatin), surgery, and nine additional cycles of the same therapy or to surgery with 12 cycles of the same therapy given postoperatively. Preoperative therapy resulted in significant downstaging compared with postoperative therapy (P = .04), with acceptable toxicity. Mature results from the FOxTROT trial reported on 1053 total randomized patients, including 699 randomized to neoadjuvant chemotherapy and 354 to the control group.[258] The primary outcome of 2-year residual or recurrent disease was 16.9% with neoadjuvant chemotherapy compared to 21.5% in the control group, representing a 28% lower recurrence rate with neoadjuvant chemotherapy. The neoadjuvant chemotherapy group showed marked T and N downstaging and histologic tumor regression. Resection was more often histopathologically complete with neoadjuvant chemotherapy compared to control (94% vs. 89%; P < .001). These results support the feasibility of neoadjuvant therapy as a treatment option for colon cancer.

For the dMMR/MSI-H population, the NICHE and NICHE-2 studies have shown high rates of pathologic response with neoadjuvant immunotherapy in early-stage colon cancers prior to resection.[259,260] The NICHE-2 study reported results from 115 enrolled patients with nonmetastatic dMMR colon cancer treated with ipilimumab plus nivolumab.[260] In the efficacy population, 109 of 111 (98%; 95% CI, 94–100) were observed to have pathologic disease response, including 95% major pathologic responses and 68% pathologic complete responses. At a median follow-up of 26 months, no cases of disease recurrence were reported. Grade 3–4 immune-related AEs were reported in 4% of patients. While neoadjuvant chemotherapy with FOLFOX or CAPEOX is considered an option by the NCCN Panel for cT4b dMMR/MSI-H disease, it is important to note that the FOxTROT trial results reported little benefit from neoadjuvant

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chemotherapy for patients with dMMR tumors, leading checkpoint inhibitor therapy to be the preferred approach in this setting.[258]

Surgical Management

For resectable nonmetastatic colon cancer, the preferred surgical procedure is colectomy with en bloc removal of the regional lymph nodes.[261,262] The extent of colectomy should be based on the tumor location, resecting the portion of the bowel and arterial arcade containing the regional lymph nodes. Other nodes, such as those at the origin of the vessel feeding the tumor (ie, apical lymph node), and suspicious lymph nodes outside the field of resection, should also be biopsied or removed if possible. Resection must be complete to be considered curative, and positive lymph nodes left behind indicate an incomplete (R2) resection.[263]

There has been some attention focused on the quality of colectomy.[264] The phase III ESCME trial compared the outcomes of patients who had undergone complete mesocolic excision (CME) to those who had a non-CME.[265] Five-year local RFS was similar between the groups; however, the absolute risk reduction of 5-year cumulative death and disease progression after CME was 9.1% for Union for International Cancer Control (UICC) stage I–III and 16.1% for UICC stage III, specifically.

In addition, a retrospective observational study found a possible OS advantage for surgery in the mesocolic plane over surgery in the muscularis propria plane.[266] A comparison of resection techniques by expert surgeons in Japan and Germany showed that CME with central vascular ligation resulted in greater mesentery and lymph node yields than the Japanese D3 high tie surgery.[267] Differences in outcomes were not reported. A retrospective, population-based study in Denmark also supports the benefit of a CME approach in patients with stage I–III colon cancer, with a significant difference in 4-year DFS (P = .001) between those undergoing CME resection (85.8%; 95% CI, 81.4–90.1) and those undergoing conventional resection (75.9%; 95% CI, 72.2–79.7).[268] A systematic review found that four of nine prospective studies reported improved lymph node harvest and survival with CME compared with non-CME colectomy; the other studies reported improved specimen quality.[269]

Minimally Invasive Approaches to Colectomy

Laparoscopic colectomy is an option in the surgical management of colon cancer.[270-273] In a small European randomized trial (Barcelona), the laparoscopic approach seemed to be associated with some modest survival advantage, significantly faster recovery, and shorter hospital stays.[274] More recently, a similar but larger trial (COLOR trial) of 1248 patients with colon cancer randomly assigned to curative surgery with either a conventional open approach or laparoscopic-assisted surgery showed a nonsignificant absolute difference of 2.0% in 3-year DFS favoring open colectomy.[275] Noninferiority of the laparoscopic approach could not be established because of study limitations. Ten-year outcomes of the COLOR trial also showed similar rates of DFS, OS, and recurrence between open and laparoscopic surgery.[276] In the CLASICC study of 794 patients with CRC, no statistically significant differences in 3-year rates of OS, DFS, and local recurrence were observed between these surgical approaches.[277] Long-term follow-up of participants in the CLASICC trial showed that the lack of differences in outcomes between arms continued over a median of 62.9 months.[278]

In another trial (COST study) of 872 patients with colon cancer randomly assigned to undergo either open or laparoscopic-assisted colectomy for curable colon cancer, similar 5-year recurrence and 5-year OS rates were seen after a median of 7-year follow-up.[279,280] A similar RCT in Australia and New Zealand also found no differences in disease outcomes.[281] In addition, results of several meta-analyses have supported the conclusion that the two surgical approaches provide similar long-term outcomes with respect to local recurrence and survival in patients with colon cancer.[282-287] Factors have been described that may confound conclusions drawn from

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randomized studies comparing open colectomy with laparoscopic-assisted surgery for colon cancer.[288,289]

A subanalysis of results from the COLOR trial evaluating short-term outcomes (eg, conversion rate to open colectomy, number of lymph nodes collected, number of complications) based on hospital case volume indicated that these outcomes were statistically significantly more favorable when laparoscopic surgery was performed at hospitals with high case volumes.[290] A meta-analysis of 18 studies (6153 patients) found a lower rate of cardiac complications with laparoscopic colectomy compared with open resection.[291] Analyses of large national databases also support the benefits of the laparoscopic approach.[292,293]

In recent years, perioperative care has improved, with reductions in the average length of hospital stay and complication rates after surgery.[294,295] The multicenter, randomized, controlled EnROL trial therefore compared conventional and laparoscopic colectomy with an enhanced recovery program in place.[296] Outcomes were the same in both arms, with the exception of median length of hospital stay, which was significantly shorter in the laparoscopic group (5 vs. 7 days; $P = .033$).

Robotic colectomy has been compared to the laparoscopic approach, mostly with observational cohort studies.[297-300] In general, the robotic approach results in longer operating times and is more expensive but may be associated with less blood loss, shorter time to recovery of bowel function, shorter hospital stays, and lower rates of complications and infections.

The Panel recommends that minimally invasive colectomy be considered only by surgeons experienced in the techniques. A thorough abdominal exploration is required as part of the procedure. Routine use of minimally invasive colon resection is generally not recommended for tumors that are acutely obstructed or perforated or tumors that are clearly locally invasive into surrounding structures (ie, T4). Patients at high risk for prohibitive abdominal adhesions should not have minimally invasive colectomy, and those who are found to have prohibitive adhesions during exploration should be converted to an open procedure.[235,301,302]

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Adjuvant Chemotherapy for Resectable Colon Cancer

Choices for adjuvant therapy for patients with resected, nonmetastatic colon cancer depend on the stage of disease:

- Patients with stage I disease and patients with MSI-H, stage II disease do not require any adjuvant therapy.
- Patients with low-risk stage II disease that is MSS or pMMR can be observed without adjuvant therapy or considered for capecitabine or 5-FU/LV. Based on results of the MOSAIC trial,[303-305] and the possible long-term sequelae of oxaliplatin-based chemotherapy, the Panel does not consider FOLFOX (infusional 5-FU, LV, oxaliplatin) to be an appropriate adjuvant therapy option for patients with stage II disease without high-risk features.
- Patients with stage II disease that is MSS/pMMR and at high risk for systemic recurrence, defined as those with poor prognostic features, including T4 tumors (stage IIB/IIC); poorly differentiated/undifferentiated histology; lymphovascular invasion; PNI; tumor budding; bowel obstruction; lesions with localized perforation or close, indeterminate, or positive margins; or inadequately sampled nodes (<12 lymph nodes), can be considered for 6 months of adjuvant chemotherapy with 5-FU/LV, capecitabine, or FOLFOX, or 3 months of adjuvant chemotherapy with CAPEOX (capecitabine and oxaliplatin).[125,306] Observation without adjuvant therapy is also an option in this population. The factors in decision-making for stage II adjuvant therapy are discussed in more detail below.

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- For patients with low-risk (T1–3, N1) stage III disease, the preferred adjuvant treatment options are 3 months of CAPEOX[307-309] or 3 to 6 months of FOLFOX.[303-305,309] Other treatment options include 6 months of single-agent capecitabine[310] or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.[311-314]

- For patients with high-risk (T4, N1–2 or any T, N2) stage III disease, the preferred adjuvant treatment options are 6 months of FOLFOX[303-305] or 3 to 6 months of CAPEOX.[307-309] Other treatment options include 6 months of single-agent capecitabine[310] or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.[311-314]

Population and institutional studies have shown that patients with resected colon cancer treated with adjuvant therapy have a survival advantage over those not treated with adjuvant therapy.[315-317] For example, patients from the National Cancer Database with stage III or high-risk stage II disease treated according to these NCCN Guidelines for Colon Cancer had a survival advantage over patients whose treatment did not adhere to these guidelines.[315] A retrospective cohort study of 852 patients with any stage of colon or rectal cancer treated at Memorial University Medical Center in Savannah, Georgia similarly found that concordance with the recommendations in these NCCN Guidelines for Colon Cancer resulted in a lower risk of death.[317]

Endpoints for Adjuvant Chemotherapy Clinical Trials

The Adjuvant Colon Cancer End Points (ACCENT) collaborative group evaluated the appropriateness of various endpoints for adjuvant chemotherapy trials in colon cancer. Results of an analysis of individual patient data from 20,898 patients in 18 randomized colon adjuvant clinical trials by the ACCENT group suggested that DFS after 2 and 3 years of follow-up are appropriate endpoints for clinical trials involving treatment of colon cancer with 5-FU–based chemotherapy in the adjuvant setting.[318] An update of this analysis showed that most relapses occur within 2 years after surgery, and that recurrence rates were <1.5% per year and <0.5% per year after 5 and 8 years, respectively.[319] More recently, however, a further update of the data suggested that the association between 2- or 3-year DFS and 5-year OS was reduced when patient survival after recurrence was hypothetically prolonged to match the current time to survival from recurrence seen with modern combination therapies (2 years), and that >5 years may now be required to evaluate the effect of adjuvant therapies on OS.[320] Further confirmation of this result comes from a new analysis by the ACCENT group of data from 12,676 patients undergoing combination therapies from six trials.[321] This study determined that 2- and 3-year DFS correlated with 5- and 6-year OS in patients with stage III disease but not in those with stage II disease. In all patients, the correlation of DFS to OS was strongest at 6-year follow-up, suggesting that at least 6 years are required for adequate assessment of OS in modern adjuvant colon cancer trials.[321]

Adjuvant Chemotherapy in Stage II Disease

The impact of adjuvant chemotherapy for patients with stage II colon cancer has been addressed in several clinical trials and practice-based studies.[125,303-306] Results from a 2015 meta-analysis of 25 high-quality studies showed that 5-year DFS in patients with stage II colon cancer who did not receive adjuvant therapy was 81.4% (95% CI, 75.4–87.4), whereas it was 79.3% (95% CI, 75.6–83.1) for patients with stage II colon cancer treated with adjuvant chemotherapy.[322] On the other hand, for patients with stage III colon cancer, the 5-year DFS was 49.0% (95% CI, 23.2–74.8) and 63.6% (95% CI, 59.3–67.9) in those treated without and with adjuvant chemotherapy, respectively. These results suggest that the benefit of adjuvant therapy is greater in patients at higher risk because of nodal status. In contrast to results from most other trials, the QUASAR trial indicated a small but statistically significant survival benefit for patients

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with stage II disease treated with 5-FU/LV compared to patients not receiving adjuvant therapy (RR of recurrence at 2 years, 0.71; 95% CI, 0.54–0.92; $P = .01$).[323] In this trial, however, approximately 64% of patients had <12 lymph nodes sampled, and thus actually may have been patients with higher risk disease who were more likely to benefit from adjuvant therapy.[324]

The benefit of oxaliplatin in adjuvant therapy for patients with stage II colon cancer has also been addressed. Results from a post-hoc exploratory analysis of the MOSAIC trial did not show a significant DFS benefit of FOLFOX over 5-FU/LV for patients with stage II disease at a follow-up of 6 years (HR, 0.84; 95% CI, 0.62–1.14; $P = .258$).[325] After longer follow-up, no difference in 10-year OS was observed in the stage II subpopulation (79.5% vs. 78.4%; HR, 1.00; $P = .98$).[305] In addition, patients with high-risk stage II disease (ie, disease characterized by at least one of the following: T4 tumor; tumor perforation; bowel obstruction; poorly differentiated tumor; venous invasion; <10 lymph nodes examined) receiving FOLFOX did not have improved DFS compared with those receiving infusional 5-FU/LV (HR, 0.72; 95% CI, 0.50–1.02; $P = .063$). Furthermore, no OS benefit was seen in the stage II population overall or in the stage II population with high-risk features. Similar results were seen in the C-07 trial, which compared FLOX to 5-FU/LV in patients with stage II and III disease.[326] Results of a large population-based study also support the lack of benefit of the addition of oxaliplatin to adjuvant regimens for patients with stage II colon cancer.[327]

Clinical trial results are supported by data from the community setting. Using the SEER databases, a 2002 analysis of outcomes of patients with stage II disease based on whether or not they had received adjuvant chemotherapy showed no statistically significant difference in 5-year OS between the groups (78% vs. 75%, respectively), with an HR for survival of 0.91 (95% CI, 0.77–1.09) when patients receiving adjuvant treatment were compared with patients who had not received adjuvant treatment.[328] In contrast, a 2016 analysis of 153,110 patients with stage II colon cancer from the National Cancer Database found that adjuvant treatment was associated with improved survival (HR, 0.76; $P < .001$) even after adjustment for comorbidity and unplanned hospital readmissions.[327] Results of another population-level analysis from the Netherlands published in 2016 suggest that the benefit of adjuvant therapy in patients with stage II colon cancer may be limited to those with pT4 tumors.[329]

Decision-making regarding the use of adjuvant therapy for patients with stage II disease should incorporate patient/physician discussions individualized for the patient, and should include explanations of the specific characteristics of the disease and its prognosis and the evidence related to the efficacy and possible toxicities associated with treatment, centering on patient choice.[306,330,331] Observation and participation in a clinical trial are options that should be considered. Patients with average-risk stage II colon cancer have a very good prognosis, so the possible benefit of adjuvant therapy is small. Patients with disease with high-risk features, on the other hand, traditionally have been considered more likely to benefit from adjuvant chemotherapy. However, the current definition of high-risk stage II colon cancer is clearly inadequate, because many patients with disease with high-risk features do not have a recurrence while some patients with disease deemed to be average-risk do.[332] Furthermore, no data point to features that are predictive of benefit from adjuvant chemotherapy, and no data correlate risk features and selection of chemotherapy in patients with high-risk stage II disease.

Overall, the NCCN Panel supports the conclusion of a 2022 ASCO Panel and believes that it is reasonable to accept the relative benefit of adjuvant therapy in stage III disease as indirect evidence of benefit for stage II disease, especially for those with high-risk features.[306] Additional information that may influence adjuvant therapy decisions for stage II

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and/or stage III disease (MSI, multigene assays, and the influence of patient age) is discussed below. Research into additional possible predictive markers may allow for more informed decision-making in the future.[333,334]

Microsatellite Instability

MSI is an important piece of information to consider when deciding whether to use adjuvant chemotherapy in patients with stage II disease. Mutation of MMR genes or modifications of these genes (eg, methylation) can result in MMR protein deficiency and MSI (see *Risk Assessment*, above).[335] Tumors showing the presence of MSI are classified as either MSI-H or MSI-low (MSI-L), depending on the extent of instability in the markers tested, whereas tumors without this characteristic are classified as MSS.[336] Patients with tumors determined to have dMMR status are biologically the same population as those with MSI-H status.

Germline mutations in the MMR genes *MLH1*, *MSH2*, *MSH6*, and/or *PMS2* or *EpCAM* are found in individuals with Lynch syndrome, which is responsible for 2% to 4% of colon cancer cases.[15,16,20,21] Somatic MMR defects have been reported to occur in approximately 19% of colorectal tumors,[337] whereas others have reported somatic hypermethylation of the *MLH1* gene promoter, which is associated with *MLH1* gene inactivation, in as many as 52% of colon tumors.[338]

Data from the PETACC-3 trial showed that tumor specimens characterized as MSI-H are more common in stage II disease than in stage III disease (22% vs. 12%, respectively; $P < .0001$).[339] In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%.[340] These results suggest that MSI-H (ie, dMMR) tumors have a decreased likelihood to metastasize. In fact, substantial evidence shows that in patients with stage II disease, a deficiency in MMR protein expression or MSI-H tumor status is a prognostic marker of a more favorable outcome.[341-343] In contrast, the favorable impact of dMMR on outcomes seems to be more limited in stage III colon cancer and may vary with primary tumor location.[341,344]

Some of these same studies also show that a deficiency in MMR protein expression or MSI-H tumor status may be a predictive marker of decreased benefit and possibly a detrimental impact from adjuvant therapy with a fluoropyrimidine alone in patients with stage II disease.[342,343,345] A retrospective study involving long-term follow-up of patients with stage II and III disease evaluated according to MSI tumor status showed that those characterized as MSI-L or MSS had improved outcomes with 5-FU adjuvant therapy. However, patients with tumors characterized as MSI-H did not show a statistically significant benefit from 5-FU after surgery, instead exhibiting a lower 5-year survival rate than those undergoing surgery alone.[342] Similarly, results from another retrospective study of pooled data from adjuvant trials by Sargent et al[343] showed that in tumors characterized as dMMR, adjuvant 5-FU chemotherapy seemed to be detrimental in patients with stage II disease, but not in those with stage III disease.

In contrast to the findings of Sargent et al,[343] a study of 1913 patients with stage II CRC from the QUASAR study, half of whom received adjuvant chemotherapy, showed that although dMMR was prognostic (the recurrence rate of dMMR tumors was 11% vs. 26% for pMMR tumors), it did not predict benefit or detrimental impact of chemotherapy.[324] A study of patients in the CALGB 9581 and 89803 trials came to a similar conclusion.[346] MMR status was prognostic but not predictive of benefit or detrimental impact of adjuvant therapy (irinotecan plus bolus 5-FU/LV [IFL regimen]) in patients with stage II colon cancer.

The Panel recommends universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome (see *Lynch Syndrome*, above), to inform use of immunotherapy in patients with metastatic disease (see *Biomarkers for*

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Systemic Therapy, below), and to inform decisions for patients with stage II disease. Patients with stage II MSI-H tumors may have a good prognosis and do not benefit from 5-FU adjuvant therapy, and adjuvant therapy should not be given to patients with low-risk stage II MSI-H tumors. An exception is with T4b (stage IIC) dMMR/MSI-H tumors, which may carry a higher risk compared to other dMMR/MSI-H stage II tumors. For these patients, fluoropyrimidine-based adjuvant therapy, with or without oxaliplatin, may be considered. It should be noted that poorly differentiated histology is not considered a high-risk feature for patients with stage II disease whose tumors are MSI-H.

Multigene Assays, Immunoscore, and Circulating Tumor DNA

Several assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer.

Oncotype DX colon cancer assay quantifies the expression of seven recurrence-risk genes and five reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.[347] Clinical validation in patients with stage II and III colon cancer from QUASAR[348] and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07[349] trials showed that recurrence scores are prognostic for recurrence, DFS, and OS in stage II and III colon cancer, but are not predictive of benefit to adjuvant therapy. For the low, intermediate, and high recurrence risk groups, recurrence at 3 years was 12%, 18%, and 22%, respectively.[348] Multivariate analysis showed that recurrence scores were related to recurrence independently from TNM staging, MMR status, tumor grade, and number of nodes assessed in both stage II and III disease. Similar results were found in a prospectively designed study that tested the correlation between recurrence score using the Oncotype DX colon cancer assay and the risk of recurrence in patients from the CALGB 9581 trial (stage II disease).[350] An additional prospectively designed clinical validation study in patients from the NSABP C-07 trial found that the assay results correlated with recurrence, DFS, and OS.[349] This study also found some evidence that patients with higher recurrence scores may derive more absolute benefit from oxaliplatin, although the authors noted that the recurrence score is not predictive of oxaliplatin efficacy in that it does not identify patients who will or will not benefit from oxaliplatin treatment. An additional study validated the recurrence score in patients with stage II/III colon cancer treated with surgery alone.[351]

ColoPrint quantifies the expression of 18 genes as a prognostic classifier of low versus high recurrence risk.[352] In a set of 206 patients with stage I–III CRC, the 5-year RFS rates were 87.6% (95% CI, 81.5–93.7) and 67.2% (95% CI, 55.4–79.0) for those classified as low and high risk, respectively. In patients with stage II disease in particular, the HR for recurrence between the high and low groups was 3.34 (P = .017).[352] This assay was further validated in a pooled analysis of 416 patients with stage II disease, 301 of whom were assessed as a T3/MSS subset.[353] In the T3/MSS subset, patients classified as low risk and high risk had a 5-year risk of relapse (survival until first event of recurrence or death from cancer) of 22.4% and 9.9%, respectively (HR, 2.41; P = .005). As with the Oncotype DX colon cancer assay, recurrence risk determined by ColoPrint is independent of other risk factors, including T stage, perforation, number of nodes assessed, and tumor grade. This assay is being further validated for its ability to predict 3-year relapse rates in patients with stage II colon cancer in a prospective trial (NCT00903565).

ColDx is a microarray-based multigene assay that uses 634 probes to identify patients with stage II colon cancer at high risk of recurrence.[354] In a 144-sample independent validation set, the HR for identification of patients with high-risk disease was 2.53 (95% CI, 1.54–4.15; P < .001) for recurrence and 2.21 (95% CI, 1.22–3.97; P = .0084) for cancer-related death. A cohort study of patients in the C9581 trial found that patients with

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stage II colon cancer identified as high risk by ColDx had a shorter recurrence-free interval than those identified as low-risk (multivariable HR, 2.13; 95% CI, 1.3–3.5; $P < .01$).[355] Similar to the other assays described here, the recurrence risk determined by ColDx is independent of other risk factors.

An international study led by the Society for Immunotherapy of Cancer aimed to validate Immunoscore, a scoring system reported as percentiles of CD3+ and CD8+ immune cell densities in prespecified regions of the tumor sample by dedicated software, for the assay's prognostic value in patients with stage III colon cancer as well as its predictive value for efficacy of adjuvant chemotherapy in these patients.[356] This study reported that patients with the highest Immunoscore showed the lowest risk of recurrence; 3-year RFS rates were 56.9%, 65.9%, and 76.4% for low, medium, and high Immunoscore (HR [high vs. low], 0.48; 95% CI, 0.32–0.71; $P = .0003$). A high Immunoscore also correlated with prolonged time to recurrence, OS, and DFS (all $P < .001$). The benefit of adjuvant chemotherapy was also associated with a high Immunoscore for both high-risk ($P = .0015$) and low-risk ($P = .0011$) tumors. The same was not true for tumors with a low Immunoscore ($P > .12$).

Post-surgical circulating tumor DNA (ctDNA) has also been studied as a marker for an elevated risk of recurrence in stage I–III colon cancer. A prospective, multicenter study of 130 patients with stage I–III colon cancer detected ctDNA by multiplex, PCR-based next-generation sequencing (NGS).[357] Thirty days after surgery, patients with positive ctDNA assays were seven times more likely to experience disease relapse than patients with negative ctDNA assays (HR, 7.2; 95% CI, 2.7–19.0; $P < .001$). Likewise, after adjuvant chemotherapy, patients with ctDNA-positive assays were 17 times more likely to have disease relapse (HR, 17.5; 95% CI, 5.4–56.5; $P < .001$). Another prospective study of 150 patients with localized colon cancer detected ctDNA with NGS following surgery.[358] In this study, detection of ctDNA was also associated with poorer DFS (HR, 17.56; log rank $P = .0014$ for ctDNA post-surgery and HR, 11.33; log rank $P = .0001$ for ctDNA in serial plasma samples during follow-up). Other studies have reported similar results.[359,360]

In the DYNAMIC study, 455 patients with stage II colon cancer were randomized to either ctDNA-guided management or standard management.[361] After a median follow-up of 37 months, a lower percentage of patients in the ctDNA-guided management group received adjuvant chemotherapy compared to the standard management group (15% vs. 28%; RR, 1.82; 95% CI, 1.25–2.65). Two-year RFS in the ctDNA-guided management group was noninferior to the standard management group (93.5% vs. 92.4%). An abstract reporting 5-year results from the DYNAMIC study showed similar results, including mature OS data. Five-year RFS rates were 88% and 87% and 5-year OS rates were 93.8% and 93.3% for ctDNA-guided and standard management, respectively.[362]

The GALAXY observational arm from the ongoing CIRCULATE-Japan study has analyzed presurgical and postsurgical ctDNA in 1039 patients with stage II–IV resectable CRC.[363] With a median follow-up of 16.74 months in this cohort, postsurgical ctDNA positivity at 4 weeks after surgery was associated with a higher recurrence risk (HR, 10.0; $P < .0001$) and identified patients with stage II or III CRC who derived a benefit from adjuvant chemotherapy (HR, 6.59; $P < .0001$). While these results support ctDNA as a prognostic marker, details such as the timing of the assay and the value of quantification of ctDNA are the subject of ongoing studies. Most importantly, the early detection of recurrent disease through ctDNA testing is not without drawbacks. A positive result in the absence of evident disease is only helpful if the patient has therapeutic options that have a reasonable chance to eradicate the disease. Early knowledge of

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cancer recurrence in the absence of effective interventions could cause significant distress to a patient.

In summary, the information from these tests can further inform the risk of recurrence over other risk factors, but the Panel questions the value added. Furthermore, evidence of predictive value in terms of the potential benefit of chemotherapy is lacking. Therefore, the Panel believes that there are insufficient data to recommend the use of multigene assays, Immunoscore, or post-surgical ctDNA to estimate risk of recurrence or determine adjuvant therapy. ESMO has released similar recommendations regarding these assays, stating that their role in predicting chemotherapy benefit is uncertain.[364] The NCCN Panel encourages enrollment in clinical trials to help with the generation of additional data on these assays.

Adjuvant Chemotherapy in Older Patients

Adjuvant chemotherapy usage declines with the age of the patient.[365] Questions regarding the safety and efficacy of chemotherapy in older patients have been difficult to answer, because older patients are underrepresented in clinical trials. Some data speaking to these questions have been reviewed.[366-368]

Population studies have found that adjuvant therapy is beneficial in older patients. A retrospective analysis of 7263 patients from the linked SEER-Medicare Databases found a survival benefit for the use of 5-FU/LV in patients ≥65 years with stage III disease (HR, 0.70; $P < .001$).[369] Another analysis of 5489 patients aged ≥75 years diagnosed with stage III colon cancer between 2004 and 2007 from four datasets, including the SEER-Medicare Databases and the NCCN Outcomes Database, showed a survival benefit for adjuvant chemotherapy in this population (HR, 0.60; 95% CI, 0.53–0.68).[365] This study also looked specifically at the benefit of the addition of oxaliplatin to adjuvant therapy in these patients ≥75 years with stage III disease, and found only a small, non-significant benefit. Analysis of almost 12,000 patients from the ACCENT database also found a reduced benefit to the addition of oxaliplatin to fluoropyrimidines in the adjuvant setting in patients ≥70 years.[370]

Subset analyses of major adjuvant therapy trials also show a lack of benefit to the addition of oxaliplatin in older patients. Subset analysis of the NSABP C-07 trial showed that the addition of oxaliplatin to 5-FU/LV gave no survival benefit in patients ≥70 years with stage II or III colon cancer (n = 396), with a trend towards decreased survival (HR, 1.18; 95% CI, 0.86–1.62).[326] Similarly, in a subset analysis of the MOSAIC trial, 315 patients aged 70 to 75 years with stage II or III colon cancer derived no benefit from the addition of oxaliplatin (OS HR, 1.10; 95% CI, 0.73–1.65).[325]

Another pooled analysis aimed to determine if patients aged ≥70 years derive a benefit with oxaliplatin-based adjuvant chemotherapy for treatment of high-risk stage II–III colon or rectal cancer.[371] This analysis included OS data from 1985 patients and showed that while oxaliplatin-based adjuvant chemotherapy reduced the mortality risk by 26% in patients <70 years, it did not yield an improvement for patients ≥70 years. Similar results were seen for DFS.

However, a pooled analysis of individual patient data from the NSABP C-08, XELOXA, X-ACT, and AVANT trials found that DFS (HR, 0.77; 95% CI, 0.62–0.95; $P = .014$) and OS (HR, 0.78; 95% CI, 0.61–0.99; $P = .045$) were improved with adjuvant CAPEOX or FOLFOX over 5-FU/LV in patients ≥70 years.[372] Likewise, a subgroup analysis of the phase III TOSCA trial (part of the IDEA collaboration) found that once the multivariable analysis was corrected for sex, performance status, tumor site, grade, treatment, treatment duration, and dose reduction, there was no significant difference in time to tumor recurrence between patients ≥70 years compared to those <70 years when treated with oxaliplatin-based adjuvant therapy (HR, 1.19; 95% CI, 0.98–1.44; $P = .082$), although worse prognostic factors and a higher rate of treatment discontinuation had a

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negative impact on efficacy measures of DFS and OS in the population ≥70 years of age.[373]

As for the risks of adjuvant therapy in older patients, a pooled analysis of 37,568 patients from adjuvant trials in the ACCENT database found that the likelihood of early mortality after adjuvant treatment increased with age in a nonlinear fashion ($P < .001$).[374] For instance, the ORs for 30-day mortality for patients aged 70 and 80 years compared to patients aged 60 years were 2.58 (95% CI, 1.88–3.54) and 8.61 (95% CI, 5.34–13.9), respectively. Patients aged 50 years, on the other hand, had a corresponding OR of 0.72 (95% CI, 0.47–1.10). However, the absolute risk of early mortality was very small, even for older patients (30-day mortality for 80-year-olds was 1.8%).

Overall, the benefit and toxicities of 5-FU/LV as adjuvant therapy seem to be similar in older and younger patients. However, the Panel cautions that a benefit for the addition of oxaliplatin to 5-FU/LV in patients ≥70 years has not been proven in stage II or stage III colon cancer.

Timing of Adjuvant Therapy

A systematic review and meta-analysis of 10 studies involving >15,000 patients examined the effect of timing of adjuvant therapy after resection.[375] 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. In addition, a retrospective study of 7794 patients with stage II or III colon cancer from the National Cancer Database found that a delay of >6 weeks between surgery and adjuvant therapy reduced survival after adjustment for clinical-, tumor-, and treatment-related factors.[376] Another retrospective study of 6620 patients with stage III colon cancer from the Netherlands Cancer Registry also found that starting adjuvant therapy after 8 weeks beyond resection was associated with worse survival.[377] However, some critics have pointed out that this type of analysis is biased by confounding factors such as comorbidities, which are likely to be higher in patients with a longer delay before initiation of chemotherapy.[378] In fact, the registry study found that patients who started therapy after 8 weeks were more likely to be >65 years, have had an emergency resection, and/or have a prolonged postoperative admission.[377] Additionally, a phase III intergroup trial of the ECOG-ACRIN Cancer Research Group (E1291) reported no significant difference in OS or DFS for perioperative therapy versus no perioperative therapy with 5-FU, although this trial was terminated early due to slow accrual.[379]

Leucovorin Shortage

A shortage of LV has existed in the United States. No specific data are available to guide management under these circumstances, and all proposed strategies are empiric. The Panel recommends several possible options to help alleviate the problems associated with this shortage. One is the use of levoleucovorin, which is commonly used in Europe. A dose of 200 mg/m^2 of levoleucovorin is equivalent to 400 mg/m^2 of standard LV. Use of levoleucovorin should only be considered during times of LV shortage since levoleucovorin is substantially more expensive than LV.

Another option is for practices or institutions to use lower doses of LV for all doses in all patients, because the Panel feels that lower doses are likely to be as efficacious as higher doses, based on several studies. The QUASAR study found that 175 mg of LV was associated with similar survival and 3-year recurrence rates as 25 mg of LV when given with bolus 5-FU as adjuvant therapy to patients after R0 resections for CRC.[380] Another study showed no difference in response rate or survival in patients with mCRC receiving bolus 5-FU with either high-dose (500 mg/m^2) or low-dose (20 mg/m^2) LV.[381] Furthermore, the Mayo Clinic and North Central Cancer Treatment Group (NCCTG) determined that no therapeutic difference was seen between the use of high-dose (200

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mg/m^2) or low-dose (20 mg/m^2) LV with bolus 5-FU in the treatment of advanced CRC, although the 5-FU doses were different in the treatment arms.[382] Finally, if none of the above options are available, treatment without LV would be reasonable. For patients who tolerate this without grade II or higher toxicity, a modest increase in 5-FU dose (in the range of 10%) may be considered.

Adjuvant FOLFOX and Infusional 5-FU/LV

The European MOSAIC trial compared the efficacy of FOLFOX and 5-FU/LV in the adjuvant setting in 2246 patients with completely resected stage II and III colon cancer. Although this initial trial was performed with FOLFOX4, mFOLFOX6 has been the control arm for all recent and current National Cancer Institute (NCI) adjuvant studies for CRC, and the Panel believes that mFOLFOX6 is the preferred FOLFOX regimen for adjuvant and metastatic treatments. Results of this study have been reported with median follow-ups of up to 9.5 years.[303-305] For patients with stage III disease, DFS at 5 years was 58.9% in the 5-FU/LV arm and 66.4% in the FOLFOX arm (P = .005), and 10-year OS of patients with stage III disease receiving FOLFOX was statistically significantly increased compared with those receiving 5-FU/LV (67.1% vs. 59.0%; HR, 0.80; P = .016).[305] Although the incidence of grade 3 peripheral sensory neuropathy was 12.4% for patients receiving FOLFOX and only 0.2% for patients receiving 5-FU/LV, long-term safety results showed a gradual recovery for most of these patients. However, neuropathy was present in 15.4% of examined patients at 4 years (mostly grade 1), suggesting that oxaliplatin-induced neuropathy may not be completely reversible in some patients.[304]

An analysis of five observational data sources, including the SEER-Medicare and NCCN Outcomes Databases, showed that the addition of oxaliplatin to 5-FU/LV gave a survival advantage to the general stage III colon cancer population treated in the community.[383] Another population-based analysis found that the harms of oxaliplatin in the Medicare population with stage III colon cancer were reasonable, even in patients ≥75 years.[384] In addition, a pooled analysis of individual patient data from four RCTs revealed that the addition of oxaliplatin to capecitabine or 5-FU/LV improved outcomes in patients with stage III colon cancer.[385] Furthermore, analysis of data from 12,233 patients in the ACCENT database of adjuvant colon cancer trials supports the benefit of oxaliplatin in patients with stage III disease.[386]

Adjuvant Capecitabine and CAPEOX

Single-agent oral capecitabine as adjuvant therapy for patients with stage III colon cancer was shown to be at least equivalent to bolus 5-FU/LV (Mayo Clinic regimen) with respect to DFS and OS, with respective HRs of 0.87 (95% CI, 0.75–1.00; P < .001) and 0.84 (95% CI, 0.69–1.01; P = .07) in the X-ACT trial.[310] Final results of this trial were subsequently reported.[387] After a median follow-up of 6.9 years, the equivalencies in DFS and OS were maintained in all subgroups, including those ≥70 years.

Capecitabine was also assessed as adjuvant therapy for stage III colon cancer in combination with oxaliplatin (CAPEOX) in the NO16968 trial and showed an improved 3-year DFS rate compared with bolus 5-FU/LV (66.5% vs. 70.9%).[307,308] Final results of this trial showed that OS at 7 years was improved in the CAPEOX arm compared with the 5-FU/LV arm (73% vs. 67%; HR, 0.83; 95% CI, 0.70–0.99; P = .04).[388] Another phase III trial compared CAPEOX to mFOLFOX6 in 408 patients with stage III or high-risk stage II colon cancer.[389] No significant differences were seen in 3-year DFS and 3-year OS. In addition, a pooled analysis of individual patient data from four RCTs revealed that the addition of oxaliplatin to capecitabine or 5-FU/LV improved outcomes in patients with stage III colon cancer.[385]

Duration of Adjuvant Therapy

The IDEA collaboration investigated whether limiting adjuvant treatment to 3 months of FOLFOX or CAPEOX—which would markedly decrease the

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incidence of neuropathy—would compromise oncologic outcomes. IDEA included 12,834 patients in an international effort that pooled data from six concurrently conducted, randomized phase III trials to assess the noninferiority of 3 months compared with 6 months of adjuvant FOLFOX or CAPEOX in patients with stage III colon cancer.[309] The median follow-up was 39 months. Importantly, grade 3+ neurotoxicity rates were lower in the 3-month versus 6-month treatment arms (3% vs. 16% for FOLFOX; 3% vs. 9% for CAPEOX; $P < .0001$), as were grade 2 neurotoxicity rates (14% vs. 32% for FOLFOX; 12% vs. 36% for CAPEOX; $P < .0001$). Grade 2 and grade 3/4 diarrhea rates were also lower with the shorter duration of therapy ($P < .0001$ for FOLFOX; $P = .01$ for CAPEOX).

The primary endpoint of 3-year DFS did not meet the prespecified cutoff for noninferiority in the overall population, despite the small absolute difference of 0.9% (74.6% for 3 months vs. 75.5% for 6 months; HR, 1.07; 95% CI, 1.00–1.15), which is of questionable clinical significance. However, noninferiority was observed within certain subgroups. Specifically, in the low-risk (T1–3, N1) subgroup, the DFS for 3 months of CAPEOX was noninferior to 6 months of CAPEOX (HR, 0.85; 95% CI, 0.71–1.01), whereas noninferiority could not be proven for 3 months versus 6 months of FOLFOX (HR, 1.10; 95% CI, 0.96–1.26). In the high-risk (T4 and/or N2) subgroup, DFS for 3 months of FOLFOX was inferior to 6 months of FOLFOX (HR, 1.20; 95% CI, 1.07–1.35), whereas noninferiority could not be proven for the 3- to 6-month comparison with CAPEOX (HR, 1.02; 95% CI, 0.89–1.17).

Results of the final analysis of IDEA were reported after an overall median survival follow-up of 72.3 months.[390] In the final analysis, 5-year OS was 82.4% for 3 months of therapy compared to 82.8% for 6 months (HR, 1.02; 95% CI, 0.95–1.11; $P = .058$). The HR for 5-year OS was 0.96 for CAPEOX (3 vs. 6 months) and 1.07 for FOLFOX (3 vs. 6 months). Likewise, long-term DFS HRs were 0.98 for CAPEOX (3 vs. 6 months) and 1.16 for FOLFOX (3 vs. 6 months). The authors of this study concluded that, while the differences in OS did not meet the statistical assumptions for noninferiority, the overall 0.4% difference in 5-year OS should be placed in clinical context, especially considering the marked reduction in toxicity associated with the shorter duration of therapy.

A pooled analysis of patients with high-risk stage II colon cancer in the IDEA collaboration did not show noninferiority of 3 months compared to 6 months of adjuvant treatment based on 5-year DFS (80.7% for 3 months vs. 83.9% for 6 months; HR, 1.17; 80% CI, 1.05–1.31). Similar to stage III, the duration of therapy was associated with a small, not statistically significant difference in 5-year DFS between 3 and 6 months of CAPEOX (HR, 1.02; 80% CI, 0.88–1.17).[391] Two of the published trials within the IDEA collaboration reported similar results for high-risk stage II disease. For the TOSCA trial, 5-year RFS was found to be similar between 3 and 6 months of CAPEOX, while the difference was more pronounced between 3 and 6 months of FOLFOX (8.56% difference favoring 6 months of FOLFOX).[392] The OS analysis of TOSCA at a median follow-up of 7 years reported an HR of 1.09 for OS in the 3- versus 6-month arms (95% CI, 0.93–1.26; P for superiority = .288).[393] In the Hellenic Oncology Research Group (HORG)-IDEA trial, 3-year DFS was 76.7% for 3 months versus 79.3% for 6 months of FOLFOX (HR, 1.21; 95% CI, 0.54–2.70) and 85.4% for 3 months versus 83.8% for 6 months of CAPEOX (HR, 0.99; 95% CI, 0.59–1.67).[394]

ACHIEVE was another phase III trial that investigated similar questions regarding duration of adjuvant therapy for 1313 patients of Asian descent with stage III colon cancer.[395] The results of ACHIEVE were consistent with IDEA, finding that the incidence of long-lasting peripheral neuropathy was significantly lower with 3 months of adjuvant therapy compared to 6 months (9.7% vs. 24.3% after 3 years; $P < .001$). DFS rates were similar between the 3- and 6-month arms (HR, 0.95; 95% CI, 0.76–1.20). Final

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results from the ACHIEVE trial showed comparable 5-year OS results between the two arms (87.0% in the 3-month treatment group and 86.4% in the 6-month treatment group).[396] Long-term peripheral neuropathy was more common following 6 months of treatment (16% vs. 8%). ACHIEVE-2 was a randomized phase III trial comparing adjuvant chemotherapy duration of 3 versus 6 months for 525 patients with high-risk stage II colon cancer.[397] Similar to the other studies, the 3-year DFS rate with CAPEOX was 88.2% in the 3-month arm and 88.4% in the 6-month arm, with a lower discontinuation rate (15% vs. 35%; $P < .0001$) and lower rate of grade 2 or higher peripheral sensory neuropathy (16% vs. 43%; $P < .0001$) for 3 months of CAPEOX compared to 6 months. Other trials, including the phase III KCSG CO09-07 trial,[398] have reported similar results when comparing 3 to 6 months of adjuvant therapy in patients with stage II–III colon cancer.

Based on these data, 3 months of CAPEOX or 3 to 6 months of FOLFOX are listed in the guidelines as preferred adjuvant therapy options for patients with low-risk stage III colon cancer. Three to 6 months of CAPEOX or 6 months of FOLFOX are listed as preferred adjuvant therapy options for patients with high-risk stage III colon cancer. Six months of infusional 5-FU/LV or single-agent capecitabine are included as other adjuvant therapy options for low- or high-risk stage III colon cancer. For stage II colon cancer at high risk for systemic recurrence, the recommended options for adjuvant treatment are 6 months of capecitabine, 5-FU/LV, or FOLFOX or 3 months of CAPEOX. Observation may also be an appropriate option for high-risk stage II disease. In this population, no adjuvant treatment option is preferred over the others.

Adjuvant Regimens Not Recommended

Other adjuvant regimens studied for the treatment of early-stage colon cancer include 5-FU–based therapies incorporating irinotecan. The CALGB 89803 trial evaluated the IFL regimen versus 5-FU/LV alone in stage III colon cancer.[399] No improvement in either OS ($P = .74$) or DFS ($P = .84$) was observed for patients receiving IFL compared with those receiving 5-FU/LV. However, IFL was associated with a greater degree of neutropenia, neutropenic fever, and death.[399,400] Similar results were observed in a randomized phase III trial comparing bolus 5-FU/LV with the IFL regimen in stage II/III colon cancer.[401] In addition, FOLFIRI (infusional 5-FU/LV/irinotecan) has not been shown to be superior to 5-FU/LV in the adjuvant setting.[402,403] Thus, data do not support the use of irinotecan-containing regimens in the treatment of stage II or III colon cancer.

In the NSABP C-08 trial comparing 6 months of mFOLFOX6 with 6 months of mFOLFOX6 with bevacizumab plus an additional 6 months of bevacizumab alone in patients with stage II or III colon cancer, no statistically significant benefit in 3-year DFS was seen with the addition of bevacizumab (HR, 0.89; 95% CI, 0.76–1.04; $P = .15$).[404] Similar results were seen after a median follow-up of 5 years.[405] The results of the phase III AVANT trial evaluating bevacizumab in the adjuvant setting in a similar protocol also did not show a benefit associated with bevacizumab in the adjuvant treatment of stage II or III CRC, and in fact showed a trend toward a detrimental effect to the addition of bevacizumab.[406,407] Furthermore, results of the open-label, randomized, phase III QUASAR 2 trial showed that bevacizumab had no benefit in the adjuvant colorectal setting when added to capecitabine.[408] Therefore, bevacizumab has no role in the adjuvant treatment of stage II or III colon cancer.

The NCCTG Intergroup phase III trial N0147 assessed the addition of cetuximab to FOLFOX in the adjuvant treatment of stage III colon cancer. In patients with wild-type or mutant *KRAS* tumors, cetuximab provided no added benefit and was associated with increases in grade 3/4 AEs.[409] In addition, all subsets of patients treated with cetuximab experienced increases in grade 3/4 AEs. The open-label, randomized, phase III PETACC-8 trial also compared FOLFOX with and without cetuximab.[410]

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Analysis of the wild-type *KRAS* exon 2 subset found that DFS was similar in both arms (HR, 0.99; 95% CI, 0.76–1.28), while AEs (ie, rash, diarrhea, mucositis, infusion-related reactions) were more common in the cetuximab group. However, a more recent analysis of PETACC-8 that looked at mutations in *KRAS, NRAS*, and *BRAF* found that patients with *RAS* wild-type/*BRAF* wild-type tumors had a non-significant trend towards improved DFS (HR, 0.76) for the addition of cetuximab to FOLFOX.[411] Therefore, cetuximab also has no role in the adjuvant treatment of colon cancer at this time, but further trials may define a subset of patients who might benefit from cetuximab in the adjuvant setting.

A randomized phase III trial (NSABP C-07) compared the efficacy of FLOX with that of bolus 5-FU/LV in 2407 patients with stage II or III colon cancer. While FLOX showed significantly higher rates of 4- and 7-year DFS, [326,412] no statistically significant differences in OS or colon-cancer–specific mortality were observed when the arms were compared. Furthermore, survival after disease recurrence was significantly shorter in the group receiving oxaliplatin (HR, 1.20; 95% CI, 1.00–1.43; P = .0497).[326] Grade 3 neurotoxicity, diarrhea, and dehydration were higher with FLOX than with 5-FU/LV,[326] and, when cross-study comparisons were made, the incidence of grade 3/4 diarrhea seemed to be considerably higher with FLOX than with FOLFOX. For example, rates of grade 3/4 diarrhea were 10.8% and 6.6% for patients receiving FOLFOX and infusional 5-FU/LV in the MOSAIC trial,[303] whereas 38% and 32% of patients were reported to have grade 3/4 diarrhea in the NSABP C-07 trial when receiving FLOX and bolus 5-FU/LV.[412] For these reasons, FLOX is no longer recommended as adjuvant treatment for colon cancer.

Perioperative Chemoradiation

Neoadjuvant or adjuvant radiation therapy (RT) delivered concurrently with fluoropyrimidine–based chemotherapy may be considered for very select patients with disease characterized as T4 tumors penetrating to a fixed structure or for patients with recurrent disease.[413] RT fields should include the tumor bed as defined by preoperative radiologic imaging and/or surgical clips. Intraoperative RT (IORT), if available, should be considered for these patients as an additional boost.[414,415] If IORT is not available, an additional 10 to 20 Gy of external beam RT (EBRT) and/or brachytherapy could be considered to a limited volume.

Chemoradiation can also be given to patients with locally unresectable disease or who are medically inoperable. In such cases, surgery with or without IORT can then be considered or additional lines of systemic therapy can be given.

Intensity-modulated RT (IMRT), which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[416] or stereotactic body RT (SBRT; also called stereotactic ablative radiotherapy [SABR]) are preferred for unique clinical situations, such as reirradiation of previously treated patients with recurrent disease or anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal issue dose-volume constraints.[417]

Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with CRC develop colorectal metastases,[418-420] and 80% to 90% of these patients have unresectable metastatic liver disease.[419,421-424] Metastatic disease most frequently develops metachronously after treatment for locoregional CRC, with the liver being the most common site of involvement.[425] However, 20% to 34% of patients with CRC present with synchronous liver metastases.[424,426] 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

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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.[427]

It has been estimated that more than half of patients who die of CRC have liver metastases at autopsy, with metastatic liver disease being the cause of death in most patients.[428] 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.[423] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[419,429] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of more than three tumors, and a disease-free interval of <12 months, have been associated with a poor prognosis in patients with CRC.[426,430-434]

Contrast-enhanced ultrasound (CEUS) can be used for detection and characterization of liver lesions as a screening tool in distinct patient populations. This population includes those who cannot safely receive contrast-enhanced CT/MRI and those who have indeterminate liver lesion on CT/MRI. Ultrasound contrast agents (UCAs) have a high sensitivity for detecting small liver metastases because of their high spacial resolution and their ability to be maintained in circulation and not in the interstitial fluid.[435] Because of the UCAs' short half-life (about 5 minutes), contrast injection for lesion detection needs to be done repeatedly; if a patient has many liver metastases the ultrasound could be a lengthy test. In addition, many institutions do not have this technology or personnel with the expertise to perform the CEUS and/or analyze the results. At this time CEUS can be considered in certain patient populations as a screening tool at capable institutions.

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.[419,436] Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,[431,434] and a meta-analysis reported a median 5-year survival of 38%.[437] 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.[438-440] 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 (discussed further in *Determining Resectability*).[441]

Colorectal metastatic disease sometimes occurs in the lung.[418] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.[248,442,443] A series of 378 patients found that resection of pulmonary metastases resulted in a 3-year RFS of 28% and a 3-year OS of 78%.[248] Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases,[444-448] and an analysis of patients who underwent hepatic resection followed by subsequent pulmonary resection showed positive outcomes.[449]

Evidence supporting resection of extrahepatic metastases in patients with mCRC is limited. In a 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.[450,451] However, an international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent

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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).[448] A systematic review concluded similarly that carefully selected patients might benefit from this approach.[452]

Data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.[453-458] 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.[454] 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.[453] A meta-analysis of 27 studies including <7200 patients found that those with longer disease-free intervals; those whose recurrences were solitary, smaller, or unilobular; and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.[459] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[443,457,460]

Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Recommendations for Resectable Synchronous Liver or Lung 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 therapy is the preferred initial maneuver (discussed further in *Recommendations for Unresectable Synchronous Metastases*).[461]

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. Image-guided thermal ablation has historically been used for non-surgical patients[462-464] but is also indicated in resectable patients with small metastases where sufficient ablative margins can be achieved.[465] Ablation is offered in combination with surgery or alone, as long as all visible disease is treated.[466] The use of ablation instead of resection is supported by recent evidence of high local tumor control rates (>93%) when thermal ablation with confirmation of tumor-free ablation zone and margins can be achieved[467-469] and within the concept of test of time.[470] With this approach ablation can be offered ahead of resection for small tumors that can be treated with margins and with close follow-up for early detection of local progression or recurrence. This strategy allows for local tumor eradication while also allowing for biology of disease to be declared over time. Most cases are controlled by ablation alone, whereas patients who develop multifocal progression in a short period of time are spared the more morbid resection. In cases where local progression or recurrence is seen, resection can be offered at a later time.[470]

SBRT is a reasonable option for patients whose disease cannot be resected or ablated, as discussed in subsequent paragraphs.[422,471,472] Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins[464] 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.[473-475]

Recently, the administration of yttrium-90 microspheres in high radiation (ablative) doses (RADSEG) has been described as a local cure for limited liver metastases that cannot be technically resected or ablated. At least three small retrospective cohorts have shown very high response rates, favorable liver disease control, and patient survival in patients with liver

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metastatic disease (including colorectal origin) after RADSEG.[476-479] 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.[480] 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 IV 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.[423,481] The study was not powered for long-term survival, but a trend (not significant) was seen toward better long-term outcomes in the group receiving HAIC at later follow-up periods.[423,482]

The phase II/III PRODIGE 43 PACHA-01 study included a phase II portion, which was a non-comparative study that randomized patients who had undergone curative-intent hepatic resection of at least four colorectal liver metastases to adjuvant systemic FOLFOX or adjuvant HAIC with oxaliplatin plus systemic 5-FU/LV.[483] The intention-to-treat (ITT) analysis of the phase II portion of the trial showed a higher median 5-year hepatic RFS (h-RFS) in the HAIC arm compared to the control arm (25 vs. 12 months; HR, 0.598; 95% CI, 0.379–0.944; P = .027). Five-year OS was 60% in the HAIC arm compared to 46% in the control arm (P = .056). The rate of grade 3–4 AEs was 58% for HAIC compared to 31% for systemic FOLFOX. The planned phase III portion of the trial was suspended for slow recruitment.[484]

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.[423] Results of some studies also suggest that HAIC may be useful in the conversion of disease from an unresectable to a resectable status.[485,486]

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAIC.[436] Limitations on the use of HAIC include the potential for biliary toxicity[423] 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.[474] The most commonly accepted variation for the treatment of mCRC involves the use of drug-eluting bead TACE (DEB-TACE) using irinotecan as the chemotherapeutic agent (DEBIRI).[487] A randomized trial reported an OS benefit (22 vs. 15 months; P = .031) of DEBIRI when compared to systemic FOLFIRI.[488] 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.[489] A 2015 trial subsequently randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to FOLFOX/bevacizumab/DEBIRI.[490] DEBIRI resulted in an

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improvement in the primary outcome measure of response rate (78% vs. 54% at 2 months; *P* = .02).

Much of these data have been more recently validated in a single-arm registry study of 152 patients with mCRC treated with DEBIRI across Europe.[491] The results of the CIREL study demonstrated DEBIRI to be feasible, safe, and performed with a high technical success rate leading its investigators to propose its use beyond subsequent-line indications alone. A 2023 single-arm study again demonstrated safety and efficacy of DEBIRI, validating the results of the previously mentioned trials, with an OS of 15.3 months when used in the setting of patients who were able to tolerate more cycles of chemotherapy.[492]

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 initial therapy (2.1 vs. 4.5 months; *P* = .03).[493] 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.[494] In the refractory setting, a CEA level ≥90 and lymphovascular invasion at the time of primary resection were negative prognostic factors for OS.[495] 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[496] and resin[497] 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.[496,498,499] Median survival after radioembolization in the chemorefractory setting has been reported from 9 to 15.1 months.[494-499] 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.[497]

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX ± bevacizumab vs. FOLFOX ± bevacizumab) were reported.[500] 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).

The FOXFIRE and FOXFIRE Global 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.[501] 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).[502] 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.

Results from the EPOCH trial show the potential utility for radioembolization in patients with liver-only mCRC who have progressed on first-line systemic therapy. EPOCH was a randomized phase III clinical

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trial evaluating radioembolization in combination with second-line chemotherapy in 428 patients with metastatic colorectal carcinoma of the liver who had progressed on oxaliplatin- or irinotecan-based first-line chemotherapy.[503] The results showed an improvement in PFS (8.0 vs. 7.2 months; HR, 0.69; $P = .0013$) and hepatic PFS (9.1 vs. 7.2 months; HR, 0.59; $P < .0001$) in favor of the radioembolization arm.

A retrospective study of yttrium-90 resin microsphere transarterial radioembolization (TARE) indicated that patients with an overall response (OR) had an OS of 17.2 months versus 6.8 months for non-responders ($P < .0001$). In addition, a mean tumor dose of ≥100 Gy predicted a significantly prolonged OS of 19 versus 11 months for those patients with tumors that received <100 Gy.[504]

In another study of glass microsphere yttrium-90 TARE, a median tumor-absorbed dose of 85 measurable metastases was 133 Gy. A significant dose-response relationship was found on a tumor level, with a significantly higher tumor-absorbed dose in metastases with complete response (+94%) and partial response (+74%) compared to metastases with progressive disease ($P < .001$). A tumor-absorbed dose of >139 Gy predicted a 3-month metabolic response with the greatest accuracy. The median healthy liver-absorbed dose was 63 Gy. While a dose-toxicity relationship was not established, treatment was generally well-tolerated. This significant relationship observed between dose and response in patients treated with glass yttrium-90 radioembolization further demonstrates the importance of tumor delivered dose and oncologic outcomes.[505]

Whereas very little data show any impact on patient survival and the data supporting its efficacy are limited, toxicity with radioembolization is relatively low.[500,506-508] Consensus amongst Panel members is that arterially directed catheter therapy and, in particular, yttrium-90 microsphere selective internal radiation is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.

Tumor Ablation

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,[509,510] or for patients with resectable disease that can be ablated with sufficient margins and within the concept of the "test of time."[465] Ablative techniques include radiofrequency ablation (RFA),[464,511] microwave ablation (MWA), cryoablation, and electro-coagulation (irreversible electroporation).[512] 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.[464,511,513-515] More recent data describe outcomes of MWA that have been superior to RFA, mostly because of the ability of MWA to overcome the limitations of RFA and, in particular, those related to the heat sink phenomenon and the inability to completely ablate tumors when located near a blood vessel.[516]

A prospective cohort study investigated patient OS when treating potentially resectable CRC liver metastasis with stereotactic MWA (SMWA) as opposed to hepatic resection.[517] Three-year OS rates were 78% for SMWA versus 76% for resection ($P = .861$). Estimated 5-year OS rates were 56% and 58%, respectively. Overall and major complications were lower after SMWA ($P < .01$), although hepatic retreatments were more frequent (percentage increase 78%, $P < .01$). This supports the use of ablation in selected patients with small resectable CRC liver metastases.

COLLISION is a randomized phase III trial comparing thermal ablation to resection of CRC liver metastases. According to an abstract presentation of data from the COLLISON trial, thermal ablation was shown to be

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noninferior to liver resection in terms of local and distant PFS as well as OS.[518] Thermal ablation showed lower rates of AEs, lower procedure-related mortality, and a shorter median length of hospitalization. Based on these results, thermal ablation should be considered a valid and potentially less invasive alternative for treatment of small-size (≤3 cm) CRC liver metastases.

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.[519] 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 RCT showed that OS was improved in the combined modality arm (HR, 0.58; 95% CI, 0.38–0.88; *P* = .01), with a 3-, 5-, and 8-year OS of 56.9%, 43.1%, and 35.9% for the combined modality arm compared to 55.2%, 30.3%, and 8.9% for the chemotherapy alone arm.[466] This study documented a long-term survival benefit for patients receiving RFA in addition to chemotherapy compared to those treated by chemotherapy only. A 2018 meta-analysis compared RFA and MWA to systemic chemotherapy and to partial hepatectomy in the treatment of CRC liver metastases and indicated that chemotherapy alone is no longer justified when metastases are amenable to thermal ablation.[520] Furthermore, it demonstrated that there was no difference in terms of local tumor control and OS between limited liver resection and MWA.

Data on ablative techniques other than RFA are growing.[510,521-528] However, in a comparison of RFA with MWA, outcomes were similar with no local tumor progression for metastases ablated with margins >10 mm (A0) and a relatively better control of perivascular tumors with the use of MWA (*P* = .021).[528] Similarly, two 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.[463,464,529] In fact, more recent data demonstrated that with confirmation of ablative margins, local tumor control after MWA can be >93%, which compares favorably with historic data for limited metastasectomy.[468,530] Several publications have indicated that the significance of margin creation is particularly important for *RAS*-mutant metastases.[531-533] Recent prospective[467] and retrospective[534] trials have also indicated the superiority of intraprocedural margin assessment in improving local tumor control of thermal ablation when treating CRC liver metastases. The ongoing ACCLAIM trial (NCT05265169) is an international multicenter single-arm phase II/III of microwave ablation which mandates intraprocedural 3D margin assessments and immediate reablation when margins are <5 mm with the aim to provide local tumor control rates to over 90%.

Regarding pulmonary ablation, a large prospective database of two French cancer centers that enrolled 566 consecutive patients with 1037 lung metastases (the majority colorectal in origin) received initial treatment with RFA and 136 patients (24%) underwent repeat RFA.[535] 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. MWA has been used increasingly within the latest years with a report indicating no local progression for small tumors ablated with margins of ≥5 mm.[536] The major complication rate within this database study was 13% with 75% of these including pneumothoraces requiring prolonged hospitalization.

A multicenter, prospective phase II study (SOLSTICE) included 128 patients with 224 metastatic lung tumors that were targeted by pulmonary cryoablation.[537] 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%, although 26% of patients on this study had a pneumothorax requiring pleural catheter placement.

The ECLIPSE prospective, single-arm study aimed to evaluate the feasibility and efficacy of cryoablation for local tumor control in patients with pulmonary metastatic disease with 5 years of follow-up.[538] The cohort included patients with 1 to 5 metastatic lung tumors, each with a diameter ≤3.5 cm. The primary endpoint was local tumor control, both per tumor and per patient; secondary endpoints included cancer-specific survival, OS, and quality of life. Overall local tumor control rates at 3 and 5 years were 87.9% and 79.2% per tumor and 83.3% and 75.0% per patient, respectively. DSS was 74.8% at 3 years and 55.3% at 5 years, and OS was 63.2% at 3 years and 46.7% at 5 years. Patient quality-of-life scores did not reach statistical significance.

An emergent indication for ablation is the discontinuation of chemotherapy while controlling oligometastatic pulmonary disease.[536,539] The median chemotherapy-free survival (time interval between ablation and resuming chemotherapy or death without chemotherapy) was 12.2 months. Patients with no extrapulmonary metastases had a longer median chemotherapy-free survival compared to those without (20.9 vs. 9.2 months).[539]

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. Results from the ORCHESTRA trial were recently reported, which was a randomized phase III trial investigating the addition of tumor debulking to first-line palliative systemic therapy in patients with multisite mCRC.[540] The study included one third of patients with peritoneal disease, and tumor debulking was defined as addressing ≥80% of metastatic disease with any combination of resection, radiation, and/or thermal ablation. No benefit in OS was observed with the addition of tumor debulking to systemic therapy alone (30.0 months with tumor debulking vs. 27.5 months with systemic therapy alone; HR, 0.88; 95% CI, 0.70–1.10; *P* = .225).

Liver- or Lung-Directed External Beam Radiation

EBRT to metastatic sites can be considered in selected cases in which the patient has a limited number of metastases, including the liver or lung or other select locations; or if 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,[422,471,472,541] and IMRT, which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to healthy tissue.[416,542-545]

While CRC has been shown to be a relatively radioresistant histology,[546,547] multiple studies have demonstrated effective local control with minimal toxicity using SBRT in the treatment of liver[542,548,549] and lung[550-555] metastases. In addition, data on the benefit of using SBRT to treat multiple metastatic lesions are emerging. SABR-COMET was a randomized phase II trial with multiple cancer types, including a small number of CRC origin, and ≤5 metastatic lesions in different organs that demonstrated an improvement in OS with the addition of SBRT to standard-of-care treatment.[556] An extended long-term analysis (5–10 years) of the SABR-COMET study showed durable improvements in OS and PFS with the addition of SBRT, with 21.3% of patients achieving >5 years without disease recurrence.[557] In patients with liver- or lung-limited disease that is not amenable to complete resection or ablation, SBRT may

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be considered as local therapy in centers with expertise. SBRT for the treatment of extrahepatic or extrapulmonary 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.[122,558] 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*) with palliative surgery or stenting if needed for obstruction or impending obstruction.[559-561] If an R0 resection can be achieved, however, surgical resection of isolated peritoneal disease may be considered at experienced centers. The Panel cautions that the use of bevacizumab in patients with colon or rectal stents is associated with a possible increased risk of bowel perforation.[562,563]

Cytoreductive Debulking with Hyperthermic Intraperitoneal Chemotherapy

Several surgical series and retrospective analyses have addressed the role of CRS (ie, peritoneal stripping surgery) in combination with perioperative HIPEC for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.[564-573] In an RCT of this approach, Verwaal et al randomized 105 patients to either standard therapy (5-FU/LV with or without palliative surgery) or to aggressive CRS and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients.[574] OS was 12.6 months in the standard arm and 22.3 months in the HIPEC arm (P = .032). However, treatment-related morbidity was high, and the mortality was 8% in the HIPEC group, mostly related to bowel leakage. In addition, long-term survival does not seem to be improved by this treatment as seen by follow-up results.[575] Importantly, this trial was performed without oxaliplatin, irinotecan, or molecularly targeted agents. Some experts have argued that the OS difference seen might have been much smaller if these agents had been used (ie, the control group would have had better outcomes).[576]

Other criticisms of the Verwaal trial have been published.[576] One important point is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group that has seen greater benefit with the CRS/HIPEC approach.[565,569,577,578] A retrospective multicenter cohort study reported median OS times of 30 and 77 months for patients with peritoneal carcinomatosis of colorectal origin and appendiceal origin, respectively, treated with HIPEC or with CRS and early postoperative intraperitoneal chemotherapy.[569] The median OS time for patients with PMP, which arises from mucinous appendiceal carcinomas, was not reached (NR) at the time of publication. A retrospective international registry study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with PMP from mucinous appendiceal carcinomas treated with CRS and HIPEC.[225] HIPEC was not shown to be associated with improvements in OS in this study, whereas completeness of cytoreduction was. Thus, for patients with PMP, optimal treatment is still unclear.[579]

More recently, the randomized, phase III, multicenter PRODIGE 7 trial reported results from 265 patients with colorectal peritoneal carcinomatosis who received standard treatment of systemic chemotherapy before and/or after CRS and were randomized to standard treatment plus HIPEC with oxaliplatin or standard treatment alone.[580] This study reported no significant difference in OS, with a median OS of 41.7 months in the HIPEC arm versus 41.2 months in the non-HIPEC arm. While the morbidity rates did not differ significantly at 30 days, the 60-day grade 3–5 morbidity rate was significantly higher in the HIPEC arm (26% vs. 16%; P = .035). Another randomized, phase III study, PROPHYLOCHIP-PRODIGE 15, reported similar results to PRODIGE 7 in that the group randomized to second-look surgery plus HIPEC showed

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worse 3-year DFS compared to surveillance (44% vs. 53%) for patients with mCRC and synchronous and localized peritoneal metastases removed during tumor resection, resected ovarian metastases, or a perforated tumor.[581] Forty-one percent of patients in the second-look surgery plus HIPEC group reported grade 3 or 4 complications.

The individual components of the HIPEC approach have not been well studied. In fact, studies in rats have suggested that the hyperthermia component of the treatment is irrelevant.[582] Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.[566] In addition, a randomized trial compared systemic 5-FU/oxaliplatin to CRS and intraperitoneal 5-FU without heat.[583] Although terminated prematurely because of poor accrual, analysis suggested that the CRS plus HIPEC approach may have been superior to the systemic therapy approach (2-year OS, 54% vs. 38%; *P* = .04) for patients with resectable colorectal peritoneal metastases.

In addition, significant morbidity and mortality are associated with this procedure. A 2006 meta-analysis of two RCTs and 12 other studies reported morbidity rates ranging from 23% to 44% and mortality rates ranging from 0% to 12%.[573] Furthermore, recurrences after the procedure are very common.[584] Whereas the risks are reportedly decreasing with time (ie, more recent studies report 1%–5% mortality rates at centers of excellence[570,576]), the benefits of the approach have not been definitively shown, and HIPEC remains very controversial.[585-588]

There are also limited data to inform the use of perioperative systemic therapy before or after resection of peritoneal metastases. An observational cohort study from the Netherlands Cancer Registry used data from 393 patients with isolated synchronous CRC peritoneal metastases to investigate the potential benefit of adjuvant chemotherapy.[589] This study found that following complete CRS and HIPEC, adjuvant systemic chemotherapy was associated with improved median OS compared to active surveillance (39.2 vs. 24.8 months; adjusted HR, 0.66; 95% CI, 0.49–0.88; *P* = .006). The CAIRO6 study is a phase II randomized, parallel-group Dutch trial of 79 patients with isolated resectable peritoneal CRC metastases who were randomized to CRS with HIPEC, plus or minus perioperative systemic therapy.[590] Comparable proportions of patients on the study had macroscopic complete CRS/HIPEC (89% vs. 86%) and major postoperative morbidity was 22% versus 33% between the perioperative systemic therapy and control arms, respectively. Grade ≥3 systemic therapy-related toxicity was observed in 35% of patients and ORRs were 28% (radiologic response) and 38% (major pathologic response) following neoadjuvant therapy.

The Panel currently believes that complete CRS and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. However, the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach very controversial.

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 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.[591-594] 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.[595] It should be noted that size alone is rarely a contraindication to resection of a tumor. Resectability differs

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fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease.[596] 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.[420,591]

The role of PET/CT in determining resectability of patients with mCRC is discussed in *Workup and Management of Synchronous Metastatic Disease*, 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 systemic therapy 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 based on a favorable response to therapy, as the probability of complete eradication of a metastatic deposit by systemic therapy 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 disease that has had significant response to conversion therapy can be converted from unresectable to resectable disease status.[597]

Any active metastatic systemic regimen can be used in an attempt to convert a patient's unresectable disease status to a resectable disease 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.[598-602] 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.[598,599,602,603] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient's disease becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed below.

In the 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.[593] 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,[421] 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 metastases 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.[430] The 5-year DFS rate for these 138 patients was 22%. In addition, results from a 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.[604] The median OS time in this group was 42.4 months.

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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.[605,606] 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[605]; and 4% versus 10%, *P* = .08 in the Gastrointestinal Committee of the HORG trial.[606] 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).[607]

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 MSI-H/dMMR or *POLE/POLD1* mutation-positive disease as an alternative to chemotherapy-containing regimens. See the following sections for data supporting these treatment approaches.

When systemic therapy is planned for patients with initially unresectable disease, the Panel recommends that a surgical re-evaluation be planned 2 months after initiation of therapy, and that those patients who continue to receive systemic therapy undergo surgical re-evaluation every 2 months thereafter.[602,608-610] Reported risks associated with chemotherapy include the potential for development of liver sinusoidal dilatation, steatosis, or steatohepatitis.[598,603,611] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient's disease becomes resectable.

Neoadjuvant Bevacizumab for Metastatic Disease

The efficacy of bevacizumab in combination with chemotherapy in the treatment of unresectable metastatic disease (see *Systemic Therapy for Advanced or Metastatic Disease*) 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. 3.4%, respectively; *P* = .28).[612] 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 in those receiving CAPEOX alone after resection of liver metastases, but no conclusions could be drawn regarding the primary endpoint of DFS.[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.[614,615] Thus, 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 setting are mixed. On one hand, a 1400-patient, randomized, double-blind, placebo-controlled trial of CAPEOX or FOLFOX with or without bevacizumab showed absolutely 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.[616] On the other hand, the randomized BECOME trial of 241 patients with initially

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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.[617] 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.[618] 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. The randomized, phase III CAIRO5 study also compared FOLFOXIRI to chemotherapy doublets, when combined with bevacizumab for patients with initially unresectable right-sided tumors in one of its cohorts.[619] This study found that the group treated with FOLFOXIRI in combination with bevacizumab had a longer PFS compared with the doublets (10.6 months vs. 9.0 months; $P = .032$). 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.[620]

The Panel recommends against the use of bevacizumab as neoadjuvant treatment of patients with resectable metastatic colon 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[621]) 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-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.[622] 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 tumors 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.[623] Another RCT compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable CRC metastatic to the liver.[624] The primary endpoint was the rate of conversion to resectability based on evaluation by a multidisciplinary team. After evaluation, 20 of 70 (29%) patients in the cetuximab arm and 9 of 68 (13%) patients 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 phase III CAIRO5 trial included a cohort of patients with initially unresectable *RAS*/*BRAF* wild-type, left-sided tumors who were randomized to receive either bevacizumab or panitumumab in combination with a chemotherapy doublet (FOLFOX or FOLFIRI).[619] While these arms

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of the study were closed prematurely for futility, collected results showed no significant difference between the two arms.

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.[625] 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 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.[626]

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.[627,628] 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 these data, the NCCN Panel does not recommend the combination of FOLFIRINOX with cetuximab or panitumumab for unresectable mCRC, while the FOLFIRI or FOLFOX combinations are included as recommendations within the same setting.

Neoadjuvant Checkpoint Inhibitors for Metastatic Disease

While there is a lack of data in this setting, the Panel considers pembrolizumab, dostarlimab-gxly, or nivolumab, as a monotherapy or in combination with ipilimumab, as preferred options for neoadjuvant therapy of resectable dMMR/MSI-H or *POLE/POLD1* mutation-positive 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 CRC or mCRC.[629-631] 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.[632] 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.[633] Additional meta-analyses have also not observed a

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statistically significant OS benefit with the addition of adjuvant chemotherapy in resectable mCRC.[634-636]

The choice of regimen in the perioperative setting depends on several factors, including the patient's history of treatment with chemotherapy or immunotherapy and the response rates and safety/toxicity issues associated with the regimens, as outlined in the guidelines. Biologics are not recommended in the perioperative metastatic setting, with the exception of initial therapy in patients with unresectable disease that may be converted to a resectable state or checkpoint inhibitor immunotherapy for dMMR/MSI-H or *POLE/POLD1* mutation-positive disease.

The phase III EORTC 40983 study, evaluating use of perioperative FOLFOX (6 cycles before and 6 cycles after surgery) for patients with resectable liver metastases, showed absolute improvements in 3-year PFS of 8.1% ($P = .041$) and 9.2% ($P = .025$) for all eligible patients and all patients with resected disease, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[637] 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 59% of the patients in the chemotherapy arm.[638] 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.[639] 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 FOLFOX or CAPEOX; patients with prior oxaliplatin received FOLFIRI).[640] 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; $P < .048$). A subsequent analysis of New EPOC, carried out 5 years after the last patient was recruited, reported a reduced median OS for chemotherapy plus cetuximab compared to chemotherapy alone (55.4 vs. 81.0 months; HR, 1.45; 95% CI, 1.02–2.05; $P = .036$).[641] 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.[642,643]

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.[423,644,645] In fact, results from 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.[645-647] 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

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developed that optimizes exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.[598]

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.[598-602] 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.

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 lines of therapy, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[648] For example, if oxaliplatin is administered as part of an initial treatment regimen but is discontinued after ≤12 weeks 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 disease exhibiting a tumor response or for disease characterized as stable or progressive; and 2) plans for adjusting therapy for patients who experience certain toxicities. For example, decisions related to therapeutic choices after first progression of disease should be based, 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 and the performance status of the patient.

Sequencing and Timing of Therapies

Few studies have addressed the sequencing of therapies in advanced metastatic disease. Prior to the use of targeted agents, several studies randomized patients to different schedules.[649-652] The data from these trials suggest that there is little difference in clinical outcomes if intensive therapy is given in first line or if less intensive therapy is given first followed by more intensive combinations.

Results from a randomized study to evaluate the efficacy of FOLFIRI and FOLFOX regimens as initial therapy and to determine the effect of using sequential therapy with the alternate regimen after first progression showed neither sequence to be significantly superior with respect to PFS or median OS.[652] A combined analysis of data from seven phase III clinical trials in advanced CRC provided support for a correlation between an increase in median survival and administration of all three cytotoxic agents (ie, 5-FU/LV, oxaliplatin, irinotecan) at some point in the continuum of care.[653] Furthermore, OS was not found to be associated with the order in which these drugs were received.

A study of 6286 patients from nine trials that evaluated the benefits and risks associated with intensive first-line treatment in the setting of mCRC treatment showed similar therapeutic efficacy for patients with a performance status of 2 or 1 or less as compared with control groups. However, the risks of certain GI toxicities were significantly increased for patients with a performance status of 2.[654]

The phase III C-cubed study compared upfront combination therapy with a fluoropyrimidine and oxaliplatin with bevacizumab to sequential treatment

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using a fluoropyrimidine with bevacizumab followed by the addition of oxaliplatin at first progression.[655] Sequential treatment showed superiority in terms of time to failure of strategy (15.2 vs. 7.8 months; $P < .001$); however, median OS was similar between the sequential and combination arms (27.5 vs. 27.0 months; HR, 0.92; 95% CI, 0.66–1.28; $P = .61$) and ORR was improved in the combination arm compared to the sequential arm (51.7% vs. 33.1%; $P = .002$).

Overall, the Panel does not consider one regimen to be preferable over another as initial therapy for metastatic disease. The Panel also does not indicate a preference for biologic agents used as part of initial therapy (ie, bevacizumab, cetuximab, panitumumab, none). See *First-Line Systemic Therapy*, below, for more information on data supporting bevacizumab versus cetuximab or panitumumab as part of the initial therapy regimen.

Therapy Retreatment/Rechallenge

Due to few efficacious options in later lines of therapy, there has been considerable interest in the possibility of retreating with a systemic therapy used during an earlier line of treatment. Most studies that have reported on this approach have been retrospective, detailing institutional experiences retreating with chemotherapeutics[656-658] or targeted therapies (eg, EGFR inhibitors)[656,659-663] and concluded that a retreatment approach was feasible, based on response and/or toxicity data. However, these studies were mainly small and did not differentiate between patients who had therapy stopped due to progression compared to other reasons, limiting the quality of these data. The randomized phase III FIRE-4 trial seeks to address this question by comparing first-line treatment efficacy of FOLFIRI in combination with cetuximab given using the standard dosing schedule compared to early switch maintenance.[664] An abstract reporting preliminary results from this trial has shown that application of one initial cycle with chemotherapy alone did not influence the efficacy of first-line FOLFIRI plus cetuximab.

Therefore, until stronger data become available, the Panel agrees that for patients who had therapy stopped for a reason other than progression (eg, use as adjuvant therapy, cumulative toxicity, treatment break, patient preference), rechallenge with this therapy would be an option. However, based on the current lack of evidence, retreatment with a therapy following progression on that regimen is not recommended.

Maintenance Therapy

Interest in the use of a maintenance therapy approach after first-line treatment of unresectable mCRC is growing. In general, this approach involves intensive first-line therapy, followed by less intensive therapy until progression in patients whose disease had a good response to initial treatment.

The CAIRO3 study was an open-label, phase III, multicenter RCT assessing maintenance therapy with capecitabine/bevacizumab versus observation in 558 patients with mCRC and with stable disease or better after first-line treatment with CAPEOX/bevacizumab.[665] Following first progression, both groups were to receive CAPEOX/bevacizumab again until second progression (PFS2). After a median follow-up of 48 months, the primary endpoint of PFS2 was significantly better in the maintenance arm (8.5 vs. 11.7 months; HR, 0.67; 95% CI, 0.56–0.81; $P < .0001$), with 54% of patients overall receiving CAPEOX/bevacizumab the second time. Quality of life was not affected by maintenance therapy, although 23% of patients in the maintenance group developed hand-foot syndrome during the maintenance period. A non-significant trend towards improved OS was seen in the maintenance arm (18.1 vs. 21.6 months; adjusted HR, 0.83; 95% CI, 0.68–1.01; $P = .06$). A molecular subgroup analysis of CAIRO3 showed that the capecitabine/bevacizumab maintenance strategy was effective across all mutational subgroups (*RAS/BRAF* wild-type, *RAS* mutant, and *BRAF* V600E), although the benefit of maintenance was most

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pronounced for patients with *RAS/BRAF* wild-type or *BRAF* V600E mutation-positive tumors.[666]

The AIO 0207 trial was an open-label, noninferiority, randomized phase III trial that randomized 472 patients whose disease did not progress on induction FOLFOX/bevacizumab or CAPEOX/bevacizumab to no maintenance therapy or to maintenance therapy with fluoropyrimidine/bevacizumab or with bevacizumab alone.[667] The planned protocol included re-introduction of primary therapy after first progression. The primary endpoint was time to failure of strategy, defined as time from randomization to second progression, death, and initiation of treatment with a new drug. After a medium follow-up of 17 months, the median time to failure of strategy was 6.4 months (95% CI, 4.8–7.6) for the no treatment group, 6.9 months (95% CI, 6.1–8.5) for the fluoropyrimidine/bevacizumab group, and 6.1 months (95% CI, 5.3–7.4) for the bevacizumab alone group. Compared with fluoropyrimidine/bevacizumab, bevacizumab alone was noninferior, whereas the absence of maintenance therapy was not. However, only about one third of trial participants received the re-induction therapy, thus limiting the interpretation of results. OS was one of the secondary endpoints of the trial, and no relevant difference was seen between the arms.

PRODIGE 9 was a randomized phase III trial that investigated the effect of bevacizumab maintenance compared to no treatment during chemotherapy-free intervals following induction chemotherapy with 12 cycles of FOLFIRI plus bevacizumab. Median tumor control duration was 15 months in both groups. PFS was 9.2 and 8.9 months and OS was 21.7 and 22.0 months for bevacizumab maintenance and no treatment, respectively. Therefore, this study concluded that bevacizumab maintenance did not improve outcomes.[668]

The randomized phase III noninferiority SAKK 41/06 trial addressed the question of continuing bevacizumab alone as maintenance therapy after chemotherapy plus bevacizumab in first-line therapy.[669] The primary endpoint of time to progression was not met (4.1 months for bevacizumab continuation vs. 2.9 months for no continuation; HR, 0.74; 95% CI, 0.58–0.96), and no difference in OS was observed (25.4 vs. 23.8 months; HR, 0.83; 95% CI, 0.63–1.1; $P = .2$). Therefore, noninferiority for treatment holidays versus bevacizumab maintenance therapy was not demonstrated.

The GERCOR DREAM trial (OPTIMOX3) was an international, open-label, phase III study that randomized patients with mCRC without disease progression on bevacizumab-based therapy to maintenance therapy with bevacizumab or bevacizumab plus erlotinib.[670] ITT analysis revealed an advantage in PFS (5.4 vs. 4.9 months; stratified HR, 0.81; 95% CI, 0.66–1.01; $P = .06$) and OS (24.9 vs. 22.1 months; stratified HR, 0.79; 95% CI, 0.63–0.99; $P = .04$) with combination therapy. A smaller randomized trial, however, showed no difference in PFS or OS between bevacizumab and bevacizumab/erlotinib maintenance therapy in patients with *KRAS* wild-type tumors.[671] A meta-analysis identified three randomized trials (682 patients) and concluded that maintenance therapy with bevacizumab/erlotinib significantly increases OS and PFS, with manageable toxicity.[672]

Another phase III trial investigated the role of capecitabine in the maintenance phase, after initial treatment with FOLFOX or CAPEOX.[673] PFS, the primary endpoint, was 6.4 months in the capecitabine maintenance group and 3.4 months in the group that was observed until progression (HR, 0.54; 95% CI, 0.42–0.70; $P < .001$). A non-statistically significant difference in the median OS was also seen (HR, 0.85; 95% CI, 0.64–1.11; $P = .2247$). Toxicities associated with the capecitabine maintenance therapy were acceptable.

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A systematic review and network meta-analysis of 12 randomized clinical trials comprising 5540 patients with mCRC concluded that a maintenance strategy with a fluoropyrimidine, with or without bevacizumab, led to a significant improvement in PFS, but not in OS.[674] Given the PFS benefit seen in some studies, but the probable lack of OS benefit, maintenance therapy may be discussed as part of shared decision-making with patients, with observation as an acceptable alternative.

Biosimilars

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing biologic therapy. Several biosimilars are now available in the U.S. market, including biosimilars to two biologics that are recommended in the NCCN Guidelines for Colon Cancer: bevacizumab and trastuzumab. The NCCN Panel has agreed that an U.S. Food and Drug Administration (FDA)-approved biosimilar may be substituted for either bevacizumab or trastuzumab wherever these therapies are recommended within the NCCN Guidelines for Colon Cancer.

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 an NGS panel, with NGS being preferred. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as *NTRK* and *RET* fusions and may be carried out using either a tissue or blood-based (eg, liquid) biopsy.[675] Specific information about each of these biomarkers may be found in the sections below.

Repeat molecular testing should not be performed after standard cytotoxic chemotherapy as significant molecular changes are rarely observed. For patients with tumors initially harboring molecular alterations eligible for targeted therapy, repeat testing may be considered to assess for a change in the molecular profile that may guide future targeted therapy decisions. A study of paired plasma samples from patients with *RAS/BRAF/EGFR* wild-type mCRC who received EGFR inhibitors compared to those who received combination cytotoxic chemotherapy found that those who received the targeted therapy were more likely to develop acquired mutations (46%) than those who received cytotoxic chemotherapy (9%).[676]

KRAS and NRAS Mutations

The MAPK pathway of RAS/RAF/MEK/ERK is downstream of EGFR; mutations in components of this pathway are now established to be strong negative predictive markers, essentially precluding efficacy of these therapies. A sizable body of literature has shown that tumors with a mutation in exons 2, 3, or 4 of either the *KRAS* or *NRAS* genes are essentially insensitive to cetuximab or panitumumab therapy.[677-687] The Panel therefore strongly recommends *RAS* (*KRAS/NRAS)* genotyping of tumor (either primary tumor or metastasis) in all patients with mCRC. Patients with known *KRAS*- or *NRAS*-mutant tumors should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. An exception to this is when cetuximab or panitumumab is given in combination with sotorasib or adagrasib for tumors with *KRAS* G12C mutation (see *Systemic Therapy Options for KRAS G12C Mutation-Positive Disease in the Non–First-Line Setting,* below*)*. ASCO released a Provisional Clinical Opinion Update on extended *RAS* testing in patients with mCRC that is consistent with the NCCN Panel's recommendations.[688] A guideline on molecular biomarkers for CRC developed by the ASCP, CAP, AMP, and

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ASCO also recommends *RAS* testing consistent with the NCCN recommendations.[30]

Studies have reported that around 40% of mCRC have *KRAS* mutations in codons 12 and 13.[689,690] Of these mutations, *KRAS* G12D was mostly commonly found (36%), followed by G12V (21.8%), and G13D (18.8%).[690] *KRAS* G12C has been reported in around 17% of *KRAS*-mutated mCRC cases.[691] Results are mixed as far as the prognostic value of *KRAS* mutations. In the Alliance N0147 trial, patients with *KRAS* exon 2-mutant tumors experienced a shorter DFS than patients with tumors without such mutations.[692] Other studies have also reported worse outcomes with *KRAS* mutations.[689,693,694]

In the AGITG MAX study, 10% of patients with tumors with wild-type *KRAS* exon 2 had mutations in *KRAS* exons 3 or 4 or in *NRAS* exons 2, 3, and 4.[695] In the PRIME trial, 17% of 641 patients with tumors without *KRAS* exon 2 mutations were found to have mutations in exons 3 and 4 of *KRAS* or mutations in exons 2, 3, and 4 of *NRAS*. A predefined retrospective subset analysis of data from PRIME revealed that PFS (HR, 1.31; 95% CI, 1.07–1.60; $P = .008$) and OS (HR, 1.21; 95% CI, 1.01–1.45; $P = .04$) were decreased in patients with tumors with any *KRAS* or *NRAS* mutation who received panitumumab plus FOLFOX compared to those who received FOLFOX alone.[686] These results show that panitumumab does not benefit patients with *KRAS*- or *NRAS*-mutant tumors and may even have a detrimental effect in these patients.

Updated analysis of the FIRE-3 trial (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-Line Therapy,* below) has been published.[696] When all *RAS* (*KRAS/NRAS*) mutations were considered, PFS was significantly worse in patients with *RAS*-mutant tumors receiving FOLFIRI plus cetuximab than in patients with *RAS*-mutant tumors receiving FOLFIRI plus bevacizumab (6.1 vs. 12.2 months; $P = .004$). On the other hand, patients with *KRAS/NRAS* wild-type tumors showed no difference in PFS between the regimens (10.4 vs. 10.2 months; $P = .54$). This result indicates that cetuximab likely has a detrimental effect in patients with *KRAS*- or *NRAS*-mutant tumors. The FDA indication for panitumumab was, therefore, updated to state that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* mutation-positive disease in combination with oxaliplatin-based chemotherapy.[697]

A retrospective study by De Roock et al[698] raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive of non-response. Another retrospective study showed similar results.[684] However, a later retrospective analysis of three randomized controlled phase III trials concluded that *KRAS* G13D-mutant tumors were unlikely to respond to panitumumab.[699] Results from a prospective, phase II, single-arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory mCRC whose tumors contained *KRAS* G13D mutations.[700] The primary endpoint of 4-month progression-free rate was not met (25%), and no responses were seen. Preliminary results of the AGITG phase II ICE CREAM trial also did not see a benefit of cetuximab monotherapy in patients with *KRAS* G13D-mutant tumors.[701] However, partial responses were reported after treatment with irinotecan plus cetuximab in 9% of this irinotecan-refractory population. A meta-analysis of eight RCTs came to the same conclusion: that tumors with *KRAS* G13D mutations are no more likely to respond to EGFR inhibitors than tumors with other *KRAS* mutations.[702]

The recommendation for *RAS* testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *RAS* status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non–time-sensitive manner and the patient and provider can discuss the implications of a *RAS* mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the

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management of stage I, II, or III disease, *RAS* genotyping of CRCs at these earlier stages is not recommended.

KRAS mutations are early events in CRC formation, and therefore a very tight correlation exists between mutation status in the primary tumor and the metastases.[703-705] For this reason, *RAS* genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *RAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable.

BRAF V600E Mutations

Although mutations in *RAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *RAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *RAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of CRCs are characterized by a specific mutation in the *BRAF* gene (V600E).[706,707] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *RAS* mutations.[706-708] Activation of the protein product of the non-mutated *BRAF* gene occurs downstream of the activated KRAS protein in the EGFR pathway. The mutated BRAF protein product is believed to be constitutively active,[709-711] thereby putatively bypassing inhibition of EGFR by cetuximab or panitumumab.

Limited data from unplanned retrospective subset analyses of patients with mCRC treated in the first-line setting suggest that although a *BRAF* V600E mutation confers a poor prognosis regardless of treatment, patients with disease characterized by this mutation may receive some benefit from the addition of cetuximab to front-line therapy.[707,712] A planned subset analysis of the PRIME trial also found that mutations in *BRAF* indicated a poor prognosis but were not predictive of benefit to panitumumab added to FOLFOX in first-line treatment of mCRC.[686] On the other hand, results from the randomized phase III Medical Research Council (MRC) COIN trial suggest that cetuximab may have no effect or even a detrimental effect in patients with *BRAF*-mutated tumors treated with CAPEOX or FOLFOX in the first-line setting.[708]

In subsequent lines of therapy, retrospective evidence suggests that mutated *BRAF* is a marker of resistance to anti-EGFR therapy in the non–first-line setting of metastatic disease.[713-715] A retrospective study of 773 primary tumor samples from patients with chemotherapy-refractory disease showed that *BRAF* mutations conferred a significantly lower response rate to cetuximab (2/24; 8.3%) compared with tumors with wild-type *BRAF* (124/326; 38.0%; $P = .0012$).[716] Furthermore, data from the multicenter randomized controlled PICCOLO trial are consistent with this conclusion, with a suggestion of harm seen for the addition of panitumumab to irinotecan in the non–first-line setting in the small subset of patients with *BRAF*-mutant tumors.[717]

A meta-analysis published in 2015 identified nine phase III trials and one phase II trial that compared cetuximab or panitumumab with standard therapy or best supportive care including 463 patients with metastatic colorectal tumors with *BRAF* mutations (first-line, second-line, or refractory settings).[718] The addition of an EGFR inhibitor did not improve PFS (HR, 0.88; 95% CI, 0.67–1.14; $P = .33$), OS (HR, 0.91; 95% CI, 0.62–1.34; $P = .63$), or ORR (RR, 1.31; 95% CI, 0.83–2.08; $P = .25$) compared with control arms. Similarly, another meta-analysis identified seven RCTs and found that cetuximab and panitumumab did not improve PFS (HR, 0.86; 95% CI, 0.61–1.21) or OS (HR, 0.97; 95% CI, 0.67–1.41) in patients with *BRAF*-mutant tumors.[719]

While the evidence suggests that *BRAF* V600E mutation makes response to panitumumab or cetuximab unlikely, the impact of other *BRAF* mutations was less clear. A multicenter pooled study included 40 patients with mCRC harboring oncogenic non-V600 *BRAF* mutations (30% class 2

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mutations, 70% class 3) who received anti-EGFR antibody treatment.[720] Of the patients with class 2 *BRAF* mutations, only 1 out of 12 had disease response to anti-EGFR therapy, compared to 50% of those with class 3 mutations (P = .02). Therefore, it is reasonable to consider anti-EGFR therapy for patients with *BRAF* mutations other than V600E, especially for class 3 mutations.

In addition to its role as a predictive marker for *BRAF*-targeted therapy, it is clear that mutations in *BRAF* are a strong prognostic marker.[339,707,708,721-726] A prospective analysis of tissues from patients with stage II and III colon cancer enrolled in the PETACC-3 trial showed that the *BRAF* mutation is prognostic for OS in patients with MSI-L or MSS tumors (HR, 2.2; 95% CI, 1.4–3.4; P = .0003).[339] Moreover, an updated analysis of the CRYSTAL trial showed that patients with metastatic colorectal tumors carrying a *BRAF* mutation have a worse prognosis than those with the wild-type gene.[707] Additionally, *BRAF* mutation status predicted OS in the AGITG MAX trial, with an HR of 0.49 (95% CI, 0.33–0.73; P = .001).[722] The OS for patients with *BRAF*-mutant tumors in the COIN trial was 8.8 months, while those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 months and 20.1 months, respectively.[708] In addition, a secondary analysis of the N0147 and C-08 trials found that *BRAF* mutations were significantly associated with worse survival after recurrence of resected stage III colon cancer, with a stronger association for primary tumors located in the distal colon.[727] Results from a systematic review and meta-analysis of 21 studies, including 9885 patients, suggest that *BRAF* mutation may accompany specific high-risk clinicopathologic characteristics.[728] In particular, an association was observed between *BRAF* mutation and proximal tumor location (OR, 5.22; 95% CI, 3.80–7.17; P < .001), T4 tumors (OR, 1.76; 95% CI, 1.16–2.66; P = .007), and poor differentiation (OR, 3.82; 95% CI, 2.71–5.36; P < .001).

Overall, the Panel believes that evidence increasingly suggests that *BRAF* V600E mutation makes response to panitumumab or cetuximab, as single agents or in combination with cytotoxic chemotherapy, highly unlikely, unless given as part of a BRAF inhibitor regimen (see *Encorafenib Plus Cetuximab or Panitumumab for BRAF V600E Mutation-Positive Disease in the Non–First-Line Setting*, below). The Panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[729]) at diagnosis of stage IV disease. If a tumor is determined to be both MSI-H/dMMR and *BRAF* V600E, first-line therapy with a checkpoint inhibitor would generally be preferred and a BRAF inhibitor regimen could be used in a later line of therapy, as directed in the algorithm.

HER2 Amplification/Overexpression

HER2 is a member of the same family of signaling kinase receptors as EGFR and has been successfully targeted in breast cancer in both the advanced and adjuvant settings. HER2 is rarely amplified/overexpressed in CRC (approximately 3% overall), but the prevalence is higher in *RAS/BRAF*–wild type tumors (reported at 5%–14%).[730,731] Specific molecular diagnostic methods have been proposed for HER2 testing in CRC,[732] and HER2-targeted therapies are now recommended as subsequent therapy options in patients with tumors that have HER2 overexpression (see *Systemic Therapy Options for HER2-Amplified Disease,* below).[730,733] Based on this, the NCCN Guidelines for Colon Cancer recommend testing for HER2 amplifications for all patients with mCRC. More information on HER2 testing methodology can be found in the *Principles of Pathologic and Molecular Review* section of the algorithm.

Evidence does not support a prognostic role of HER2 overexpression.[734] In addition to its role as a predictive marker for HER2-targeted therapy, initial results indicate HER2 amplification/overexpression may be predictive of resistance to EGFR-targeting monoclonal antibodies.[731,735,736]

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For example, in a cohort of 98 patients with *RAS/BRAF*–wild type mCRC, median PFS on therapy without an EGFR inhibitor was similar regardless of HER2 status.[736] However, in therapy with an EGFR inhibitor, the PFS was significantly shorter in those with HER2 amplification compared with those without HER2 amplification (2.8 vs. 8.1 months; HR, 7.05; 95% CI, 3.4–14.9; $P < .001$).

dMMR/MSI-H Status

The percentage of stage IV colorectal tumors characterized as MSI-H or dMMR ranged from 3.5% to 5.0% in clinical trials and was 6.5% in the Nurses' Health Study and Health Professionals Follow-up Study.[340,737,738] dMMR tumors contain thousands of mutations, which can encode mutant proteins with the potential to be recognized and targeted by the immune system. However, programmed death ligands 1 and 2 (PD-L1 and PD-L2) on tumor cells can suppress the immune response by binding to the programmed cell death protein 1 (PD-1) receptor on T-effector cells. This system evolved to protect the host from an unchecked immune response. Many tumors upregulate PD-L1 and thus evade the immune system.[739] It was therefore hypothesized that dMMR tumors may be sensitive to PD-1 inhibitors. Subsequently, this hypothesis was confirmed in clinical trials, leading to the addition of recommendations for checkpoint inhibitors for dMMR/MSI-H disease (see *Checkpoint Inhibitor Immunotherapy for dMMR/MSI-H or POLE/POLD1 Mutation-Positive Disease in the First-Line Setting and in the Non–First-Line Settings,* below). The NCCN Guidelines for Colon Cancer recommend universal MMR or MSI testing for all patients with a personal history of colon or rectal cancer. In addition to its role as a predictive marker for immunotherapy use in the advanced CRC setting, MMR/MSI status can also help to identify individuals with Lynch syndrome (see *Lynch Syndrome*, above), and to inform adjuvant therapy decisions for patients with stage II disease (see *Microsatellite Instability* under *Adjuvant Chemotherapy for Resectable Colon Cancer*, above). It is important to note that there is currently no role for PD-L1 testing in CRC, outside a clinical trial, and that PD-L1 testing is not recommended.

POLE/POLD1 Mutations

The polymerase genes, *POLE* and *POLD1*, encode proteins with proofreading functions that correct mistakes created during DNA replication. Pathologic variants within the endonuclease domain of these proteins results in loss of the proofreading function, leading to subsequent acquisition of downstream mutations.[740,741] Germline pathologic variants of *POLE* or *POLD1* are found in polymerase proofreading-associated polyposis (PPAP), which predisposes patients to colorectal adenomas and carcinomas. Management recommendations for PPAP are described in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric. Somatic *POLE* pathologic variants occur in approximately 2% to 8% of patients with MSS/pMMR CRC while somatic *POLD1* pathologic variants are extremely rare.[740,742]

Similar to dMMR/MSI-H, CRC with *POLE/POLD1* pathologic variants has a more favorable prognosis for stage II/III, likely due to enhanced immune response, although this association may be strongest for stage II disease.[743] Since *POLE/POLD1* pathologic variants also cause a hypermutated phenotype in CRC, similar to dMMR/MSI-H, it was theorized that pMMR CRC with *POLE/POLD1* pathologic variants may also benefit from checkpoint inhibitor therapy.[744] A retrospective analysis of 458 patients with *POLE* mutation-positive tumors tested this.[745] Of the identified *POLE* mutations, 15.0% were pathogenic, 15.9% were benign, and 69.1% were of unknown significance. Eighty-two patients received a PD-1/PD-L1 inhibitor, either as monotherapy or in combination. Compared to those with benign variants, patients with *POLE* pathogenic variants had improved clinical benefit rates (82.4% vs. 30.0%; $P = .013$), improved median PFS (15.1 vs. 2.2 months; $P < .001$), longer OS (29.5 vs. 6.8 months; $P < .001$), and longer treatment duration (15.5 vs. 2.5 months).

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Based on these results, the NCCN Panel recommends that mCRC with functional *POLE/POLD1* pathologic variants should be treated consistently with the recommendations for dMMR/MSI-H disease (see *Checkpoint Inhibitor Immunotherapy for dMMR/MSI-H or POLE/POLD1 Mutation-Positive Disease in the First-Line Setting and the Non–First-Line Settings,* below).

NTRK Fusions

Three *NTRK* genes encode the TRK proteins. TRK expression is primarily in the nervous system where these kinases help to regulate pain, perception of movement/position, appetite, and memory. *NTRK* gene fusions lead to overexpression of the TRK fusion protein, resulting in constitutively active downstream signaling.[746] Studies have estimated that about 0.2% to 1% of CRCs carry *NTRK* gene fusions.[747,748] A study of 2314 CRC specimens, of which 0.35% had *NTRK* fusions, found that *NTRK* fusions were limited to cancers that were wild-type for *KRAS*, *NRAS*, and *BRAF*. Furthermore, a majority of the CRCs harboring *NTRK* fusions were also MMR-deficient.[749] Similarly, in a smaller study that aimed to characterize the molecular and clinical landscape of *ALK*, *ROS1*, and *NTRK* rearranged mCRC, 76.9% of *NTRK* rearranged tumors were MMR-deficient.[750] NTRK inhibitors are treatment options for patients with mCRC that is *NTRK* gene fusion-positive (see *Systemic Therapy Options for NTRK Fusion-Positive Disease in the Non-First-Line Setting,* below).

RET Fusions

RET is a transmembrane glycoprotein receptor-tyrosine kinase that plays an important role in the homeostasis of several different types of tissues, including neural, hematopoietic, and neuroendocrine tissues.[751] *RET* gene fusions lead to constitutively active, ligand-independent activation of the RET pathway.[752] *RET* gene fusions are implicated in the pathogenesis of several solid tumors including thyroid and non-small-cell lung cancer, as well as in a small subset (<1%) of CRCs.[751,753] A systematic review analyzed data from 24 *RET* gene fusion-positive mCRC cases from three screening sources and found *RET* gene fusions to be more prevalent with increased age (median age, 66 vs. 60 years; $P = .052$), in those with ECOG PS of 1–2 compared to those with ECOG PS of 0 (90 % vs. 50%; $P = .02$), in those with right-sided tumors (55% vs. 32%; $P = .013$), and in those with unresected primary tumors (58% vs. 21%; $P < .001$).[753] MSI-H status was also found to be more prevalent in *RET* gene fusion-positive samples compared to *RET*-negative samples (48% vs. 7%; $P < .001$). All *RET* gene fusion-positive samples were *RAS* and *BRAF* wild-type.[753] The highly selective RET kinase inhibitor, selpercatinib, is a treatment option for patients with mCRC that is *RET* gene fusion-positive (see *Selpercatinib for RET Gene Fusion-Positive Disease in the Non-First-Line Setting*, below).

Tumor Mutational Burden

Tumor mutational burden (TMB) measures the total amount of somatic coding mutations within a given coding area of the tumor genome and can be quantified using NGS techniques.[754] Research has identified TMB as a potential biomarker for response to immunotherapy and pembrolizumab has been FDA-approved for patients with unresectable or metastatic, TMB-high (TMB-H) solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options.[755] TMB-H is defined in the label as ≥10 mutations/megabase by an FDA-approved test. This approval was based on results of the phase 2, KEYNOTE-158 study that enrolled patients with advanced solid tumors.[756] Patients with TMB-H tumors who were treated with pembrolizumab had an ORR of 29% compared to 6% of those with non–TMB-H tumors. However, of the 796 patients who were evaluated for efficacy on this study, none had CRC.

The phase II TAPUR basket study included a cohort of 28 patients with TMB-H advanced CRC who were treated with pembrolizumab.[757] For the

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CRC cohort, the disease control rate (DCR) was 31% and the ORR was 11%. Another abstract on the TAPUR study, reporting results for 12 patients with TMB-H advanced CRC treated with nivolumab plus ipilimumab, concluded that the combination therapy does not have sufficient clinical activity in MSS, TMB-H CRC.[758]

Based on the limited data in the CRC population, the NCCN Panel does not currently recommend TMB biomarker testing, unless measured as part of a clinical trial.

DPYD Testing and Fluoropyrimidine-Associated Toxicity

Dihydropyrimidine dehydrogenase (DPYD) is the enzyme that catabolizes fluoropyrimidines.[759,760] Variants of the *DPYD* gene that encodes the enzyme exist across populations and these may lead to alterations in DPYD activity. These variants are not usually clinically relevant unless an individual with subnormal DPYD activity is exposed to a high pyrimidine load, such as when treated with a fluoropyrimidine. That individual is likely to have prolonged exposure to the fluoropyrimidine and its metabolites.[761-765] While higher drug levels do not necessarily lead to severe toxicity, these patients are at much higher risk for such complications.[766-768] A systematic review of the published literature found that, amongst 13,929 patients, *DPYD* variants were identified in 4.1% of patients.[768] Treatment-related deaths were reported in 0.1% in patients without identified *DPYD* variants and in 2.3% of those with known *DPYD* variants (95% CI, 1.3%–3.9%).

DPYD variants have been most thoroughly characterized in individuals of European ancestry. While about 96% of these individuals have wild type *DPYD* (normal) genes at both alleles, hundreds of variants exist in the other 4% of the population. However, only four of the hundreds of variants—(rs3918290), c.1905+1G>A [DPYD*2A]; (rs67376798), c.2846A>T [949V]; (rs55886062), c.1679T>G [DPYD*13]; (rs56038477), c.1236G>A [tagging DPYD-HapB3]—are common enough to have been adequately characterized.[769] Each of these is believed to diminish pyrimidine metabolism although the net effect is dependent on both alleles and other undefined factors. Prospective studies have shown that dose reductions in individuals with one of these *DPYD* variants at a single allele decreases both the likelihood and degree of toxicity.[770-772] Other deleterious variants have been identified in non-European populations, for example, p.Y186C in African Americans[773] and c.704G>A in people of South Asian ancestry,[774] but these variants and populations have not been nearly as well-studied.

*DPYD*2A* is the most common and best characterized variant and in one prospective study, patients with one such variant allele (22 of 2038 patients screened; 1.1%) received dose-reduced fluoropyrimidine. This led to a significant reduction in the risk of grade ≥3 toxicity compared with historic controls (28% vs. 73%; $P < .001$).[772] While this study confirms the importance of *DPYD* and the impact of variants at just one allele, it is otherwise not generalizable. The protocol left the specific dosing decision to the physician and fluoropyrimidine dose reductions ranged from 17% to 91% (median 48%).[772] Also, there were a variety of chemotherapy combinations used with the fluoropyrimidine, which was either 5-FU or capecitabine. Efficacy was not an endpoint in this study.

Other studies have also shown that targeted dose reductions of fluoropyrimidines decrease the incidence of severe toxicity. An analysis that matched patients with four of the most common variants, some of whom received dose-reduced fluoropyrimidine based on prospective testing, to others who were not prospectively tested, confirmed the diminution of toxicity[775] as did a recent prospectively randomized trial.[776]

In an effort to standardize the dose adjustment recommendations indicated by any of these most common *DPYD* variants, the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline for Dihydropyrimidine Dehydrogenase Genotype and Fluoropyrimidine Dosing

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provides dosing recommendations for 5-FU and 5-FU prodrug-based regimens.[769] Patients are categorized as normal, intermediate, or poor metabolizers based on their mix of alleles; an individual heterozygous for *DPYD* decreased/no function variants, for example, would be in the intermediate group. A 50% starting dose reduction is recommended for such individuals with the option to increase the dose in later cycles for patients with minimal or no toxicity in the first two cycles of treatment. Further dose reduction is recommended for those who do not tolerate the reduced starting dose. For those classified as poor metabolizers, the CPIC Guidelines recommend avoiding fluoropyrimidines, if possible.

CPIC reviewed data from thousands of patients in developing the parameters; this included individuals who received IV 5-FU or the oral pro-drug capecitabine, either as monotherapy or in various combinations. Prospective assessment of metabolic efficiency, such as serum uracil levels or drug exposure, were not included in these data. CPIC's goal was not to define exact dosing for each individual patient, but rather to provide a recommendation for a safe starting dose. Furthermore, the algorithm recommends similar dose reductions for 5-FU and capecitabine even though they are quite different; there is marked interpatient variability of capecitabine absorption, and the drug is not fully activated until it is intracellular. Based on clinical trial experience, capecitabine is uniformly used at reduced dose in the United States compared to Europe.[777]

While preemptive dose adjustment of fluoropyrimidines based on *DPYD* genotype diminishes the risk of life-threatening toxicity in patients with well-characterized variants, it is not certain that dose reductions do not result in inferior efficacy. In fairness, proving non-inferiority in outcomes in any cancer treatment is a very high bar to achieve. This is especially the case because studying individuals with rare variant genotypes requires casting a broad net that captures patients with various types and stage cancers treated with numerous fluoropyrimidine-chemotherapy drug combinations. Even the best conducted and reported studies, such as Knikman *et al* and Roncato *et al* cited above, are vastly underpowered to address clinical outcomes in a particular disease setting.

This issue is specifically pertinent for patients receiving fluoropyrimidines in the colon cancer adjuvant setting.[778] The only large series addressing *DPYD* variants in stage III colon cancer is a retrospective analysis of the N0147 patient population.[761] In that study, all patients received mFOLFOX6 and no benefit was seen with the addition of cetuximab. The DNA of all 2886 patients was analyzed for 25 *DPYD* variants and 55 individuals were identified with the most common variants. This correlated with grade ≥3 toxicity, the need for dose reductions, and delivery of fewer cycles of treatment. However, survival was not affected overall. There were 20 treatment-related deaths in the study, one of which was in a patient with a compound heterozygous DPYD*2A/D949V variant. In retrospect, because there is no alternative to a fluoropyrimidine in the adjuvant setting, recognition of this variant would have prompted a 75% dose-reduction per CPIC guidelines which might have avoided the fatal complication. In contrast, had pre-emptive testing been in practice, more than 50 patients with variants who were safely managed with conventional dose adjustments would have had a 50% reduction in starting fluoropyrimidine dose. Although it is not proven, dose intensity in the initial cycles of adjuvant therapy is thought to be critically important, which raises concern that preemptive dose reductions could compromise curability. While data indicates that drug exposure is similar in genotype vs non-genotype-guided dosing[771] without compromising efficacy in advanced disease,[770] that has not been demonstrated in the adjuvant setting.

Because 5-FU and capecitabine are used across so many diseases and in so many different combinations, toxic deaths appear to be more common than with other cancer therapies. Recently, very public lawsuits and advocacy efforts have heightened awareness that these risks could be

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mitigated by pretreatment *DPYD* testing which could identify some of the highest-risk individuals—those with low or non-metabolizing variants at both alleles. Such patients would be treated with great caution or not at all with fluoropyrimidines.

Historically, analyses of germline DNA would take weeks and was impractical when facing a patient in need of chemotherapy. Recent technologic advances that make the turn-around time 7-10 days has enabled some selected centers and health systems to implement preemptive testing. For example, the death of a woman with breast cancer who had died from capecitabine toxicity led the Dana Farber Cancer Institute (DFCI) to roll out preemptive testing even though an offending variant was not identified in the patient herself.[779] Other NCCN institutions, such as the University of California, San Francisco (UCSF), have also implemented pharmacogenomics testing which includes *DPYD* as well as 14 other genes.[780]

While these (and other NCCN) institutions offer non-mandatory pretreatment *DPYD* testing, there are practical considerations that have led the US Food and Drug Administration (FDA) and NCCN Guidelines panel to withhold a recommendation for universal pretreatment *DPYD* genotyping for patients who are to receive a fluoropyrimidine. The first issue is determining the breadth of the search for *DPYD* genetic variants. Gene sequencing would be likeliest to identify variants, but the majority of these would be rare, at a single allele and of unknown significance. More focused assays, such as at DFCI and UCSF, may not include variants found in populations uncommonly seen at the institutions; therefore, some patients at the greatest risk would be mischaracterized as being normal metabolizers.

Meanwhile, testing needs to be associated with dosing recommendations. The NCCN Panel believes that the CPIC guidelines lack granularity and that a starting dose reduction of 50% will leave many patients potentially undertreated. Emerging pharmacokinetic data including 5-FU serum levels or measures of metabolizing efficiency, such as serum uracil levels, will be critical to inform dosing recommendations. CPIC also lumps dosing adjustments for capecitabine and 5-FU; while these are both fluoropyrimidines and depend on DPYD for their metabolism, there are many unpredictable factors that make the pro-drug capecitabine difficult to dose.

This NCCN Panel endorses the principle of identifying the patients at the greatest risk for severe fluoropyrimidine toxicity. Testing for *DPYD* genetic variants should be discussed with patients prior to fluoropyrimidine therapy and should be considered in the context of the patient's circumstances. Patients receiving chemotherapy for palliation might more logically be dose-reduced than patients being treated in the curative setting. As with all guideline decisions, the Panel reviews all new data and considers input from stakeholders in real time and guidelines are continuously reassessed.

Vigilant attention to toxicity for patients receiving fluoropyrimidines is also necessary. In particular, patients who suffer early and severe toxicities should have *DPYD* genotyping and must be considered for uridine triacetate administration.[781] The drug is an orally administered pyrimidine analog that is believed to compete for receptors on normal cells and, as such, decreases the toxic effects of excessive fluoropyrimidines. It is FDA approved for the emergency treatment of both adult and pediatric patients exhibiting early-onset, severe or life-threatening toxicity. Uridine triacetate was evaluated in two single-arm, multicenter open-label trials in which a total of 135 patients were treated with uridine triacetate following 5-FU or capecitabine overdose or upon early onset of severe toxicities.[782,783] In these studies, a total of 96% of the patients treated with uridine triacetate survived and exhibited rapid reversal of severe cardiac and neurologic toxicities. Thirty-eight percent of these patients were able to resume

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chemotherapy within 30 days, with a mean time to resumption of chemotherapy of 19.6 days.[782] The importance of administration of uridine triacetate within the first 96 hours must be noted. While most patients on these trials were treated within the first 96 hours, 50% of the four patients who were treated beyond 96 hours died.[783]

Regimens Not Recommended

The consensus of the Panel is that infusional 5-FU regimens seem to be less toxic than bolus regimens and that any bolus regimen of 5-FU is inappropriate when administered with either irinotecan or oxaliplatin. Therefore, the Panel no longer recommends using the IFL regimen (which was shown to be associated with increased mortality and decreased efficacy relative to FOLFIRI in the BICC-C trial[614,784] and inferior to FOLFOX in the Intergroup trial[785]) at any point in the therapy continuum. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,[312] or capecitabine can be used with oxaliplatin.[786]

The Dutch CAIRO trial showed promising results for the use of capecitabine/irinotecan (CapeIRI) in the first-line treatment of mCRC.[650] However, in the American BICC-C trial, CapeIRI showed worse PFS than FOLFIRI (5.8 vs. 7.6 months; $P = .015$), and was considerably more toxic with higher rates of severe vomiting, diarrhea, and dehydration.[614] In this trial, the CapeIRI arm was discontinued. The EORTC study 40015 also compared FOLFIRI with CapeIRI and was discontinued after enrollment of only 85 patients because seven deaths were determined to be treatment-related (five in the CapeIRI arm).[787] Several European studies have assessed the safety and efficacy of CapeIRI in combination with bevacizumab (CapeIRI/Bev) in the first-line metastatic setting. A small Spanish study of 46 patients who received CapeIRI/Bev showed encouraging results with good tolerability.[788] A similar trial by the Spanish group found similar results in 77 patients.[789] Preliminary results from a randomized phase II study conducted in France were presented in 2009, showing a manageable toxicity profile for CapeIRI/Bev in this setting.[790] Additionally, a randomized phase III HeCOG trial compared CapeIRI/Bev and FOLFIRI/Bev in the first-line metastatic setting and found no significant differences in efficacy between the regimens.[791] Despite the differing toxicity profiles reported, the toxicities seemed to be reasonable in both arms. Finally, a randomized phase II study of the AIO colorectal study group compared CAPEOX plus bevacizumab with a modified CapeIRI regimen plus bevacizumab and found similar 6-month PFS and similar toxicities.[792] Because of the concerns about the toxicity of the CapeIRI combination, which may differ between patients of American and European descent, the Panel does not recommend CapeIRI or CapeIRI/Bev for the first-line treatment of mCRC.

Other drug combinations that have produced negative results in phase III trials for the treatment of advanced CRC include sunitinib plus FOLFIRI, cetuximab plus brivanib, erlotinib plus bevacizumab, cediranib plus FOLFOX/CAPEOX, and atezolizumab plus cobimetinib.[793-797] These regimens are not recommended for the treatment of patients with CRC.

Results from two randomized phase III trials have shown that combination therapy with more than one biologic agent is not associated with improved outcomes and can cause increased toxicity.[798,799] In the PACCE trial, the addition of panitumumab to a regimen containing oxaliplatin- or irinotecan-based chemotherapy plus bevacizumab was associated with significantly shorter PFS and higher toxicity in both *KRAS* exon 2 wild-type and mutant gene groups.[798] Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.[799] Therefore, the Panel strongly recommends against the use of therapy involving the concurrent combination of an anti-EGFR agent (cetuximab or panitumumab) and an anti-vascular endothelial growth factor (VEGF) agent (bevacizumab).

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First-Line Systemic Therapy

FOLFOX for First-Line Therapy

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy,[616,800] as is the addition of panitumumab or cetuximab for patients with disease characterized by wild-type *KRAS*, *NRAS*, and *BRAF.* With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, Panel consensus is that FOLFOX and CAPEOX can be used interchangeably. Results from a registry-based cohort analysis of >2000 patients support the equivalence of these combinations.[801]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[802] Results of the OPTIMOX1 study showed that a "stop-and-go" approach using oxaliplatin-free intervals resulted in decreased neurotoxicity but did not affect OS in patients receiving FOLFOX as initial therapy for metastatic disease.[803] Other trials have also addressed the question of treatment breaks, with or without maintenance therapy, and found that toxicity can be minimized with minimal or no effect on survival.[804] A meta-analysis of RCTs also concluded that intermittent delivery of systemic therapy does not compromise OS compared to continuous treatment.[805] Therefore, the Panel recommends adjusting the schedule/timing of the administration of this drug as a means of limiting this AE. Discontinuation of oxaliplatin from FOLFOX or CAPEOX should be strongly considered after 3 months of therapy, or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained for the entire 6 months or until time of tumor progression. Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity.

In the phase II OPTIMOX2 trial, patients were randomized to receive either an OPTIMOX1 approach (discontinuation of oxaliplatin after 6 cycles of FOLFOX to prevent or reduce neurotoxicity with continuance of 5-FU/LV followed by reintroduction of oxaliplatin on disease progression) or an induction FOLFOX regimen (6 cycles) followed by discontinuation of all chemotherapy until tumor progression reached baseline, followed by reintroduction of FOLFOX.[806] Results of the study showed no difference in OS for patients receiving the OPTIMOX1 approach compared with those undergoing an early, pre-planned, chemotherapy-free interval (median OS, 23.8 vs. 19.5 months; $P = .42$). However, the median duration of disease control, which was the primary endpoint of the study, reached statistical significance at 13.1 months in patients undergoing maintenance therapy and 9.2 months in patients with a chemotherapy-free interval ($P = .046$).[806]

The CONcePT trial also tested an intermittent oxaliplatin approach in patients with advanced CRC and found that it improved acute peripheral sensory neuropathy ($P = .037$) over continuous oxaliplatin.[807] The addition of oxaliplatin breaks also improved time to treatment failure (HR, 0.581; $P = .0026$) and time to tumor progression (HR, 0.533; $P = .047$).

Early data suggested that calcium/magnesium infusion might prevent oxaliplatin-related neurotoxicity.[808-815] However, the phase III, randomized, double-blind N08CB study, which randomized 353 patients with colon cancer receiving adjuvant FOLFOX to calcium/magnesium infusion or placebo, found that calcium/magnesium did not reduce cumulative sensory neurotoxicity.[816] The Panel therefore recommends against calcium/magnesium infusions for this purpose.

CAPEOX for First-Line Therapy

The combination of capecitabine and oxaliplatin, known as CAPEOX or XELOX, has been studied as an active first-line therapy for patients with mCRC.[817-821] In a randomized phase III trial comparing CAPEOX and FOLFOX in 2034 patients, the regimens showed similar median PFS intervals of 8.0 and 8.5 months, respectively, and CAPEOX was

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determined to be noninferior to FOLFOX as first-line treatment of metastatic disease.[817] Meta-analyses of RCTs also showed that CAPEOX and FOLFOX had similar benefits for patients with mCRC.[822,823]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy (see *FOLFOX*, above). Discontinuation of oxaliplatin from FOLFOX or CAPEOX should be strongly considered after 3 months of therapy (the OPTIMOX1 approach[803]), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until tumor progression. A Turkish Oncology Group Trial showed that this stop-and-go approach is safe and effective in first-line therapy with CAPEOX/bevacizumab.[824] The randomized FOCUS4-N trial compared capecitabine maintenance therapy to active monitoring in patients with disease responding to first-line therapy.[825] While there was no significant difference in OS between the two groups (15.2 months in the capecitabine arm vs. 14.8 months in the active monitoring arm [adjusted HR, 0.93; P = .66]), median PFS was longer in the capecitabine arm (3.88 months compared to 1.87 months in the active monitoring arm [adjusted HR, 0.40; P < .0001]).

Patients experiencing neurotoxicity on oxaliplatin should not receive subsequent oxaliplatin therapy until and unless they experience near-total resolution of that neurotoxicity. The Panel recommends against the use of calcium/magnesium infusion to prevent oxaliplatin-related neurotoxicity.[816]

Regarding the toxicities associated with capecitabine use, the Panel noted that: 1) patients with diminished creatinine clearance may accumulate levels of the drug, and therefore may require dose modification; 2) the incidence of hand-foot syndrome was increased for patients receiving capecitabine-containing regimens versus either bolus or infusional regimens of 5-FU/LV[800]; and 3) patients of North American descent may experience a higher incidence of AEs with certain doses of capecitabine compared with patients from other countries.[777] These toxicities may necessitate modifications in the dosing of capecitabine.[800,826] Patients on capecitabine should be monitored closely so that dose adjustments can be made at the earliest signs of certain side effects, such as hand-foot syndrome. Interestingly, an analysis of patients from the AIO's KRK-0104 trial and the Mannheim rectal cancer trial found that capecitabine-related hand-foot skin reactions were associated with an improved OS (75.8 vs. 41.0 months; P = .001; HR, 0.56).[827]

The addition of bevacizumab is an option if CAPEOX is chosen as initial therapy.[616,800] With respect to the treatment of metastatic disease with bevacizumab-containing regimens or chemotherapy without an additional biologic agent, the consensus of the Panel is that FOLFOX and CAPEOX can be used interchangeably. Results from a registry-based cohort analysis of >2000 patients support the equivalence of these combinations.[801]

FOLFIRI for First-Line Therapy

Evidence for the comparable efficacy for FOLFOX and FOLFIRI comes from a crossover study in which patients received either FOLFOX or FOLFIRI as initial therapy and were then switched to the other regimen at disease progression.[652] Similar response rates and PFS times were obtained when these regimens were used as first-line therapy. Further support for this conclusion has come from results of a phase III trial comparing the efficacy and toxicity of FOLFOX and FOLFIRI regimens in previously untreated patients with mCRC.[828] No differences were observed in response rate, PFS times, and OS between the treatment arms.

A randomized phase III study compared FOLFIRI to 5-FU/LV in first-line treatment of patients ≥75 years with mCRC.[829] In this population of patients, grade 3–4 toxicities were increased with the addition of irinotecan (52.2% vs. 76.3%), without an improvement in PFS or OS.

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Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[830] Irinotecan is inactivated by the enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which is also involved in converting substrates such as bilirubin into more soluble forms through conjugation with certain glycosyl groups. Deficiencies in UGT1A1 can be caused by certain genetic polymorphisms and can result in conditions associated with accumulation of unconjugated hyperbilirubinemias, such as types I and II of the Crigler-Najjar and Gilbert syndromes. Thus, irinotecan should be used with caution and at a decreased dose in patients with Gilbert syndrome or elevated serum bilirubin. Similarly, certain genetic polymorphisms in the gene encoding for UGT1A1 can result in a decreased level of glucuronidation of the active metabolite of irinotecan, resulting in an accumulation of the drug and increased risk for toxicity,[830-832] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[832] Results from a dose-finding and pharmacokinetic study suggest that dosing of irinotecan should be individualized based on UGT1A1 genotype.[833] The maximum tolerated dose of IV irinotecan every 3 weeks was 850 mg, 700 mg, and 400 mg in patients with the *1/*1, *1/*/28, and *28/*28 genotypes, respectively.

Commercial tests are available to detect the UGT1A1*28 allele, which is associated with decreased gene expression and, hence, reduced levels of UGT1A1 expression. Also, a warning was added to the label for irinotecan indicating that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.[834] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[832] although guidelines for use of this test in clinical practice have not been established. Furthermore, UGT1A1 testing on patients who experience irinotecan toxicity is not recommended, because they will require a dose reduction regardless of the UGT1A1 test result.

Results from a phase IV trial in 209 patients with mCRC who received bevacizumab in combination with FOLFIRI as first-line therapy showed that this combination was as effective and well-tolerated as bevacizumab with other 5-FU–based therapies.[835] A phase III trial in Japan also showed that FOLFIRI plus bevacizumab is noninferior to mFOLFOX6 plus bevacizumab with regard to PFS.[836] Therefore, the addition of bevacizumab to FOLFIRI is recommended as an option for initial therapy; alternatively, cetuximab or panitumumab (only for left-sided tumors characterized by wild-type *RAS/BRAF*) can be added to this regimen.[685,707,837-839]

Infusional 5-FU/LV and Capecitabine for First-Line Therapy

For patients with impaired tolerance to aggressive initial therapy, the guidelines recommend infusional 5-FU/LV or capecitabine with or without bevacizumab as an option.[312,786,800,840-842] Patients with metastatic cancer with no improvement in functional status after this less intensive initial therapy should receive best supportive care. Patients showing improvement in functional status should be treated with one of the options specified for initial therapy for advanced or metastatic disease. Toxicities associated with capecitabine use are discussed earlier (see *CAPEOX*).

In a pooled analysis of results from two randomized clinical trials involving patients with a potentially curative resection of liver or lung metastases randomly assigned to either postoperative systemic chemotherapy with 5-FU/LV or observation alone after surgery, the median PFS was 27.9 months in the chemotherapy arm and 18.8 months for those undergoing surgery alone (HR, 1.32; 95% CI, 1.00–1.76; $P = .058$), with no significant difference in OS.[843]

Results were published from the open-label phase III AVEX trial, in which 280 patients ≥70 years were randomized to capecitabine with or without bevacizumab.[844] The trial met its primary endpoint, with the addition of

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bevacizumab giving a significantly improved median PFS (9.1 vs. 5.1 months; HR, 0.53; 95% CI, 0.41–0.69; *P* < .0001).

FOLFOXIRI or FOLFIRINOX for First-Line Therapy

Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in two randomized phase III trials.[605,606] In a trial by the GONO group, statistically significant improvements in PFS (9.8 vs. 6.9 months; HR, 0.63; *P* = .0006) and median OS (22.6 vs. 16.7 months; HR, 0.70; *P* = .032) were observed in the FOLFOXIRI arm,[605] although no OS difference was seen between treatment arms in the HORG study (median OS was 19.5 and 21.5 months for FOLFIRI and FOLFOXIRI, respectively; *P* = .337).[606] Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia,[605] diarrhea, alopecia, and neurotoxicity[606]), but no differences in the rate of toxic death were reported in either study. Long-term outcomes of the GONO trial with a median follow-up of 60.6 months were later reported.[607] The improvements in PFS and OS were maintained.

The Panel includes the possibility of adding bevacizumab to FOLFIRINOX for initial therapy of patients with unresectable metastatic disease. Results of the GONO group's phase III TRIBE trial showed that FOLFOXIRI/bevacizumab significantly increased PFS (12.1 vs. 9.7 months; HR, 0.75; 95% CI, 0.62–0.90; *P* = .003) and response rate (65% vs. 53%; *P* = .006) compared to FOLFIRI/bevacizumab in patients with unresectable mCRC.[845] Subgroup analyses indicated that no benefit to the addition of oxaliplatin was seen in patients who received prior adjuvant therapy (64% of cases included oxaliplatin in the adjuvant regimen). Diarrhea, stomatitis, neurotoxicity, and neutropenia were significantly more prevalent in the FOLFOXIRI arm. In an updated analysis on the TRIBE trial, investigators reported the median OS at 29.8 months (95% CI, 26.0–34.3) in the FOLFOXIRI plus bevacizumab arm and 25.8 months (95% CI, 22.5–29.1) in the FOLFIRI plus bevacizumab arm (HR, 0.80; 95% CI, 0.65–0.98; *P* = .03).[846]

The randomized, phase III TRIBE2 compared first-line FOLFOXIRI plus bevacizumab to a sequential strategy of first-line FOLFOX plus bevacizumab followed by FOLFIRI plus bevacizumab after progression in 679 patients with unresectable, previously untreated mCRC.[847] The primary endpoint of median PFS was 19.2 months for FOLFOXIRI compared to 16.4 months for the sequential strategy (HR, 0.74; 95% CI, 0.63–0.88; *P* = .0005). Serious AEs were reported in 25% of patients in the FOLFOXIRI group compared to 17% in the sequential therapy group.

Results from the randomized phase II OLIVIA trial, which compared mFOLFOX6/bevacizumab to FOLFOXIRI/bevacizumab in patients with unresectable colorectal liver metastases, were also reported.[848] Improvement in R0 resection rate was seen in the FOLFOXIRI/bevacizumab arm (49% vs. 23%; 95% CI, 4%–48%) and in the primary endpoint of overall (R0/R1/R2) resection rate (61% vs. 49%; 95% CI, −11%–36%). Other phase II trials, including CHARTA and STEAM, have also reported improved outcomes for FOLFOXIRI plus bevacizumab when compared to a chemotherapy doublet plus bevacizumab for first-line treatment of mCRC.[620,849]

A pooled analysis of TRIBE and TRIBE2[850] and a meta-analysis of individual patient data from CHARTA, OLIVIA, STEAM, TRIBE, and TRIBE2[620] reached similar conclusions as the clinical trials. These analyses concluded that first-line treatment with FOLFOXIRI plus bevacizumab yields significantly better outcomes, albeit at the expense of higher toxicity, compared to sequential treatment with chemotherapy doublets in combination with bevacizumab. An additional pooled analysis of TRIBE and TRIBE2[851] evaluated toxicity based on age with FOLFOXIRI plus bevacizumab and found lower risks of grade 3 or higher neutropenia (*P* = .07), diarrhea (*P* = .04), and asthenia (*P* = .008) in patients aged <50

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years but higher rates of any grade nausea ($P < .01$) and vomiting ($P < .01$) in this age group. There was no impact on PFS ($P = .81$), OS ($P = .44$), or ORR ($P = .50$) based on age. Based on these results, the NCCN Panel strongly recommends first-line FOLFIRINOX for patients with excellent performance status who can withstand the higher toxicity of the triplet regimen.

The Panel recommends FOLFIRINOX instead of FOLFOXIRI because FOLFOXIRI uses a high dose of 5-FU (3200 mg/m^2 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/m^2 over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for patients in the United States.

Bevacizumab for First-Line Therapy

Bevacizumab is a humanized monoclonal antibody that blocks the activity of VEGF, a factor that plays an important role in tumor angiogenesis.[621] The NCCN Panel notes that FDA-approved biosimilars may be substituted for bevacizumab wherever the therapy is recommended within these Guidelines (see *Biosimilars*, above, for more information). Pooled results from several randomized phase II studies have shown that the addition of bevacizumab to first-line 5-FU/LV improved OS in patients with unresectable mCRC compared with those receiving these regimens without bevacizumab.[615,852,853] A combined analysis of the results of these trials showed that the addition of bevacizumab to 5-FU/LV was associated with a median survival of 17.9 versus 14.6 months for regimens consisting of 5-FU/LV or 5-FU/LV plus irinotecan without bevacizumab ($P = .008$).[841] A study of previously untreated patients receiving bevacizumab plus IFL also provided support for the inclusion of bevacizumab in initial therapy.[615] In that pivotal trial, a longer survival time was observed with the use of bevacizumab (20.3 vs. 15.6 months; HR, 0.66; $P < .001$).

Results have also been reported from a large, head-to-head, randomized, double-blind, placebo-controlled, phase III study (NO16966) in which CAPEOX (capecitabine dose, 1000 mg/m^2, twice daily for 14 days) with bevacizumab or placebo was compared with FOLFOX with bevacizumab or placebo in 1400 patients with unresectable metastatic disease.[616] The addition of bevacizumab to oxaliplatin-based regimens was associated with a more modest increase of 1.4 months in PFS compared with these regimens without bevacizumab (HR, 0.83; 97.5% CI, 0.72–0.95; $P = .0023$), and the difference in OS, which was also a modest 1.4 months, did not reach statistical significance (HR, 0.89; 97.5% CI, 0.76–1.03; $P = .077$).[616] Researchers have suggested that differences observed in cross-study comparisons of NO16966 with other trials might be related to differences in the discontinuation rates and durations of treatment between trials, although these hypotheses are conjectural.[616] However, in this 1400-patient randomized study, absolutely no difference in response rate was seen with and without bevacizumab, and this finding could not have been influenced by the early withdrawal rates, which would have occurred after the responses would have occurred. Results of subset analyses evaluating the benefit of adding bevacizumab to either FOLFOX or CAPEOX indicated that bevacizumab was associated with improvements in PFS when added to CAPEOX but not FOLFOX.[616]

The combination of FOLFIRI and bevacizumab in the first-line treatment of advanced CRC has been studied, although no RCTs have compared FOLFIRI with and without bevacizumab. A systematic review with a pooled analysis (29 prospective and retrospective studies, 3502 patients) found that the combination gave a response rate of 51.4%, a median PFS of 10.8 months (95% CI, 8.9–12.8), and a median OS of 23.7 months (95% CI, 18.1–31.6).[854] FOLFIRINOX with bevacizumab is also an accepted combination (see *FOLFOXIRI or FOLFIRINOX for First-Line Therapy*, above), although no RCTs have compared FOLFIRINOX with and without bevacizumab.

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A prospective observational cohort study (ARIES) included 1550 patients who received first-line therapy with bevacizumab with chemotherapy for mCRC and 482 patients treated with bevacizumab in second-line.[855] Median OS was 23.2 months (95% CI, 21.2–24.8) for the first-line cohort and 17.8 months (95% CI, 16.5–20.7) for the second-line group. A similar cohort study (ETNA) of first-line bevacizumab use with irinotecan-based therapy reported a median OS of 25.3 months (95% CI, 23.3–27.0).[856]

Several meta-analyses have shown a benefit for the use of bevacizumab in first-line therapy for mCRC.[857-865] A meta-analysis of six randomized clinical trials (3060 patients) that assessed the efficacy of bevacizumab in first-line treatment of mCRC found that bevacizumab gave a PFS (HR, 0.72; 95% CI, 0.66–0.78; $P < .00001$) and OS (HR, 0.84; 95% CI, 0.77–0.91; $P < .00001$) advantage.[866] However, subgroup analyses showed that the advantage was limited to irinotecan-based regimens. In addition, an analysis of the SEER-Medicare database found that bevacizumab added a modest improvement to OS of patients with stage IV CRC diagnosed between 2002 and 2007 (HR, 0.85; 95% CI, 0.78–0.93).[867] The survival advantage was not evident when bevacizumab was combined with oxaliplatin-based chemotherapy, but was evident in irinotecan-based regimens. Limitations of this analysis have been discussed,[868,869] but, overall, the addition of bevacizumab to first-line chemotherapy appears to offer a modest clinical benefit.

A meta-analysis of RCTs showed that the addition of bevacizumab to chemotherapy is associated with a higher incidence of treatment-related mortality than chemotherapy alone (RR, 1.33; 95% CI, 1.02–1.73; $P = .04$), with hemorrhage (23.5%), neutropenia (12.2%), and GI perforation (7.1%) being the most common causes of fatality.[870] Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[871] Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension, GI hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is quite low.[872] The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those ≥65 years. GI perforation is a rare but important side effect of bevacizumab therapy in patients with CRC.[612,800] Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to GI perforation. A small cohort of patients with advanced ovarian cancer had an unacceptably high rate of GI perforation when treated with bevacizumab.[873] This result illustrated that peritoneal debulking surgery may be a risk factor for GI perforation, whereas the presence of an intact primary tumor does not seem to increase the risk for GI perforation. The FDA approved a safety label warning of the risk for necrotizing fasciitis, sometimes fatal and usually secondary to wound healing complications; GI perforation; or fistula formation after bevacizumab use.[621]

Use of bevacizumab may interfere with wound healing.[612,621,800] A retrospective evaluation of data from two randomized trials of 1132 patients undergoing 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 compared with the group receiving chemotherapy alone while undergoing major surgery (13% vs. 3.4%, respectively; $P = .28$).[612] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered after surgery, with a delay between surgery and bevacizumab administration of at least 6 weeks, the incidence of wound healing complications in either group of patients was low (1.3% vs. 0.5%; $P = .63$). Similarly, results of a single-center, nonrandomized phase II trial of patients with potentially resectable liver metastases showed no increase in bleeding or wound complications when the bevacizumab component of CAPEOX plus bevacizumab therapy was stopped 5 weeks before surgery

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(ie, bevacizumab excluded from the sixth cycle of therapy).[874] In addition, no significant differences in bleeding, wound, or hepatic complications were seen in a retrospective trial evaluating the effects of preoperative bevacizumab stopped at ≤8 weeks versus at ≥8 weeks before resection of liver colorectal metastases in patients receiving oxaliplatin- or irinotecan-containing regimens.[875] The Panel recommends an interval of at least 6 weeks (which corresponds to two half-lives of the drug[621]) between the last dose of bevacizumab and any elective surgery. Additionally, re-initiation of bevacizumab should be delayed at least 6 to 8 weeks postoperatively.

Preclinical studies suggested that cessation of anti-VEGF therapy might be associated with accelerated recurrence, more aggressive tumors on recurrence, and increased mortality. A retrospective meta-analysis of five placebo-controlled, randomized, phase III trials including 4205 patients with metastatic colorectal, breast, renal, or pancreatic cancer found no difference in time to disease progression and mortality with discontinuation of bevacizumab versus discontinuation of placebo.[876] Although this meta-analysis has been criticized,[877,878] the results are supported by results from the NSABP Protocol C-08 trial.[404] This trial included patients with stage II and stage III CRC, and no differences in recurrence, mortality, or mortality 2 years after recurrence were seen between patients receiving bevacizumab versus patients in the control arm. These results suggest that no “rebound effect” is associated with bevacizumab use.

Cetuximab or Panitumumab for First-Line Therapy in KRAS/NRAS Wild-Type Disease

Cetuximab and panitumumab are monoclonal antibodies directed against EGFR that inhibit its downstream signaling pathways. Panitumumab is a fully human monoclonal antibody, whereas cetuximab is a chimeric monoclonal antibody.[879] Cetuximab and panitumumab have been studied in combination with FOLFIRI and FOLFOX as initial therapy options for treatment of mCRC. The randomized, phase II PLANET-TTD trial comparing patients treated with panitumumab plus either FOLFOX or FOLFIRI found no significant differences in efficacy between the two regimens.[880]

Meta-analyses of RCTs have concluded that EGFR inhibitors provide a clear clinical benefit in the treatment in patients with *RAS* wild-type mCRC.[687,881] Patients with known *KRAS*- or *NRAS*-mutant tumors should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified (see *Biomarkers for Systemic Therapy, KRAS and NRAS Mutations*, above for more information). Individual trials are discussed below.

Administration of either cetuximab or panitumumab has been associated with severe infusion reactions, including anaphylaxis, in 3% and 1% of patients, respectively.[879] Based on case reports and a small trial, administration of panitumumab seems to be feasible for patients experiencing severe infusion reactions to cetuximab.[882-884] Skin toxicity is a side effect of both of these agents and is not considered part of the infusion reactions. The incidence and severity of skin reactions with cetuximab and panitumumab seem to be very similar. Furthermore, the presence and severity of skin rash in patients receiving either of these drugs have been shown to predict increased response and survival.[683,685,885-888] An NCCN task force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.[889] Cetuximab and panitumumab have also been associated with a risk for venous thromboembolic and other serious AEs.[890,891]

Based on the results of the PACCE and CAIRO2 trials, the Panel strongly advises against the concurrent use of bevacizumab with either cetuximab or panitumumab (see *Bevacizumab*, above).[798,799] Several trials that

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assessed EGFR inhibitors in combination with various chemotherapy agents are discussed below.

Cetuximab/Panitumumab and Primary Tumor Sidedness: A growing body of data has shown that the location of the primary tumor can be both prognostic and predictive of response to EGFR inhibitors in mCRC.[892-900] For example, outcomes of 75 patients with mCRC treated with cetuximab, panitumumab, or cetuximab/irinotecan in first-line or subsequent lines of therapy at three Italian centers were analyzed based on sidedness of the primary tumor.[893] No responses were seen in the patients with right-sided primary tumors compared with a response rate of 41% in those with left-sided primaries (P = .003). The median PFS was 2.3 and 6.6 months in patients with right-sided and left-sided tumors, respectively (HR, 3.97; 95% CI, 2.09–7.53; P < .0001).

The strongest evidence for the predictive value of primary tumor sidedness and response to EGFR inhibitors is in the first-line treatment of patients in the phase III CALGB/SWOG 80405 trial.[897] The study showed that patients with *RAS* wild-type, right-sided primary tumors (cecum to hepatic flexure) had longer OS if treated with bevacizumab than if treated with cetuximab in first line (HR, 1.36; 95% CI, 0.93–1.99; P = .10), whereas patients with all *RAS* wild-type, left-sided primary tumors (splenic flexure to rectum) had longer OS if treated with cetuximab than if treated with bevacizumab (HR, 0.77; 95% CI, 0.59–0.99; P = .04).[901] OS was prolonged with cetuximab versus bevacizumab in the left-sided primary group (39.3 vs. 32.6 months) but shortened in the right-sided primary group (13.6 vs. 29.2 months). Retrospective analyses of other contemporary studies have confirmed this finding.[900]

These and other data suggest that cetuximab and panitumumab confer little if any benefit to patients with mCRC if the primary tumor originated on the right side. The Panel believes that primary tumor sidedness is a surrogate for the non-random distribution of molecular subtypes across the colon and that the ongoing analysis of genomic differences between right- and left-sided tumors[902] will enable a better understanding of the biologic explanation of the observed difference in response to EGFR inhibitors. Until that time, only patients whose primary tumors originated on the left side of the colon (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of metastatic disease. Evidence also suggests that sidedness is predictive of response to EGFR inhibitors in subsequent lines of therapy, [892,893,895] but the Panel awaits more definitive studies. Until such data are available, all patients with *RAS/BRAF* wild-type tumors can be considered for panitumumab or cetuximab in subsequent lines of therapy if neither was previously given.

Cetuximab with FOLFIRI: Use of cetuximab as initial therapy for metastatic disease was investigated in the CRYSTAL trial, in which patients were randomly assigned to receive FOLFIRI with or without cetuximab.[685] Retrospective analyses of the subset of patients with known *KRAS* exon 2 tumor status showed a statistically significant improvement in median PFS with the addition of cetuximab in the wild-type (9.9 vs. 8.7 months; HR, 0.68; 95% CI, 0.50–0.94; P = .02).[685] The statistically significant benefit in PFS for patients with *KRAS* exon 2 wild-type tumors receiving cetuximab was confirmed in a publication of an updated analysis of the CRYSTAL data.[707] This study included a retrospective analysis of OS in the *KRAS* exon 2 wild-type population and found an improvement with the addition of cetuximab (23.5 vs. 20.0 months; P = .009). Importantly, the addition of cetuximab did not affect the quality of life of participants in the CRYSTAL trial.[903] As has been seen with other trials, when DNA samples from the CRYSTAL trial were re-analyzed for additional *KRAS* and *NRAS* mutations, patients with *RAS* wild-type tumors derived a clear OS benefit (HR, 0.69; 95% CI, 0.54–0.88), whereas those with any *RAS* mutation did not (HR, 1.05; 95% CI, 0.86–1.28).[904]

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Panitumumab with FOLFIRI: FOLFIRI with panitumumab is listed as an option for first-line therapy in mCRC based on extrapolation from data in second-line treatment.[717,839,905,906]

Cetuximab with FOLFOX: Several trials have assessed the combination of FOLFOX and cetuximab in first-line treatment of mCRC. In a retrospective evaluation of the subset of patients with known tumor *KRAS* exon 2 status enrolled in the randomized phase II OPUS trial, addition of cetuximab to FOLFOX was associated with an increased ORR (61% vs. 37%; OR, 2.54; *P* = .011) and a very slightly lower risk of disease progression (7.7 vs. 7.2 months [a 15-day difference]; HR, 0.57; 95% CI, 0.36–0.91; *P* = .016) compared with FOLFOX alone in the subset of patients with *KRAS* exon 2 wild-type tumors.[679] Although data supporting the statistically significant benefits in ORR and PFS for patients with tumors characterized by *KRAS* wild-type exon 2 were upheld in an update of this study, no median OS benefit was observed for the addition of cetuximab to chemotherapy (22.8 months in the cetuximab arm vs. 18.5 months in the arm undergoing chemotherapy alone; HR, 0.85; *P* = .39).[907]

Furthermore, in the randomized phase III MRC COIN trial, no benefit in OS (17.9 vs. 17.0 months; *P* = .067) or PFS (8.6 months in both groups; *P* = .60) was seen with the addition of cetuximab to FOLFOX or CAPEOX as first-line treatment of patients with locally advanced CRC or mCRC and wild-type *KRAS* exon 2.[708] Exploratory analyses of the COIN trial, however, suggest that there may be a benefit to the addition of cetuximab in patients who received FOLFOX instead of CAPEOX.[708]

Notably, additional trials examining the efficacy of the addition of cetuximab to oxaliplatin-containing regimens in the first-line treatment of patients with advanced CRC or mCRC and wild-type *KRAS* exon 2 have not shown any benefit. The addition of cetuximab to the Nordic FLOX regimen showed no benefit in OS or PFS in this population of patients in the randomized phase III NORDIC VII study of the Nordic Colorectal Cancer Biomodulation Group.[908]

However, results from the randomized phase III CALGB/SWOG 80405 trial of >1000 patients (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-Line Therapy*, below) showed that the combination of FOLFOX with cetuximab can be effective in first-line treatment of mCRC.[909] The phase III open-label, randomized TAILOR trial confirmed this result, reporting benefits in PFS (9.2 vs. 7.4 months; *P* = .004), OS (20.7 vs. 17.8 months; *P* = .02), and ORR (61.1% vs. 39.5%; *P* < .001) with first-line cetuximab plus FOLFOX compared to FOLFOX alone in patients with *RAS* wild-type mCRC.[910] Therefore, the Panel recommends cetuximab plus FOLFOX as an initial therapy option for *RAS/BRAF* wild-type patients with advanced or metastatic disease.

Panitumumab with FOLFOX: Panitumumab in combination with either FOLFOX[686,837] or FOLFIRI[838] has also been studied in the first-line treatment of patients with mCRC. Results from the large, open-label, randomized PRIME trial comparing panitumumab plus FOLFOX versus FOLFOX alone in patients with *KRAS/NRAS* wild-type advanced CRC showed a statistically significant improvement in PFS (HR, 0.72; 95% CI, 0.58–0.90; *P* = .004) and OS (HR, 0.77; 95% CI, 0.64–0.94; *P* = .009) with the addition of panitumumab.[686] Therefore, the combination of FOLFOX and panitumumab remains an option as initial therapy for patients with advanced or metastatic disease. Importantly, the addition of panitumumab had a detrimental impact on PFS for patients with tumors characterized by mutated *KRAS/NRAS* in the PRIME trial (discussed further in *KRAS and NRAS Mutations* within *Biomarkers for Systemic Therapy*, above).[686]

The phase III randomized GONO TRIPLETE study compared mFOLFOXIRI plus panitumumab with mFOLFOX6 plus panitumumab as initial therapy in patients with unresectable *RAS/BRAF* wild-type mCRC and found that more intensive mFOLFOXIRI plus panitumumab did not

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provide additional benefit and resulted in non-negligible increases in GI toxicity.[911] The two groups had similar OR rates, at 76% for mFOLFOX6 plus panitumumab versus 73% for mFOLFOXIRI plus panitumumab (OR, 0.87; 95% CI, 0.56–1.34; *P* = .526). Median PFS was also similar at a median follow-up of 26.5 months, at 12.7 months for mFOLFOX6 plus panitumumab versus 12.3 months for mFOLFOXIRI plus panitumumab (HR, 0.88; 95% CI, 0.70–1.11; *P* = .277). There were also no significant differences in early tumor shrinkage (58% vs. 57%; *P* = .878) or deepness of response (47% vs. 48%; *P* = .845) noted. Grade >2 diarrhea occurred in 7% of patients in the mFOLFOX6 plus panitumumab versus 23% of patients in the mFOLFOXIRI plus panitumumab group.

Cetuximab with CAPEOX: In a trial comparing CAPEOX/cetuximab versus FOLFOX/cetuximab, 88 patients with extended *RAS/BRAF/PIK3CA* wild-type mCRC were evaluated.[912] There was no significant difference in response rate between the CAPEOX/cetuximab versus FOLFOX/cetuximab arms, at 61.5% and 66.7%, respectively (*P* = .298). DCRs were also similar, at 86.5% (95% CI, 74.2%–94.4%) for the CAPEOX/cetuximab group versus 88.9% (95% CI, 73.9%–96.9%) for the FOLFOX/cetuximab group. Based on these data, the Panel now recommends CAPEOX plus cetuximab or panitumumab in addition to FOLFOX plus cetuximab or panitumumab for initial therapy for advanced CRC or mCRC.

Cetuximab or Panitumumab vs. Bevacizumab in First-Line Therapy: The randomized, open-label, multicenter FIRE-3 trial from the German AIO group compared the efficacy of FOLFIRI plus cetuximab to FOLFIRI plus bevacizumab in first-line, *KRAS* exon 2 wild-type, metastatic disease.[696] This trial did not meet its primary endpoint of investigator-read ORR in the 592 patients (62.0% vs. 58.0%; *P* = .18). PFS was nearly identical between the study arms, but a statistically significant improvement in OS was reported in the cetuximab arm (28.7 vs. 25.0 months; HR, 0.77; 95% CI, 0.62–0.96; *P* = .017). The Panel has several criticisms of the trial, including the lack of third-party review and low rates of second-line therapy.[913,914] While the rate of AEs was similar between the arms, more skin toxicity was observed in those receiving cetuximab. A final survival analysis of the FIRE-3 study reported a median OS in the *RAS* wild-type population of 31 months with cetuximab versus 26 months with bevacizumab, along with improved outcomes for ORR and median OS in the per-protocol population with cetuximab.[915] PFS was similar between the groups and the advantage for cetuximab only occurred in patients with left-sided primary tumors.

The phase III PARADIGM trial evaluated the use of panitumumab versus bevacizumab when combined with FOLFOX as first-line therapy in 823 patients with *RAS* wild-type mCRC.[916] In the as-treated population, 75.3% had left-sided tumors. After a median follow-up of 61 months, panitumumab showed a significantly higher median OS when used as part of the first-line regimen compared to bevacizumab. This was true for both the left-sided tumor population (37.9 vs. 34.3 months; *P* = .03) as well as the full analysis set (36.2 vs. 31.3 months; *P* = .03). While PFS was similar between the treatment groups, RR and R0 resection rates were higher with panitumumab. The Panel notes that since the OS curves do not separate until well after the median PFS, the improvement in OS with panitumumab may be related to what the patients received in later lines of therapy rather than the choice of first-line therapy.

Results of the phase III CALGB/SWOG 80405 trial, comparing FOLFOX/FOLFIRI with cetuximab or bevacizumab, were reported.[909] In this study, patients with wild-type *KRAS* exon 2 tumors received either FOLFOX (73%) or FOLFIRI (27%) and were randomized to receive cetuximab or bevacizumab. The primary endpoint of OS was equivalent between the arms, at 29.0 months in the bevacizumab arm versus 30.0 months in the cetuximab arm (HR, 0.88; 95% CI, 0.77–1.01; *P* = .08).

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Results for the randomized multicenter phase II PEAK trial, which compared FOLFOX/panitumumab with FOLFOX/bevacizumab in first-line treatment of patients with wild-type *KRAS* exon 2 tumors, were also published.[917] In the subset of 170 participants with wild-type *KRAS/NRAS* based on extended tumor analysis, PFS was better in the panitumumab arm (13.0 vs. 9.5 months; HR, 0.65; 95% CI, 0.44–0.96; *P* = .03). A trend towards improved OS was seen (41.3 vs. 28.9 months; HR, 0.63; 95% CI, 0.39–1.02; *P* = .06). The final analysis of the PEAK trial confirmed that FOLFOX/panitumumab showed a longer PFS compared to FOLFOX/bevacizumab in patients with wild-type *RAS* tumors (12.8 vs. 10.1 months; HR, 0.68; 95% CI, 0.48–0.96; *P* = .029).[918] Although these data are intriguing, definitive conclusions are hindered by the small sample size and limitations of subset analyses.[919]

Economic analyses suggest that bevacizumab may be more cost-effective than EGFR inhibitors in first-line therapy for mCRC,[920] although more recent analyses have shown the opposite.[921,922]

At this time, the Panel considers the addition of cetuximab, panitumumab, or bevacizumab to chemotherapy as equivalent choices in the first-line, *RAS/BRAF* wild-type, metastatic setting.

Checkpoint Inhibitor Immunotherapy for dMMR/MSI-H or POLE/POLD1 Mutation-Positive Disease in the First-Line Setting

The phase III, randomized, open-label KEYNOTE-177 study evaluated the use of pembrolizumab compared to chemotherapy with or without bevacizumab or cetuximab as first-line therapy for 307 patients with MSI-H/dMMR mCRC.[923] Median PFS was found to be longer with pembrolizumab compared to chemotherapy (16.5 vs. 8.2 months; HR, 0.60; 95% CI, 0.45–0.80; *P* = .0002). Confirmed ORR was 43.8% with pembrolizumab versus 33.1% with chemotherapy. Grade ≥3 treatment-related AEs were reported in 22% of patients treated with pembrolizumab compared to 66% of those treated with chemotherapy. In an updated final analysis of KEYNOTE-177, with a median follow-up of 44.5 months, median OS was NR with pembrolizumab (NR; 95% CI, 49.2–NR) compared to 36.7 months (NR; 95% CI, 27.6–NR) with chemotherapy (HR, 0.74; 95% CI, 0.53–1.03; *P* = .036).[924] While the survival difference was not significant between the two arms, the study did report a 60% crossover rate, with 60% of patients on the chemotherapy-first arm crossing over to pembrolizumab or another checkpoint inhibitor during the course of the study.

A follow-up health-related quality-of-life analysis of 294 patients treated as part of KEYNOTE-177 revealed a clinically meaningful improvement in quality of life with pembrolizumab versus chemotherapy based on European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires (*P* = .0002).[925]

Likewise, the phase II CheckMate-142 trial evaluated the role of nivolumab in combination with ipilimumab for first-line treatment of dMMR/MSI-H mCRC.[926] In the first-line cohort, ORR was found to be 69% (95% CI, 53%–82%) and DCR 84% (95% CI, 70.5%–93.5%), with a median follow-up of 29 months. Thirteen percent of patients had complete disease response and the median duration of response, median PFS, and median OS had not been reached. Twenty percent of patients had grade 3 or 4 treatment-related AEs and AEs led to discontinuation in 13% of patients. A 2022 abstract reported 5-year follow-up results of CheckMate-142.[927] ORR by investigator assessment increased to 71% (95% CI, 56–84), with progressive disease rate of 16%. PFS and OS rates at 48 months were 51% and 72%, respectively. Additional results from CheckMate-142 (including nivolumab alone or in combination with ipilimumab as subsequent therapy) are discussed in *Checkpoint Inhibitor Immunotherapy for dMMR/MSI-H or POLE/POLD1 Mutation-Positive Disease in the Non–First-Line Setting,* below.

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CheckMate 8HW is an ongoing phase III study comparing nivolumab in combination with ipilimumab to nivolumab alone or chemotherapy for dMMR/MSI-H mCRC. In a prespecified interim analysis, PFS was compared between nivolumab plus ipilimumab (202 patients) and chemotherapy (101 patients) in the first-line setting.[928] With a median follow-up of 24.3 months, the combination of nivolumab plus ipilimumab showed a significant improvement in PFS compared to chemotherapy, with a 79% reduction in the risk of disease progression or death (HR, 0.21; 95% CI, 0.14–0.32; $P < .0001$). No new safety signals were observed, and nivolumab plus ipilimumab had a lower percentage of grade ≥3 treatment-related AEs compared to chemotherapy (23% vs. 48%), although there were two treatment-related deaths on the immunotherapy combination and none with chemotherapy. OS data have not yet been presented.

Although PD-1 immune checkpoint inhibitors are generally well tolerated, serious adverse reactions—many immune-mediated—occur in as many as 21% to 41% of patients.[929-932] The most common immune-mediated side effects are to the skin, liver, kidneys, GI tract, lungs, and endocrine systems.[933-935] Pneumonitis, occurring in approximately 3% to 7% of patients on checkpoint inhibitor therapy, is one of the most serious side effects of PD-1 inhibitors.[933,936-938]

Based on these data, the Panel recommends pembrolizumab; dostarlimab-gxly; or nivolumab, alone or in combination with ipilimumab, as first-line treatment options for patients with MSI-H/dMMR mCRC, regardless of whether intensive therapy is recommended. The recommendation for nivolumab plus ipilimumab is category 2B when intensive therapy is not recommended due to concerns about potential toxicity from the combination therapy. While dostarlimab-gxly does not have clinical trial data for untreated mCRC, the Panel feels that the checkpoint inhibitors may be used interchangeably for dMMR/MSI-H mCRC and the clinical trial data for dostarlimab-gxly in both the previously untreated, locally advanced and the previously treated mCRC settings support its use in the first-line setting. As discussed in the *Biomarkers for Systemic Therapy* section, above, checkpoint inhibitor immunotherapy is also recommended for mCRC with functional *POLE/POLD1* mutations.

Second-Line or Subsequent Systemic Therapy

The recommended therapy options after first progression for patients who have received prior therapy are dependent on the initial treatment regimen and are outlined in the guidelines. Single-agent irinotecan administered after first progression has been shown to significantly improve OS relative to best supportive care [939] or infusional 5-FU/LV.[940] In the study of Rougier et al,[940] median PFS was 4.2 months for irinotecan versus 2.9 months for 5-FU ($P = .030$), whereas Cunningham et al[939] reported a survival rate at 1 year of 36.2% in the group receiving irinotecan versus 13.8% in the supportive care group ($P = .0001$). A meta-analysis of five RCTs showed that there was no OS benefit to FOLFIRI over that obtained with irinotecan alone.[941] Furthermore, no significant differences in OS were observed in the Intergroup N9841 trial when FOLFOX was compared with irinotecan monotherapy after first progression of mCRC.[942]

A meta-analysis of randomized trials found that the addition of a targeted agent after first-line treatment improves outcomes but also increases toxicity.[943] Another meta-analysis showed an OS and PFS benefit to continuing an anti-angiogenic agent after progression on an anti-angiogenic agent in first-line.[944] Data relating to specific biologic therapies are discussed below.

Cetuximab and Panitumumab in the Non–First-Line Setting

For patients with wild-type *KRAS/NRAS/BRAF* tumors who experienced progression on therapies *not* containing an EGFR inhibitor, cetuximab or panitumumab plus irinotecan, cetuximab or panitumumab plus FOLFIRI, or single-agent cetuximab or panitumumab[681] is recommended. For patients with wild-type *KRAS/NRAS/BRAF* tumors progressing on

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therapies that *did* contain an EGFR inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy, except for anti-EGFR rechallenge. No data support switching to either cetuximab or panitumumab after disease progression on the other drug, and the Panel recommends against this practice. While there is limited evidence suggesting that sidedness is predictive of response to EGFR inhibitors in subsequent lines of therapy, the Panel awaits more definitive studies to set this limitation. Until such data are available, all patients with *RAS/BRAF* wild-type tumors can be considered for panitumumab or cetuximab in subsequent lines of therapy if neither was previously given. See section on *Cetuximab/Panitumumab and Primary Tumor Sidedness*, above, for discussion of data.

Panitumumab has been studied as a single agent in the setting of mCRC for patients with disease progression on oxaliplatin/irinotecan-based chemotherapy in an open-label phase III trial.[945] In a retrospective analysis of the subset of patients in this trial with known *KRAS* exon 2 tumor status, the benefit of panitumumab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[677] PFS was 12.3 weeks versus 7.3 weeks in favor of the panitumumab arm. Response rates to panitumumab were 17% versus 0% in the wild-type and mutant arms, respectively.[677] A more recent phase III trial compared single-agent panitumumab to best supportive care in patients with wild-type *KRAS* exon 2 mCRC and disease progression on oxaliplatin- and irinotecan-based chemotherapy.[946] The primary endpoint of OS was improved with panitumumab (10.0 vs. 7.4 months; HR, 0.73; 95% CI, 0.57–0.93; $P < .01$).

Panitumumab has also been studied in combination therapy in the setting of progressing mCRC. Among patients with *KRAS* exon 2 wild-type tumors enrolled in the large Study 181 comparing FOLFIRI alone versus FOLFIRI plus panitumumab as second-line therapy for mCRC, addition of the biologic agent was associated with improvement in median PFS (5.9 vs. 3.9 months; HR, 0.73; 95% CI, 0.59–0.90; $P = .004$), although differences in OS between the arms did not reach statistical significance.[839] These results were confirmed in the final results of Study 181.[906] Furthermore, re-analysis of samples from the trial showed that the benefit of the combination was limited to participants with no *RAS* mutations.[947] In addition, secondary analysis from the STEPP trial showed that panitumumab in combination with irinotecan-based chemotherapy in second-line therapy has an acceptable toxicity profile.[905] The randomized multicenter PICCOLO trial, which assessed the safety and efficacy of irinotecan/panitumumab, did not meet its primary endpoint of improved OS in patients with wild-type *KRAS/NRAS* tumors.[717]

Cetuximab has been studied both as a single agent[681,885,948,949] and in combination with irinotecan[948] in patients experiencing disease progression on initial therapy not containing cetuximab or panitumumab for metastatic disease. Results of a large phase III study comparing irinotecan with or without cetuximab did not show a difference in OS, but showed significant improvement in response rate and in median PFS with irinotecan and cetuximab compared with irinotecan alone.[950] Importantly, *KRAS* status was not determined in this study and toxicity was higher in the cetuximab-containing arm (eg, rash, diarrhea, electrolyte imbalances).[950] In a re-analysis of *RAS* status, median PFS (5.4 vs. 2.6 months; HR, 0.57; 95% CI, 0.46–0.69; $P < .0001$) and ORR (29.4% vs. 5.0%; OR, 8.12; 95% CI, 4.04–17.40; $P < .0001$) were improved with cetuximab plus irinotecan compared to irinotecan alone.[951] Median OS was similar between the two groups (12.3 months for cetuximab plus irinotecan vs. 12.0 months for irinotecan alone [HR, 0.91; 95% CI, 0.71–1.17; $P = .4645$]). Almost 50% of patients in the irinotecan alone arm received cetuximab post-study, potentially masking an OS benefit with the addition of cetuximab.

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In a retrospective analysis of the subset of patients with known *KRAS* exon 2 tumor status receiving cetuximab monotherapy as second-line therapy,[885] the benefit of cetuximab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[681] For those patients, median PFS was 3.7 versus 1.9 months (HR, 0.40; 95% CI, 0.30–0.54; $P < .001$) and median OS was 9.5 versus 4.8 months (HR, 0.55; 95% CI, 0.41–0.74; $P < .001$), in favor of the cetuximab arm.[681]

The randomized, multicenter, open-label, noninferiority phase III ASPECCT trial compared single-agent cetuximab with single-agent panitumumab in the chemotherapy-refractory metastatic setting.[952] The primary noninferiority OS endpoint was reached, with a median OS of 10.4 months (95% CI, 9.4–11.6) with panitumumab and 10.0 months (95% CI, 9.3–11.0) with cetuximab (HR, 0.97; 95% CI, 0.84–1.11). The incidence of AEs was similar between the groups. The final analysis of ASPECCT came to the same conclusion, reporting a median OS of 10.2 months with panitumumab and 9.9 months with cetuximab (HR, 0.98; 95% CI, 0.82–1.07).[953]

The randomized, multicenter, phase II SPIRITT trial randomized 182 patients with *KRAS* wild-type tumors whose disease progressed on first-line oxaliplatin-based therapy plus bevacizumab to FOLFIRI plus bevacizumab or FOLFIRI plus panitumumab.[954] No difference was seen in the primary endpoint of PFS between the arms (7.7 months in the panitumumab arm vs. 9.2 months in the bevacizumab arm; HR, 1.01; 95% CI, 0.68–1.50; $P = .97$).

A pooled analysis of the TRIBE and TRIBE2 studies assessed treatments administered after second disease progression in 1187 patients with mCRC who received upfront FOLFOXIRI/ bevacizumab versus FOLFOX or FOLFIRI/bevacizumab.[955] In third-line therapy, patients with *RAS/BRAF* wild-type tumors achieved longer PFS with EGFR inhibitors compared to other therapies (6.4 vs. 3.9 months, $P = .02$)

Bevacizumab in the Non–First-Line Setting

In the TML (ML18147) trial, patients with mCRC who progressed on regimens containing bevacizumab received second-line therapy consisting of a different chemotherapy regimen with or without bevacizumab.[956] This study met its primary endpoint, with patients continuing on bevacizumab having a modest improvement in OS (11.2 vs. 9.8 months; HR, 0.81; 95% CI, 0.69–0.94; $P = .0062$). Subgroup analyses from this trial found that these treatment effects were independent of *KRAS* exon 2 status.[957]

Similar results were reported from the GONO group's phase III randomized BEBYP trial, in which the PFS of patients who continued on bevacizumab plus a different chemotherapy regimen following progression on bevacizumab was 6.8 months compared to 5.0 months in the control arm (HR, 0.70; 95% CI, 0.52–0.95; $P = .001$).[958] An improvement in OS was also seen in the bevacizumab arm (HR, 0.77; 95% CI, 0.56–1.06; $P = .04$). The EAGLE trial randomized 387 patients with disease progression following oxaliplatin-based therapy with bevacizumab to second-line therapy with FOLFIRI plus either 5 or 10 mg/kg bevacizumab.[959] No difference was seen in PFS or time to treatment failure between the arms, indicating that 5 mg/kg of bevacizumab is an appropriate dose in second-line treatment of mCRC.

The continuation of bevacizumab following progression on bevacizumab was also studied in a community oncology setting through a retrospective analysis of 573 patients from the US Oncology iKnowMed electronic medical record system.[960] Bevacizumab beyond progression was associated with a longer OS (HR, 0.76; 95% CI, 0.61–0.95) and a longer post-progression OS (HR, 0.74; 95% CI, 0.60–0.93) on multivariate analysis. Analyses of the ARIES observational cohort found similar results, with longer post-progression survival with continuation of bevacizumab (HR, 0.84; 95% CI, 0.73–0.97).[961]

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Overall, these data (along with data from the VELOUR trial, discussed below) show that the continuation of VEGF blockade in second-line therapy offers a very modest but statistically significant OS benefit. The Panel added the continuation of bevacizumab to the second-line treatment options in the 2013 versions of the NCCN Guidelines for Colon and Rectal Cancers. It may be added to any regimen that does not contain another targeted agent. The Panel recognizes the lack of data suggesting a benefit to bevacizumab with irinotecan alone in this setting, but believes that the option is acceptable, especially in patients whose disease progressed on a 5-FU– or capecitabine-based regimen. When an angiogenic agent is used in second-line therapy, bevacizumab is preferred over ziv-aflibercept and ramucirumab (discussed below), based on toxicity and/or cost.[962] Beyond the second-line setting, bevacizumab may be combined with trifluridine-tipiracil [see *Trifluridine-Tipiracil (TAS-102)*, below, for more information].

It may also be appropriate to consider using bevacizumab with second-line therapy after progression on a first-line regimen that did not contain bevacizumab.[963] However, there are no data to support adding bevacizumab to a regimen after progression on that same regimen. The randomized phase III ECOG E3200 study in patients who experienced disease progression through a first-line non-bevacizumab–containing regimen showed that the addition of bevacizumab to second-line FOLFOX modestly improved survival.[963] Median OS was 12.9 months for patients receiving FOLFOX plus bevacizumab compared with 10.8 months for patients treated with FOLFOX alone (P = .0011).[963] Use of single-agent bevacizumab is not recommended because it was shown to have inferior efficacy compared with the FOLFOX alone or FOLFOX plus bevacizumab treatment arms.[963]

Ziv-Aflibercept

Ziv-aflibercept is a recombinant protein that has part of the human VEGF receptors (VEGFR) 1 and 2 fused to the Fc portion of human immunoglobulin G1 (IgG1). It is designed to function as a VEGF trap to prevent activation of VEGFR and thus inhibit angiogenesis. The VELOUR trial tested second-line ziv-aflibercept in patients with mCRC that progressed after one regimen containing oxaliplatin. The trial met its primary endpoint with a small improvement in OS (13.5 months for FOLFIRI/ziv-aflibercept vs. 12.1 months for FOLFIRI/placebo; HR, 0.82; 95% CI, 0.71–0.94; P = .003).[964] A prespecified subgroup analysis from the VELOUR trial found that median OS in the ziv-aflibercept arm versus the placebo arm was 12.5 months (95% CI, 10.8–15.5) versus 11.7 months (95% CI, 9.8–13.8) in patients with prior bevacizumab treatment and 13.9 months (95% CI, 12.7–15.6) versus 12.4 months (95% CI, 11.2–13.5) in patients with no prior bevacizumab treatment.[965]

AEs associated with ziv-aflibercept treatment in the VELOUR trial led to discontinuation in 26.6% of patients compared to a 12.1% discontinuation in the placebo group.[964] The most common causes for discontinuation were asthenia/fatigue, infections, diarrhea, hypertension, and venous thromboembolic events.

Ziv-aflibercept has only shown activity when given in conjunction with FOLFIRI in patients without prior exposure to FOLFIRI. No data suggest activity of FOLFIRI plus ziv-aflibercept in patients whose disease progressed on FOLFIRI plus bevacizumab or vice-versa, and no data suggest activity of single-agent ziv-aflibercept. Furthermore, the addition of ziv-aflibercept to FOLFIRI in first-line therapy of patients with mCRC in the phase II AFFIRM study had no benefit and increased toxicity.[966] Thus, the Panel added ziv-aflibercept as a second-line treatment option in combination with FOLFIRI or irinotecan only following progression on therapy not containing irinotecan. However, the Panel prefers bevacizumab over ziv-aflibercept and ramucirumab (discussed below) in this setting, based on toxicity and/or cost.[962]

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Ramucirumab

Another anti-angiogenic agent, ramucirumab, is a human monoclonal antibody that targets the extracellular domain of VEGFR 2 to block VEGF signaling. In the multicenter, phase III RAISE trial, 1072 patients with mCRC whose disease progressed on first-line therapy with fluoropyrimidine/oxaliplatin/bevacizumab were randomized to FOLFIRI with either ramucirumab or placebo.[967] The primary endpoint of OS in the ITT population was met at 13.3 months and 11.7 months in the ramucirumab and placebo groups, respectively, for an HR of 0.84 (95% CI, 0.73–0.98; $P = .02$). PFS was also improved with the addition of ramucirumab, at 5.7 months and 4.5 months for the two arms (HR, 0.79; 95% CI, 0.70–0.90; $P < .0005$). A subgroup analysis of the RAISE trial subsequently reported similar efficacy and safety among patient subgroups with different *KRAS* mutation tumor status, time to progression on first-line therapy, and age.[968]

Rates of discontinuation due to AEs in the RAISE trial were 11.5% in the ramucirumab arm and 4.5% in the placebo arm. The most common grade 3 or worse AEs were neutropenia, hypertension, diarrhea, and fatigue. In addition, a meta-analysis of six phase III trials showed that ramucirumab did not increase the risk of arterial thromboembolic events, venous thromboembolic events, high-grade bleeding, or high-grade GI bleeding compared to placebo controls.[969] These results suggest that ramucirumab may be distinct among antiangiogenic agents in that it does not increase the risk of these events.

Considering the results of the RAISE trial, the Panel added ramucirumab as a second-line treatment option in combination with FOLFIRI or irinotecan following progression on therapy not containing irinotecan. As with ziv-aflibercept, no data suggest activity of FOLFIRI plus ramucirumab in patients whose disease progressed on FOLFIRI plus bevacizumab or vice-versa, and no data suggest activity of single-agent ramucirumab.

When an angiogenic agent is used in this setting, the Panel prefers bevacizumab over ziv-aflibercept and ramucirumab, because of toxicity and/or cost.[962]

Encorafenib Plus Cetuximab or Panitumumab for BRAF V600E Mutation-Positive Disease in the Non–First-Line Setting

A combination of the BRAF inhibitor, encorafenib, and the MEK inhibitor, binimetinib, with cetuximab has been investigated in the randomized, phase III BEACON trial for metastatic, *BRAF* V600E mutation-positive CRC.[970,971] The safety lead-in of the BEACON trial showed promising efficacy results with an ORR of 48% (95% CI, 29.4%–67.5%) among the 29 patients included in the efficacy analysis. Among the 30 treated patients in the safety lead-in, the most common grade 3 or 4 AEs were fatigue (13%), anemia (10%), increased creatine phosphokinase (10%), increased aspartate transaminase (AST) (10%), and urinary tract infections (10%).[970]

Subsequently, the randomized portion of the BEACON trial reported similarly encouraging results, including a positive OS result.[971] Within this portion of the study, 665 patients were randomized to receive either the triplet combination, an encorafenib and cetuximab doublet, or a control regimen of cetuximab plus either irinotecan or FOLFIRI. Updated results of BEACON reported a median OS of 5.9 months, 9.3 months, and 9.3 months for the control, doublet, and triplet arms, respectively.[972] The confirmed ORRs were 1.8%, 19.5%, and 26.8%, respectively, and grade 3 or higher AE rates were highest in the triplet arm, although the addition of binimetinib did not improve OS over the doublet. Quality-of-life assessments showed that the doublet and triplet regimens led to a similarly longer maintenance of quality of life compared with control.[973] Based on these reports, the NCCN Panel concluded that only the doublet regimen of encorafenib with either cetuximab or panitumumab should be recommended for patients with *BRAF* V600E-mutated mCRC.

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Data exist on the use of cetuximab or panitumumab in combination with irinotecan and vemurafenib[974] or dabrafenib plus trametinib[975] for *BRAF* V600E mutation-positive mCRC. However, based on superior data and/or lower toxicity with the encorafenib-containing doublets, the Panel voted to not include recommendations for these regimens within the current version of the guidelines.

Systemic Therapy Options for HER2-Amplified Disease

Four different regimens are recommended by the Panel as options for subsequent treatment of mCRC with HER2 amplifications: fam-trastuzumab deruxtecan-nxki (T-DXd) monotherapy or trastuzumab in combination with pertuzumab, lapatinib, or tucatinib. These regimens (with the exception of T-DXd) may also be appropriate for patients with previously untreated HER2-amplified mCRC when intensive therapy is not recommended. The NCCN Panel notes that FDA-approved biosimilars may be substituted for trastuzumab wherever the therapy is recommended within these Guidelines (see *Biosimilars*, above, for more information). The results of clinical trials supporting each of these regimens are detailed below.

Trastuzumab Plus Pertuzumab: A combination regimen of the HER2 inhibitors trastuzumab and pertuzumab was studied in a subset analysis of MyPathway, a phase IIa multiple basket study.[976] This subset included 57 patients with previously treated, HER2-amplified mCRC who were treated with the combination of pertuzumab and trastuzumab. ORR was 32% (95% CI, 20–45), with 1 complete response and 17 partial responses. Thirty-seven percent of patients treated with trastuzumab plus pertuzumab had grade 3 or 4 AEs, with hypokalemia and abdominal pain being most common. Another phase II basket study, TAPUR, also investigated the combination of trastuzumab and pertuzumab in HER2-amplified mCRC.[977] In this study, 28 patients with heavily pretreated, HER2-amplified advanced CRC were treated with the combination. The DCR was 54% and OR was observed in 25% of patients. The median PFS and median OS were 9.6 weeks and 28.8 weeks, respectively. Four patients had at least one grade 3 AE or serious AE, including anemia, infusion reaction, left ventricular dysfunction, and decreased lymphocyte count.

Trastuzumab Plus Lapatinib: The combination of trastuzumab plus the dual HER2/EGFR inhibitor, lapatinib, was studied in the multicenter, phase II HERACLES trial.[730] This trial included 27 patients with previously treated, HER2-positive tumors that were treated with trastuzumab and lapatinib. ORR was 30% (95% CI, 14–50), with one complete response, seven partial responses, and 12 patients with stable disease. Twenty-two percent of patients treated with trastuzumab plus lapatinib had grade 3 AEs, including fatigue (four patients), skin rash (one patient), and increased bilirubin (one patient).[730]

Trastuzumab Plus Tucatinib: A combination regimen of the HER2 inhibitors trastuzumab and tucatinib was studied in the multicenter, phase II MOUNTAINEER trial.[978] This trial included 117 patients with chemotherapy-refractory, HER2-positive, *RAS* wild-type mCRC. Initially, all patients on this study were treated with the combination (cohort A), while later, patients were randomized to receive either tucatinib monotherapy (cohort C) or the combination of tucatinib and trastuzumab (cohort B). Of the 84 patients who received the combination in cohorts A and B, the confirmed ORR was 38.1% (95% CI, 27.7-49.3), with three patients having a complete response to the treatment. In all three cohorts, the most common AE was diarrhea. Three percent of patients who received the combination had tucatinib-related serious AEs (acute kidney injury, colitis, and fatigue).

T-DXd: The HER2-directed antibody and topoisomerase inhibitor conjugate was studied in the phase 2, multicenter DESTINY-CRC01 trial of 78 patients with HER2-expressing, *RAS/BRAF* wild-type unresectable CRC and/or mCRC that had already progressed on at least two prior

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regimens.[979] Patients were split into three cohorts based on the level of tumor HER2 expression (cohort A: IHC 3+ or IHC 2+/ISH+; cohort B: IHC 2+/ISH-; cohort C: IHC 1+). In cohort A, the primary endpoint of ORR was 45.3%, with one complete response and 23 partial responses. Median PFS in this group was 6.9 months, and median OS had not yet been reached at the time of data cutoff. No responses were reported in cohorts B or C. Thirty percent of patients in cohort A had received prior anti-HER2 therapy; for these patients ORR was 43.8%. The most common grade ≥3 treatment-emergent AEs were decreased neutrophil count (22%) and anemia (14%). In the final analysis of DESTINY-CRC01, no responses occurred in cohorts B or C.[980] In cohort A, confirmed ORR was 45.3%, all of which were partial responses, with a median duration of response of 7.0 months. Median PFS and OS were 6.9 and 15.5 months, respectively. Of note, across all three cohorts, eight patients on this trial developed interstitial lung disease or pneumonitis related to T-DXd, including three deaths due to this complication (3.5% of all patients).

The ongoing DESTINY-CRC02 trial includes patients with HER2-positive (IHC 3+ or IHC 2+/ISH+) mCRC, with either *RAS* wild-type or mutant disease.[981] Patients were randomized to either 5.4 or 6.4 mg/kg T-DXd. An abstract presented primary results, reporting an ORR of 37.8% for the 5.4 mg/kg dose and 27.5% for 6.4 mg/kg. T-DXd showed antitumor activity irrespective of *RAS* mutation status and in those who were previously treated with anti-HER2 therapy, suggesting that this agent may be considered as an option for HER2-amplified mCRC regardless of *RAS* mutation status or previous HER2 targeted therapy.

Systemic Therapy Options for KRAS G12C Mutation-Positive Disease in the Non–First-Line Setting

Two KRAS G12C inhibitors, sotorasib and adagrasib, are recommended for treatment of previously treated mCRC, which harbors this mutation. Sotorasib or adagrasib should be given in combination with cetuximab or panitumumab or may be considered as a single agent if there are concerns about toxicities from EGFR inhibitors. Mechanisms for acquired resistance to adagrasib and sotorasib have been described.[982]

The phase I portion of the CodeBreaK 100 trial was a basket study of sotorasib monotherapy. It included 129 patients with solid tumors harboring the *KRAS* G12C mutation, 42 with CRC.[983] Of the subgroup with CRC, 7.1% had a confirmed response and 73.8% had disease control. A prespecified subset analysis of the phase II portion of CodeBreaK 100 investigated sotorasib monotherapy for previously treated mCRC with *KRAS* G12C mutation.[984] OR was observed in 9.7% of the 62 treated patients. Grade ≥3 treatment-related AEs occurred in 11.6% of patients treated with sotorasib monotherapy. The phase Ib/2 CodeBreaK 101 trial looked at various doublets including sotorasib. One cohort of this trial investigated the combination of sotorasib plus panitumumab in 40 patients with previously treated *KRAS* G12C-mutated mCRC. Results from the dose expansion cohort reported a confirmed ORR of 30% (95% CI, 16.6%–46.5%).[985] Median PFS and OS were 5.7 and 15.2 months, respectively. Grade ≥3 treatment-related AEs occurred in 27% of patients who received the combination therapy.

KRYSTAL-1 is a phase 1/2 clinical trial evaluating the safety and efficacy of adagrasib, alone or in combination with other anticancer therapies, in patients with advanced solid tumors that had been previously treated. One publication of this study reported results for patients with *KRAS* G12C-mutated mCRC treated with adagrasib alone (n = 44) or adagrasib in combination with cetuximab (n = 32).[986] In this subgroup, disease response was reported in 19% of patients treated with adagrasib monotherapy, with a median duration of response of 4.3 months (95% CI, 8–33) and median PFS of 5.6 months (95% CI, 2.3–8.3). For the combination of adagrasib and cetuximab, responses were noted in 46% of patients, with a median response duration of 7.6 months (95% CI, 5.7–not

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estimable [NE]) and median PFS of 6.9 months (95% CI, 5.4–8.1). Grade ≥3 treatment-related AEs were reported in 34% of patients who received the monotherapy and 16% of those who received the combination. A 2024 American Association for Cancer Research (AACR) abstract on this study presented updated results from 94 patients who received the combination of adagrasib and cetuximab.[987] With a median follow-up of 11.9 months, the ORR was 34.0%, DCR was 85.1%, and median duration of response was 5.8 months. Median PFS was 6.9 months and median OS was 15.9 months.

Checkpoint Inhibitor Immunotherapy for dMMR/MSI-H or POLE/POLD1 Mutation-Positive Disease in the Non–First-Line Setting

The Panel currently recommends that dMMR/MSI-H or *POLE/POLD1* mutation-positive mCRC be treated with a checkpoint inhibitor as first-line therapy if no prior immunotherapy has been received and the patient is a candidate for immunotherapy. However, if a different therapy was used in the first-line setting, checkpoint inhibitor immunotherapy is also appropriate for use in the non–first-line setting.

Pembrolizumab is a humanized, IgG4 monoclonal antibody that binds to PD-1 with high affinity, preventing its interaction with PD-L1 and PD-L2 and thus allowing immune recognition and response.[755] A phase II study evaluated the activity of pembrolizumab in 11 patients with dMMR CRC, 21 patients with pMMR CRC, and nine patients with dMMR non-colorectal carcinomas.[929] All patients had progressive metastatic disease; the patients in the colorectal arms had progressed through two to four previous therapies. The primary endpoints were the immune-related ORR and the 20-week immune-related PFS rate. The immune-related ORRs were 40% (95% CI, 12–74) in the dMMR CRC group, 0% (95% CI, 0–20) in the pMMR CRC group, and 71% (95% CI, 29–96) in the dMMR non-colorectal group. The 20-week immune-related PFS rates were 78% (95% CI, 40–97), 11% (95% CI, 1–35), and 67% (95% CI, 22–96), respectively. These results indicate that MSI is a predictive marker for the effectiveness of pembrolizumab across tumor types. Furthermore, the median PFS and OS were NR in the arm with dMMR CRC and were 2.2 and 5.0 months, respectively, in the pMMR CRC group (HR for disease progression or death, 0.10; $P < .001$). Another phase II study, KEYNOTE-164, investigated the efficacy of pembrolizumab in 124 patients with MSI-H/dMMR mCRC that had been treated with at least one previous line of therapy.[988] The patients on this study were divided into two cohorts based on whether they had received ≥2 lines of therapy including fluoropyrimidine, oxaliplatin, and irinotecan (cohort A) or ≥1 lines of therapy (cohort B). ORR was reported as 33% for both cohorts, with the median duration of response not reached at the time of publication. Median PFS was 2.3 months and 4.1 months, for cohorts A and B, respectively. Median OS was 31.4 months for cohort A and had not been reached for cohort B. Treatment-related AEs of grade ≥3 occurred in 16% of patients in cohort A and 13% in cohort B, with pancreatitis, fatigue, increased alanine aminotransferase, and increased lipase being most common.

Nivolumab is another humanized IgG4 PD-1 blocking antibody,[989] which was studied with or without ipilimumab in patients with mCRC in the phase II, multi-cohort, CheckMate-142 trial.[931,932] One cohort of this trial included 74 patients with dMMR CRC who were treated with nivolumab. ORR for these patients was 31.1% (95% CI, 20.8–42.9) with 69% of patients having disease control for at least 12 weeks. Median duration of response had not yet been reached at the time of data collection. PFS and OS were 50% and 73%, respectively, at 1 year. Grade 3 or 4 drug-related AEs occurred in 20% of patients, with increased amylase and increased lipase being most common.[931] Emerging 5-year long-term data revealed an ORR of 39% (95% CI, 28–51).[927] PFS and OS at 48 months were 36% and 49%, respectively.

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Another cohort of the CheckMate-142 included 119 patients with dMMR CRC who were treated with nivolumab in combination with ipilimumab. For this cohort, ORR was 55% (95% CI, 45.2–63.8) and the DCR for at least 12 weeks was 80%. PFS and OS were 71% and 85%, respectively, at 1 year. In addition, significant, clinically meaningful improvements were observed in patient-reported outcomes of functioning, symptoms, and quality of life. Grade 3 to 4 treatment-related AEs occurred in 32% of patients, but were manageable.[932] An in-depth analysis of the safety profile of nivolumab plus ipilimumab on the CheckMate-142 trial reported that AEs predefined in the study protocol as being of special clinical interest (eg, endocrine, GI, hepatic, pulmonary, renal, and skin events) tended to occur early in treatment, were managed using evidence-based treatment algorithms, and resolved.[990] Emerging 5-year long-term data from this cohort revealed an ORR of 65% (95% CI, 55–73).[927] PFS and OS at 48 months were 54% and 71%, respectively.

A third humanized IgG4 PD-1 blocking antibody, dostarlimab-gxly, has been FDA-approved for the treatment of adult patients with dMMR recurrent or advanced solid tumors that have progressed on or following treatment and who have no satisfactory alternative treatment options.[991] The safety and efficacy of dostarlimab-gxly was evaluated in the phase I GARNET study of patients with advanced solid tumors who had previously received systemic therapy for advanced disease.[992] Cohort F of this trial enrolled patients with dMMR- or *POLE*-mutant non-endometrial solid tumors, the majority of which were GI cancers. Of the 115 patients with CRC in the efficacy analysis, confirmed ORR was 43.5% (95% CI, 34.3–53.0), with 12.2% achieving complete response. Median PFS for this group was 8.4 months and median DOR and OS were not yet reached. Treatment-related AEs grade ≥3 were reported in 16.3% of 363 patients included in the safety analysis. Dostarlimab-gxly was discontinued in 25 patients due to a treatment-related AE.

Based on these data, the Panel recommends pembrolizumab, nivolumab, nivolumab plus ipilimumab, or dostarlimab-gxly as subsequent-line treatment options in patients with metastatic dMMR/MSI-H CRC who have not previously received checkpoint inhibitor immunotherapy. As discussed in the *Biomarkers for Systemic Therapy* section above, checkpoint inhibitor immunotherapy is also recommended for mCRC with functional *POLE/POLD1* mutations.

Systemic Therapy Options for NTRK Gene Fusion-Positive Disease in the Non–First-Line Setting

Studies have estimated that about 0.2% to 1% of CRCs carry *NTRK* gene fusions.[747,748] Three targeted therapies: larotrectinib, entrectinib, and repotrectinib have been FDA-approved for the treatment of patients with metastatic, unresectable solid tumors that have an *NTRK* gene fusion and no satisfactory alternative treatment options, regardless of the location of the primary tumor. The Panel recommends larotrectinib, entrectinib, or repotrectinib as subsequent treatment options for patients with *NTRK* gene fusion-positive disease, acknowledging that these therapies will not be appropriate for most patients due to the rarity of the *NTRK* fusion in CRC.

Larotrectinib: A pooled analysis of three studies (a phase I including adults, a phase I/II involving children, and the phase II NAVIGATE study involving adolescents and adults) studied the safety and efficacy of larotrectinib in 55 patients with *NTRK* gene fusion-positive tumors, including four patients with colon cancer.[746] For the whole population, the ORR was 75% (95% CI, 61–85) by independent review and 80% (95% CI, 67–90) by investigator assessment,[746] although the package insert cites a 25% ORR for colon tumors specifically.[993] Larotrectinib was found to be well-tolerated as the majority (93%) of AEs were grades 1 or 2 and no treatment-related AEs of grades 3 or 4 occurred in >5% of patients.[746] A subsequent analysis of these three studies included 159 patients, eight

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with colon cancer, and reported similar results compared to the earlier analysis.[994] In this later analysis, the ORR was 79% (95% CI, 72–85) by investigator assessment with 16% complete responses. An analysis of 14 patients with GI cancer who were treated with larotrectinib in the NAVIGATE study reported a median PFS of 5.3 months (95% CI, 2.2–9.0) and a median OS of 33.4 months (95% CI, 2.8–36.5).[995] Responses were ongoing for five patients, leading their results to be censored. Of the 8 patients with colon cancer, 50% showed a partial response and 50% had stable disease.

Entrectinib: An integrated analysis of three global phase I/II studies (ALKA-372-001, STARTRK-1, and STARTRK-2) tested the efficacy and safety of entrectinib in 54 adult patients with advanced or metastatic *NTRK* gene fusion-positive solid tumors.[996] For the whole population, ORR was 57% (95% CI, 43.2–70.8), median PFS was 11 months (95% CI, 8.0–14.9), and median OS was 21 months (95% CI, 14.9–NE) by independent review. Median duration of response was 10 months (95% CI, 7.1–NE). Of the four patients with CRC in this study, one was recorded as having a response. Notably, a similar ORR (50% vs. 60%) was observed among those with central nervous system metastasis, indicating that entrectinib has activity in this population. Entrectinib was found to be well-tolerated as most treatment-related AEs were grade 1 or 2 and managed with dose reduction, leading few (4%) patients to discontinue therapy due to treatment-related AEs.

Repotrectinib: The phase I/II TRIDENT-1 trial tested repotrectinib in two cohorts of patients with *NTRK* gene fusion-positive advanced solid tumors; 40 patients in the NTRK TKI-naïve cohort, who received repotrectinib as their first NTRK TKI treatment, and 48 patients in the NTRK TKI-pretreated cohort, who had already received larotrectinib or entrectinib.[997] One patient on the NTRK TKI-naïve cohort had CRC and two had CRC in the NTRK TKI-pretreated cohort. An abstract presented at ESMO Congress 2023 reported a confirmed ORR of 58%, 12-month DOR of 86%, and 12-month PFS of 56% for the TKI-naïve group and a confirmed ORR of 50%, 12-month DOR of 39%, and 12-month PFS of 22% for the TKI-pretreated population. Grade ≥3 treatment-emergent AEs occurred in 51% of patients (29% were treatment-related), with dizziness being most common. Treatment discontinuation due to AEs occurred in 7% of patients.

Selpercatinib for RET Gene Fusion-Positive Disease in the Non-First-Line Setting

In the ongoing phase 1/2 LIBRETTO-001 trial, the efficacy and safety of the highly selective RET kinase inhibitor selpercatinib is being investigated in a diverse group of patients with *RET* gene fusion-positive tumors, including 10 patients with colon cancer.[752] Patients in this trial had received a median of 2 prior lines of systemic therapy and 31% of patients received 3 or more prior lines of treatment. Of a total of 41 efficacy-evaluable patients, the ORR for the entire cohort by independent review was 43.9% (95% CI, 28.5–60.3) and 20% in the colon cancer subgroup (95% CI, 2.5–55.6). There were 2 complete responses (5%), although neither patient had colon cancer. For the entire cohort, median PFS was 13.2 months (95% CI, 7.4–26.2) by independent review, median OS was 18 months (95% CI, 10.7–NE), and median duration of response was 24.5 months (95% CI, 9.2–NE). For the colon cancer subgroup, median duration of response was 9.4 months (95% CI, 5.6–13.3). The most common grade 3 or higher treatment-emergent AEs were hypertension and transaminitis. The most common treatment-related serious AEs were drug-induced livery injury, fatigue, and hypersensitivity. One patient had to permanently discontinue selpercatinib due to drug-induced liver injury.

Based on these data, the FDA has approved selpercatinib for locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment or who have no satisfactory alternative treatment options.[998]

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Regorafenib

Regorafenib is a small-molecule inhibitor of multiple kinases (including VEGFR, fibroblast growth factor [FGF] receptors, platelet-derived growth factor [PDGF] receptors, BRAF, KIT, and RET) that are involved with various processes including tumor growth and angiogenesis.[999] The phase III CORRECT trial randomized 760 patients whose disease progressed on standard therapy to best supportive care with placebo or regorafenib.[1000] The trial met its primary endpoint of OS (6.4 months for regorafenib vs. 5.0 months for placebo; HR, 0.77; 95% CI, 0.64–0.94; $P = .005$). PFS was also significantly but modestly improved (1.9 vs. 1.7 months; HR, 0.49; 95% CI, 0.42–0.58; $P < .000001$).

The randomized, double-blind, phase III CONCUR trial was performed in China, Hong Kong, South Korea, Taiwan, and Vietnam.[1001] Patients with progressive mCRC were randomized 2:1 to receive regorafenib or placebo after two or more previous treatment regimens. After a median follow-up of 7.4 months, the primary endpoint of OS was met in the 204 randomized patients (8.8 months in the regorafenib arm vs. 6.3 months in the placebo arm; HR, 0.55; 95% CI, 0.40–0.77; $P < .001$).

The most common grade 3 or higher AEs in the regorafenib arm of the CORRECT trial were hand-foot skin reaction (17%), fatigue (10%), hypertension (7%), diarrhea (7%), and rash/desquamation (6%).[1000] Severe and fatal liver toxicity occurred in 0.3% of 1100 patients treated with regorafenib across all trials.[999] In a meta-analysis of four studies that included 1078 patients treated with regorafenib for CRC, GI stromal tumor (GIST), renal cell carcinoma, or hepatocellular carcinoma, the overall incidence of all-grade and high-grade hand-foot skin reactions was 60.5% and 20.4%, respectively.[1002] In the subset of 500 patients with CRC, the incidence of all-grade hand-foot skin reaction was 46.6%.

Other studies have also investigated regorafenib for treatment of refractory mCRC. The phase IIIb CONSIGN trial assessed the safety of regorafenib in 2872 patients from 25 countries with refractory mCRC.[1003] The REBECCA study assessed the safety and efficacy of regorafenib in a cohort of 654 patients with mCRC within a compassionate use program.[1004] The prospective, observational CORRELATE study assessed the safety and efficacy of regorafenib in 1037 patients with mCRC in real-world clinical practice.[1005] The safety and efficacy profiles of regorafenib in all of these trials were consistent with that seen in the CORRECT trial.

The randomized, phase II ReDOS trial investigated the use of an alternative dose schedule to reduce the toxicities related to regorafenib treatment.[1006] Of the 116 evaluable patients, the dose-escalation group had a higher percentage of patients who initiated cycle 3 of regorafenib (43%) compared to the standard dosing group (26%). Rates of several of the most common AEs were also lower among the dose-escalation group compared to the standard dosing group. Based on these results, the Panel agreed that a dose-escalation strategy is an appropriate alternative approach for regorafenib dosing. The phase II REARRANGE study has also supported alternative dosing schedules for regorafenib as feasible and safe in patients with previously treated mCRC.[1007]

Regorafenib has only shown activity in patients whose disease has progressed on all standard therapy. Therefore, the Panel added regorafenib as an additional line of therapy for patients with mCRC refractory to chemotherapy. It can be given before or after trifluridine-tipiracil or fruquintinib; no data inform the best order of these therapies.

Trifluridine-Tipiracil (TAS-102)

Trifluridine-tipiracil is an oral combination drug, consisting of a cytotoxic thymidine analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, which prevents the degradation of trifluridine. Early clinical studies of the drug in patients with CRC were promising.[1008,1009]

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Results of the double-blind, randomized, controlled, international phase III RECOURSE trial were published in 2015,[1010] followed shortly thereafter by approval of trifluridine-tipiracil by the FDA.[1011] With 800 patients with mCRC who progressed through at least two prior regimens randomized 2:1 to receive trifluridine-tipiracil or placebo, the primary endpoint of OS was met (5.3 vs. 7.1 months; HR, 0.68; 95% CI, 0.58–0.81; $P < .001$).[1010] Improvement was also seen in the secondary endpoint of PFS (1.7 vs. 2.0 months; HR, 0.48; 95% CI, 0.41–0.57; $P < .001$). The most common AEs associated with trifluridine-tipiracil in RECOURSE were neutropenia (38%), leukopenia (21%), and febrile neutropenia (4%); one drug-related death occurred.[1010] A postmarketing surveillance study did not reveal any unexpected safety signals[1012] and a subgroup analysis of the RECOURSE trial reported similar efficacy and safety regardless of age, geographical origin, or *KRAS* mutation status.[1013]

The combination of trifluridine-tipiracil and bevacizumab has also been studied in the non-first-line setting. The regimen was initially studied in the phase I/II C-TASK FORCE trial[1014] and a subsequent randomized phase II trial that compared trifluridine-tipiracil with and without bevacizumab.[1015] Following positive results on these early trials, the phase III SUNLIGHT trial was conducted to compare trifluridine-tipiracil plus bevacizumab to trifluridine-tipiracil alone in 492 patients with previously treated mCRC.[1016] Nearly all patients on the trial had previously received a fluoropyrimidine, irinotecan, and oxaliplatin; 72% had received an anti-VEGF antibody; and 93.7% of those with *RAS* wild-type disease had received an anti-EGFR antibody. Median OS was longer for the bevacizumab combination compared to trifluridine-tipiracil alone (10.8 vs. 7.5 months; HR, 0.61; 95% CI, 0.49–0.77; $P < .001$). Median PFS was also longer for the combination at 5.6 months versus 2.4 months for trifluridine-tipiracil alone (HR, 0.44; 95% CI, 0.36–0.54; $P < .001$). The most common Aes reported for both groups were neutropenia, nausea, and anemia and no treatment-related deaths occurred in either group. A retrospective study of 57 patients with refractory mCRC showed similar results to the clinical trial data, with an improved median OS for trifluridine-tipiracil with bevacizumab versus without (14.4 vs. 4.5 months; $P < .001$).[1017] Another retrospective study similarly reported improved OS and time to treatment discontinuation for trifluridine-tipiracil plus bevacizumab compared to either trifluridine-tipiracil alone or regorafenib.[1018]

Based on these data, the Panel added trifluridine-tipiracil, with or without bevacizumab, as a treatment option for patients whose disease has progressed through standard therapies. The bevacizumab combination is preferred over trifluridine-tipiracil alone. It can be given before or after regorafenib or fruquintinib; no data inform the best order of these therapies, although real-world data have shown that patients show better adherence to trifluridine-tipiracil compared to regorafenib.[1019] The 144 patients in RECOURSE who had prior exposure to regorafenib obtained similar OS benefit from trifluridine-tipiracil (HR, 0.69; 95% CI, 0.45–1.05) as the 656 patients who did not (HR, 0.69; 95% CI, 0.57–0.83).

The combination of trifluridine-tipiracil and bevacizumab has also been studied in the first-line setting in both the phase III SOLSTICE study[1020] and the phase II TASCO1 study.[1021,1022] Both of these studies compared trifluridine-tipiracil plus bevacizumab to capecitabine plus bevacizumab in patients who were not candidates for intensive therapy and have shown similar OS and PFS results between the two treatment groups. Based on concerns about the hematologic and financial toxicities with trifluridine-tipiracil compared to capecitabine, the NCCN Panel does not currently recommend trifluridine-tipiracil, with or without bevacizumab, as first-line therapy for mCRC.

Fruquintinib

Fruquintinib is an orally administered kinase inhibitor that targets VEGFR 1, 2, and 3. Its efficacy and safety has been evaluated in two randomized, double-blind, phase 3 clinical trials, FRESCO and FRESCO-2.[1023,1024]

Discussion Undergoing Progress

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FRESCO was conducted at 28 hospitals in China and randomized 416 patients with mCRC that had progressed after at least 2 lines of chemotherapy, but had not received VEGFR inhibitor therapy, to either fruquintinib or placebo.[1024] Patients treated with fruquintinib had significantly longer median OS compared to those who received placebo (9.3 vs. 6.6 months; HR, 0.65; $P < .001$). Median PFS was also longer with fruquintinib (3.7 vs. 1.8 months; HR, 0.26; $P < .001$). FRESCO-2 was a larger study, conducted at 124 hospitals and cancer centers across 14 countries, and enrolled 691 patients with mCRC who had previously received all available cytotoxic and targeted therapies and had progressed on or were intolerant to trifluridine-tipiracil and/or regorafenib.[1023] Patients were randomized to receive fruquintinib or placebo, plus best supportive care. Patients in the FRESCO-2 study had received a median of 4 previous lines of systemic therapy for metastatic disease and 73% had received >3 lines of therapy. As opposed to FRESCO, 97% of patients had received prior VEGF inhibitor therapy and nearly half had progressed on both trifluridine-tipiracil and regorafenib. Patients received fruquintinib for a median of 3.1 months (compared to 1.8 months on placebo) and just 20% discontinued fruquintinib due to toxicities. Median OS was 7.4 months with fruquintinib compared to 4.8 months with placebo (HR, 0.66; 95% CI, 0.55–0.80; $P < .0001$). Grade ≥3 AEs occurred in 63% of patients who received fruquintinib compared to 50% who received placebo. The most common grade ≥3 AEs with fruquintinib were hypertension (14%), asthenia (8%), and hand-foot syndrome (6%). Based on these data, the NCCN Panel recommends fruquintinib as a treatment option for mCRC that has progressed through all other available regimens. It can be given before or after trifluridine-tipiracil or regorafenib; no data inform the best order of these therapies.

Workup and Management of Synchronous Metastatic Disease

The workup for patients in whom metastatic synchronous adenocarcinoma from the large bowel (eg, colorectal liver metastases) is suspected should include a total colonoscopy, CBC, chemistry profile, CEA determination, biopsy if indicated, and CT scan with IV contrast of the chest, abdomen, and pelvis.[244] MRI with IV contrast should be considered if CT is inadequate. The Panel also recommends testing for tumor *KRAS/NRAS and BRAF* gene status and HER2 amplifications at diagnosis of metastatic disease (see *Biomarkers for Systemic Therapy*, above). However, if the tumor is known to have a *RAS* or *BRAF* mutation, HER2 testing is not indicated, as amplification is very rare in this subset.[730,731] NGS panels can be used to detect these biomarkers and have the advantage of also detecting other rare and actionable mutations (eg, *NTRK* and *RET* fusions).

The Panel strongly discourages the routine use of PET/CT scanning for staging, baseline imaging, or routine follow-up. However, the Panel recommends consideration of a preoperative PET/CT scan at baseline in selected cases if prior anatomic imaging indicates the presence of potentially surgically curable M1 disease. The purpose of this PET/CT scan is to evaluate for unrecognized metastatic disease that would preclude the possibility of surgical management. A randomized clinical trial of patients with resectable metachronous metastases assessed the role of PET/CT in the workup of potential curable disease.[1025] 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 (ie, bone, peritoneum/omentum, abdominal nodes). In addition, 1.5% of patients had more extensive hepatic resections and 3.4% had additional organ surgery. An additional 8.4% of patients in the PET/CT arm had false-positive results, many of which were investigated with biopsies or additional imaging. A meta-analysis of 18 studies including 1059 patients with hepatic colorectal metastases found that PET or PET/CT results changed management in 24% of patients.[1026]

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Patients with clearly unresectable metastatic disease should not have baseline PET/CT scans. The Panel also notes that PET/CT scans should not be used to assess response to chemotherapy, because a PET/CT scan can become transiently negative after chemotherapy (eg, in the presence of necrotic lesions).[1027] False-positive PET/CT scan results can occur in the presence of tissue inflammation after surgery or infection.[1027] An MRI with IV contrast can be considered as part of the preoperative evaluation of patients with potentially surgically resectable M1 liver disease. For example, an MRI with contrast may be of use when the PET and CT scan results are inconsistent with respect to the extent of disease in the liver.

The criterion of potential surgical cure includes patients with metastatic disease that is not initially resectable but for whom a surgical cure may become possible after preoperative chemotherapy. In most cases, however, the presence of extrahepatic disease will preclude the possibility of resection for cure; *conversion to resectability* for the most part refers to a patient with liver-only disease that, because of involvement of critical structures, cannot be resected unless regression is accomplished with chemotherapy (see *Neoadjuvant Therapy and Conversion to Resectability*, above).

Close communication among members of the multidisciplinary treatment team is recommended, including an upfront evaluation by a surgeon experienced in the resection of hepatobiliary or lung metastases.

Recommendations for Resectable Synchronous Liver or Lung Metastases

When patients present with CRC and synchronous liver metastases, resection of the primary tumor and liver can be performed in a simultaneous or staged approach.[1028-1037] Historically, in the staged approach, the primary tumor was usually resected first. However, the approach of liver resection before resection of the primary followed by adjuvant chemotherapy is now well-accepted.[1029,1031,1038,1039] In addition, emerging data suggest that systemic therapy, 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.[1040-1047]

Adjuvant chemotherapy following resection of the primary and metastases may be recommended for pMMR/MSS disease or dMMR/MSI-H/POLE/POLD1 disease where checkpoint inhibitor immunotherapy was not given neoadjuvantly, although the benefit of adjuvant chemotherapy in this setting remains controversial. The phase II/III JCOG0603 trial of 300 patients with liver-only CRC metastases compared hepatectomy alone to hepatectomy followed by 12 courses of adjuvant mFOLFOX6.[1048] Five-year DFS was significantly longer with adjuvant chemotherapy compared to hepatectomy alone (49.8% vs. 38.7%; HR, 0.67; 95% CI, 0.50–0.92; *P* = .006). However, the 5-year OS rate was higher with hepatectomy alone compared to hepatectomy with adjuvant chemotherapy (83.1% vs. 71.2%).

If a patient with resectable liver or lung metastases is a candidate for surgery, the Panel recommends the following options for pMMR/MSS disease: 1) synchronous or staged colectomy with liver or lung resection[425,433] followed by adjuvant chemotherapy (FOLFOX [preferred], CAPEOX [preferred], 5-FU/LV, or capecitabine[308,637]); 2) neoadjuvant chemotherapy for 2 to 3 months (ie, FOLFOX [preferred],[424] CAPEOX [preferred], FOLFIRI [category 2B], or FOLFIRINOX [category 2B][618]) followed by synchronous or staged colectomy with liver or lung resection, then adjuvant chemotherapy; or 3) colectomy followed by chemotherapy (see neoadjuvant options above) and a staged resection of metastatic disease, then adjuvant chemotherapy. Based on the limited data that are available, as well as their own institutional practice patterns, the NCCN Panel has included FOLFIRI and FOLFIRINOX as options for neoadjuvant treatment of resectable synchronous mCRC. These recommendations' category 2B rating reflects the relative scarcity of data supporting these treatment options.

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For dMMR/MSI-H or *POLE/POLD1* mutation-positive disease, the first option listed above is an option, although neoadjuvant immunotherapy with a checkpoint inhibitor is the preferred approach. While resection of metastatic disease is the preferred approach, local therapy for metastases may be considered in addition, or instead of, resection in select cases. For dMMR/MSI-H or *POLE/POLD1* mutation-positive disease, any of the checkpoint inhibitor regimens that are recommended for metastatic disease may be used in the neoadjuvant setting. Overall, combined neoadjuvant and adjuvant treatments should not exceed 6 months.

In the case of liver metastases only, HAIC with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure.

Recommendations for Unresectable Synchronous Metastases

Patients with dMMR/MSI-H or *POLE/POLD1* mutation-positive synchronous unresectable metastatic disease should preferentially receive checkpoint inhibitor immunotherapy as their first-line option as long as the patient is a candidate for immunotherapy and no prior immunotherapy has been received. Disease status should be reevaluated every 2 to 3 months, followed by a continuation of immunotherapy; resection, with or without RT; surveillance; or additional lines of systemic therapy based on disease response.

For patients with pMMR/MSS metastatic disease that is deemed to be potentially convertible (see *Neoadjuvant Therapy and Conversion to Resectability*, above),[1049] chemotherapy regimens with high response rates should be considered, and these patients should be reevaluated for resection after 2 months of preoperative chemotherapy and every 2 months thereafter while undergoing this therapy. If bevacizumab is included as a component of the conversion therapy, an interval of at least 6 weeks between the last dose of bevacizumab and surgery should be applied, with a 6- to 8-week postoperative period before re-initiation of bevacizumab. Patients with disease converted to a resectable state should undergo synchronized or staged resection of colon and metastatic cancer, including treatment with pre- and postoperative chemotherapy for a preferred total perioperative therapy duration of 6 months. Recommended options for adjuvant therapy for these patients include active systemic therapy regimens for advanced or metastatic disease (category 2B for the use of biologic agents in this setting); observation or a shortened course of chemotherapy can also be considered for patients who have completed preoperative chemotherapy. In the case of liver metastases only, HAIC with or without systemic 5-FU/LV (category 2B) remains an option at centers with experience in the surgical and medical oncologic aspects of this procedure. Ablative therapy of metastatic disease, either alone or in combination with resection, can also be considered when all measurable metastatic disease can be treated (see *Management of Metastatic Disease*). Patients with disease that is not responding to therapy should receive systemic therapy for advanced or metastatic disease with treatment selection based partly on whether intensive therapy is recommended. Debulking surgery or ablation without curative intent is not recommended.

Results from one study suggest that there may be some benefit in both OS and PFS from resection of the primary in the setting of unresectable colorectal metastases.[1050] Other systematic reviews and retrospective analyses also have shown a potential benefit.[1050-1056] Separate analyses of the SEER database and the National Cancer Database also identified a survival benefit of primary tumor resection in this setting.[1057,1058]

On the other hand, a different analysis of the National Cancer Database came to the opposite conclusion.[1059] 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.[1060] For the 160

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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. Three patients on this study died following primary tumor resection due to postoperative complications. The phase III CAIRO4 study has also shown a higher 60-day mortality rate in patients with unresectable mCRC randomized to primary tumor resection followed by systemic therapy (11%) compared to those who were randomized to systemic therapy alone (3%).[1061] 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.[1062] 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,[461] and its removal delays initiation of systemic chemotherapy. In fact, a systematic review concluded that resection of the primary does not reduce complications and does not improve OS.[1063] Another systematic review and meta-analysis identified five studies that compared open to laparoscopic palliative colectomies in this setting.[1064] 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 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 is not a contraindication to bevacizumab use. The risk of GI 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.

Recommendations for Synchronous Abdominal/Peritoneal Metastases

For patients with peritoneal metastases causing obstruction or that may cause imminent obstruction, palliative surgical options include colon resection, diverting colostomy, a bypass of impending obstruction, or stenting, followed by systemic therapy for advanced or metastatic disease.

The primary treatment of patients with nonobstructing metastases is chemotherapy. As mentioned above (see *Cytoreductive Debulking with Hyperthermic Intraperitoneal Chemotherapy*), the Panel currently believes that the treatment of disseminated carcinomatosis with complete CRS and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. However, the significant morbidity and mortality associated with HIPEC, as well as the conflicting data on clinical efficacy, make this approach very controversial.

Workup and Management of Metachronous Metastatic Disease

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.[1025,1065,1066] Specifically, Joyce et al[1065] reported that the preoperative PET changed or precluded curative-intent liver resection in 25% of patients. A randomized clinical trial assessed the role of PET/CT in the workup of patients with resectable metachronous metastases.[1025]

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While there was no impact of PET/CT on survival, surgical management was changed in 8% of patients after PET/CT. This trial is discussed in more detail in *Workup and Management of Synchronous Metastatic Disease*, above.

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 to define whether targeted therapies can be considered among the potential options (see *Biomarkers for Systemic Therapy*).

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 or immunotherapy history of the patient and through the absence of colectomy.

Patients with resectable disease are classified according to whether they have undergone previous chemotherapy or immunotherapy. For patients who have resectable pMMR/MSS metastatic disease, treatment is resection with 6 months of perioperative chemotherapy (pre- or postoperative or a combination of both), with choice of regimens based on previous therapy. For patients with resectable dMMR/MSI-H or *POLE/POLD1* mutation-positive metastatic disease, neoadjuvant immunotherapy with a checkpoint inhibitor is an option, if no previous immunotherapy was given. 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 is preferred for pMMR/MSS disease, with capecitabine or 5-FU/LV as additional category 2B options. There are also cases when perioperative chemotherapy is not recommended in resectable metachronous disease. In particular, patients with a history of previous chemotherapy and an 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 or immunotherapy history (see *Second-Line or Subsequent Systemic Therapy*, above). 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.[1067] Quality of life is an outcome that is rarely measured but of unquestioned clinical relevance.[1068] 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.[1068] PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.[1068-1070] In 2011, The Grupo Español Multidisciplinar en Cancer Digestivo (GEMCAD) proposed particular aspects of clinical trial design to be incorporated into trials that use PFS as an endpoint.[1071]

A study, in which individual patient data from three RCTs were pooled, tested endpoints that take into account subsequent lines of therapy:

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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).[1069] 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.[1072,1073] 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, randomized trials showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor,[319] and a another study found that 95% of recurrences occurred in the first 5 years.[1074]

Surveillance for Locoregional Disease

Advantages of more intensive follow-up of patients with stage II and/or stage III disease have been shown prospectively in several older studies[1075-1077] and in multiple meta-analyses of RCTs designed to compare low- and high-intensity programs of surveillance.[1078-1083] Intensive postoperative surveillance has also been suggested to be of benefit to patients with stage I and IIA disease.[1084] Furthermore, a population-based report indicates increased rates of resectability and survival in patients treated for local recurrence and distant metastases of CRC in more recent years, thereby providing support for more intensive post-treatment follow-up in these patients.[1085]

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).[1086] In this study, no mortality benefit to regular monitoring with CEA, CT, or both was observed compared with minimum follow-up (death rate, 18.2% vs. 15.9%; difference, 2.3%; 95% CI, −2.6%–7.1%). The authors concluded that any strategy of surveillance is unlikely to provide a large survival advantage over a symptom-based approach. 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).[1087] 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 at 11 hospitals treated for non-mCRC in the Netherlands.[1088] The intensive CEA surveillance protocol resulted in the detection of more recurrences and recurrences that could be treated with curative intent than usual follow-up, and the time to detection of recurrent disease was shorter. Another randomized trial of 1228 patients found that more intensive surveillance led to earlier detection of recurrences than a less intensive program (less frequent colonoscopy and liver ultrasound and the absence of an annual chest x-ray) but did not affect OS.[1089]

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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.[1090] A 2020 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% of patients in the maximum surveillance group with both CEA and CT ($P = .0035$).[1091] A 2022 abstract that reported final RFS results from PRODIGE 13 found that, with a median follow-up of 7.8 years, cancer recurrence was detected in 22.3% of patients (89.5% metastatic recurrence, 10.5% local recurrence).[1092] Five-year RFS rates were 73.2% with CT surveillance versus 68.2% without CT ($P = .052$) while they were 70.4% and 71.0% with and without CEA screening, respectively. The authors concluded that intensive imaging, but not CEA screening, provided an increased opportunity for curative-intent surgical treatment of recurrence and a trend toward better 5-year RFS with CT surveillance.

Clearly, controversies remain regarding selection of optimal strategies for following up 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 with potentially curable metastatic disease with surgical resection.

For patients with stage I disease, the Panel believes that a less intensive surveillance schedule is appropriate because of the low risk of recurrence and the harms associated with surveillance. Possible harms include radiation exposure with repeated CT scans, psychological stress associated with surveillance visits and scans, and stress and risks from following up on false-positive results. Therefore, for patients with stage I disease, the Panel recommends colonoscopy at 1 year after surgery. Repeat colonoscopy is recommended at 3 years, and then every 5 years thereafter, unless advanced adenoma (villous polyp, polyp >1 cm, or high-grade dysplasia) is found. In this case, colonoscopy should be repeated in 1 year.[1083]

The following Panel recommendations for post-treatment surveillance pertain to patients with stage II/III disease who have undergone successful treatment (ie, no known residual disease). History and physical examination should be given every 3 to 6 months for 2 years, and then every 6 months for a total of 5 years. A CEA test (also see *Managing an Increasing CEA Level*, below) is recommended at baseline and every 3 to 6 months for 2 years,[1093] 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.[1078,1093] Colonoscopy is recommended at approximately 1 year after resection (or at 3–6 months postresection if not performed preoperatively because of 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.[1083] More frequent colonoscopies may be indicated in patients who present with colon cancer before 50 years of age. Chest, abdominal, and pelvic CT scan are recommended every 6 to 12 months (category 2B for more frequently than annually) for up to 5 years in patients with stage III disease and those with stage II disease at a high risk for recurrence.[1078,1094] Routine CEA monitoring and CT scanning are not recommended beyond 5 years. Use of PET/CT to monitor for disease recurrence is not recommended.[1094,1095] The CT that accompanies a

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PET/CT is usually a noncontrast CT, and therefore not of ideal quality for routine surveillance.

Surveillance colonoscopies are primarily aimed at identifying and removing metachronous polyps, because data show that patients with a history of CRC have an increased risk of developing second cancers, particularly in the first 2 years after resection.[1083,1096] Furthermore, use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original CRC.[1083] The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with Lynch syndrome.[31]

CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and liver.[1078] Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases.[1078,1094]

The 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).[1097] These guidelines differ only slightly from the surveillance recommendations in these NCCN Guidelines for Colon Cancer. While ASCO/CCO recommend abdominal and chest CT annually for 3 years in patients with stage II and III disease, the NCCN Panel recommends semi-annual to annual scans for 5 years (category 2B for more frequent than annual scanning). The Panel bases its recommendation on the fact that approximately 10% of patients will recur after 3 years.[319,1074] The American Society of Colon and Rectal Surgeons also released surveillance guidelines, which are also very similar to NCCN surveillance recommendations.[1098] One exception is the inclusion of intensive surveillance for patients with resected stage I colon or rectal cancer if the provider deems the patient to be at increased risk for recurrence.

Surveillance for Metastatic Disease

Patients who had resection of mCRC can undergo subsequent curative-intent resection of recurrent disease (see *Surgical Management of Colorectal Metastases*, above). A retrospective analysis of 952 patients who underwent resection at Memorial Sloan Kettering Cancer Center showed that 27% of patients with recurrent disease underwent curative-intent resection and that 25% of those patients (6% of recurrences; 4% of the initial population) were free of disease for ≥36 months.[1099]

Panel recommendations for surveillance of patients with stage IV CRC with no evidence of disease (NED) after curative-intent surgery and subsequent adjuvant treatment are similar to those listed for patients with stage II/III disease, except that certain evaluations are performed more frequently. Specifically, the Panel recommends that these patients undergo contrast-enhanced CT scan of the chest, abdomen, and pelvis every 3 to 6 months in the first 2 years after adjuvant treatment (category 2B for frequency <6 months) and then every 6 to 12 months for up to a total of 5 years. CEA testing is recommended every 3 to 6 months for the first 2 years and then every 6 months for a total of 5 years, as in early-stage disease. Again, use of PET/CT scans for surveillance is not recommended. An 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.[1100] Those scanned once per year survived a median of 54 versus 43 months for those scanned 3 to 4 times per year (P = .08), suggesting that annual scans may be sufficient in this population.

Managing an Increasing CEA Level

Workup for patients with an elevated CEA level after resection should include colonoscopy; chest, abdominal, and pelvic CT scans; physical examination; and consideration of PET/CT scan. If imaging study results are normal in the face of a rising CEA, repeat CT scans are recommended

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every 3 months until either disease is identified or CEA level stabilizes or declines.

In a 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.[1101] In this study, false-positive results >15 ng/mL were rare, and all results >35 ng/mL represented true positives. Following a systematic review and meta-analysis, the pooled sensitivity and specificity of CEA at a cutoff of 10 ng/mL were calculated at 68% (95% CI, 53–79) and 97% (95% CI, 90–99), respectively.[1102,1103] 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.

Panel opinion was divided on the usefulness of PET/CT scan in the scenario of an elevated CEA with negative, good-quality CT scans (ie, some Panel members favored use of PET/CT in this scenario whereas others noted that the likelihood of PET/CT identifying surgically curable disease in the setting of negative good-quality CT scans is vanishingly small). A systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.[1104] 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.[1105]

Use of PET/CT scans in this scenario is permissible within these guidelines. The Panel does not recommend a so-called blind or CEA-directed laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,[1106] nor does it recommend use of anti-CEA-radiolabeled scintigraphy.

Survivorship

The Panel recommends that a prescription for survivorship and transfer of care to the primary care physician be written.[1107] 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 systemic therapies. 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.[1108]

Other recommendations include monitoring for late sequelae of colon cancer or the treatment of colon cancer, such as chronic diarrhea or incontinence (eg, patients with stoma).[1109-1114] Other long-term problems common to CRC survivors include oxaliplatin-induced peripheral neuropathy, fatigue, insomnia, cognitive dysfunction, body image issues (especially as related to an ostomy), and emotional or social distress.[1115-1121] Specific management interventions to address these and other side effects are described in a review,[1122] and a survivorship care plan for patients with CRC have been published.[1123]

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The NCCN Guidelines for Survivorship provide screening, evaluation, and treatment recommendations for common consequences of cancer and cancer treatment to aid health care professionals who work with survivors of adult-onset cancer in the post-treatment period, including those in specialty cancer survivor clinics and primary care practices. The NCCN Guidelines for Survivorship include many topics with potential relevance to survivors of CRC, including Anxiety, Depression, and Distress; Cognitive Dysfunction; Fatigue; Pain; Sexual Dysfunction; Healthy Lifestyles; and Immunizations. Concerns related to employment, insurance, and disability are also discussed. The American Cancer Society 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.[1108]

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 colon cancer.

In a prospective observational study of patients with stage III colon cancer enrolled in the CALGB 89803 adjuvant chemotherapy trial, DFS was found to be directly related to the amount of exercise in which the patients engaged.[1124] An analysis of physical activity in the CALGB/SWOG 80702 (Alliance) trial reported similar results.[1125] In addition, a study of a large cohort of men treated for stage I through III CRC showed an association between increased physical activity and lower rates of CRC-specific mortality and overall mortality.[1126] More recent data support the conclusion that physical activity improves outcomes. In a cohort of >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.[1127] In addition, evidence suggests that both pre- and post-diagnosis physical activity decreases CRC mortality. Women 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.[1128] Similar results were seen in other studies and in meta-analyses of prospective studies.[1129-1132] Dietary and physical activity interventions were also found to have positive effects on quality of life and depression for CRC survivors in a randomized study.[1133]

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 had an increased risk of disease recurrence and death.[1134] 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.[1135] An 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.[1136] A meta-analysis of prospective cohort studies found that pre-diagnosis obesity was associated with increased CRC-specific and all-cause mortality.[1137] Other analyses confirm the increased risk for recurrence and death in patients with obesity.[94,1138-1141]

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.[1142] In addition, results of one retrospective observational study of a cohort of 3408 patients with resected stage I to III CRC suggest that the relationship between mortality and BMI might be U shaped, with the lowest mortality for those with BMI 28 kg/m^2.[1143] However, several possible explanations for this so-called “obesity paradox” have been suggested.[1144]

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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 has been found to be associated with an improved outcome in terms of cancer recurrence or death.[1145] 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.[100] Analysis of the CALGB 89803 trial found that higher dietary glycemic load was also associated with an increased risk of recurrence and mortality in patients with stage III disease.[1146] 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.[1147] The link between red and processed meats and mortality in survivors of non-mCRC has been further supported by 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).[92]

A discussion of lifestyle characteristics that may be associated with a decreased risk of colon cancer recurrence, such as those recommended by the American Cancer Society,[1148] 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, telephone-based health behavior coaching has been shown to have a positive effect on physical activity, diet, and BMI in survivors of CRC, suggesting that survivors may be open to health behavior change.[1149]

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.[1148] 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.[1150]

Secondary Chemoprevention for CRC Survivors

Limited data suggest a link between post-colorectal-cancer-diagnosis statin use and increased survival.[117,1151,1152] 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; $P < .001$).[1151]

Abundant data show that low-dose aspirin therapy after a diagnosis of CRC decreases the risk of recurrence and death.[1153-1159] 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).[1153] Some evidence suggests that tumor mutations in *PIK3CA* may be predictive for response to aspirin, although the data are somewhat inconsistent and other predictive markers have also been suggested.[1155,1160-1165] 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.[1166]

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 GI bleeding and hemorrhagic stroke, and these risks should be discussed with CRC survivors.[1167]

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Summary

The Panel believes that a multidisciplinary approach is necessary for managing CRC. The Panel endorses the concept that treating patients in a clinical trial has priority over standard or accepted therapy. The Panel stresses the importance of determining MSI and MMR status at diagnosis as treatment recommendations can vary considerably at all stages of colon cancer based on these biomarker results.

The recommended surgical procedure for resectable colon cancer is an en bloc resection and adequate lymphadenectomy. Adequate pathologic assessment of the resected lymph nodes is important with a goal of evaluating at least 12 nodes. Adjuvant chemotherapy is recommended for patients with stage III disease and is also an option for some patients with high-risk stage II disease. The preferred regimens for adjuvant therapy, as well as the recommended duration of therapy, depends on the pathologic stage of the tumor and the risk of recurrence. Patients with resectable T4b tumors or with bulky nodal disease may be treated with neoadjuvant systemic therapy prior to colectomy.

Patients with metastatic disease in the liver or lung should be considered for surgical resection if they are candidates for surgery and if all original sites of disease are amenable to resection (R0) and/or ablation. Six months of perioperative systemic therapy should be administered to patients with synchronous or metachronous resectable metastatic disease. When a response to systemic therapy would likely convert a patient from an unresectable to a resectable disease state (ie, conversion therapy), this therapy should be initiated.

The recommended post-treatment surveillance program for patients with resected disease includes serial CEA determinations; periodic chest, abdomen, and pelvis CT scans; colonoscopic evaluations; and a survivorship plan to manage long-term side effects of treatment, facilitate disease prevention, and promote a healthy lifestyle.

Recommendations for patients with disseminated metastatic disease represent a continuum of care in which lines of treatment are blurred rather than discrete. Principles to consider at initiation of therapy include pre-planned strategies for altering therapy for patients in both the presence and absence of disease progression, including plans for adjusting therapy for patients who experience certain toxicities. In addition to fluoropyrimidine-, oxaliplatin-, and/or irinotecan-containing chemotherapy regimens, immunotherapy and targeted therapy regimens are becoming an increasingly important part of the mCRC treatment landscape. Combination of a biologic agent (eg, bevacizumab, cetuximab, panitumumab) with some of the chemotherapy regimens is an option, depending on available data. Systemic therapy options for patients with progressive disease depend on the choice of initial therapy and biomarker status of the tumor.

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