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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colon Cancer

NCCN Evidence Blocks™

Version 4.2019 — November 8, 2019

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Colon Cancer
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¤ Gastroenterology
¶ Surgery/Surgical oncology
§ Radiotherapy/Radiation oncology
≠ Pathology
Þ Internal medicine
¥ Patient advocate
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NCCN Colon Cancer Panel Members
NCCN Evidence Blocks Definitions (EB-1)

Clinical Presentations and Primary Treatment:
- Pedunculated Polyp (Adenoma) with Invasive Cancer (COL-1)
- Sessile Polyp (Adenoma) with Invasive Cancer (COL-1)
- Colon Cancer Appropriate for Resection (COL-2)
- Suspected or Proven Metastatic Synchronous Adenocarcinoma (COL-4)

Pathologic Stage, Adjuvant Treatment (COL-3)
Surveillance (COL-8)
Recurrence and Workup (COL-9)
Metachronous Metastases (COL-9)

Principles of Imaging (COL-A)
Principles of Pathologic Review (COL-B)
Principles of Surgery (COL-C)
Systemic Therapy for Advanced or Metastatic Disease (COL-D)
Principles of Radiation Therapy (COL-E)
Principles of Risk Assessment for Stage II Disease (COL-F)
Principles of Adjuvant Therapy (COL-G)
Principles of Survivorship (COL-H)

Staging (ST-1)

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/clinicians.aspx.

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

See NCCN Categories of Evidence and Consensus.

NCCN Guidelines for Patients® available at www.nccn.org/patients

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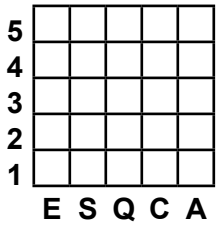
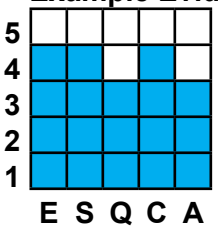
NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Cure likely and often provides long-term survival advantage
4	**Very effective:** Cure unlikely but sometimes provides long-term survival advantage
3	**Moderately effective:** Modest impact on survival, but often provides control of disease
2	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs
2	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent
1	**Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** One or more well-designed randomized trials
3	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s)
2	**Low quality:** Case reports or extensive clinical experience
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

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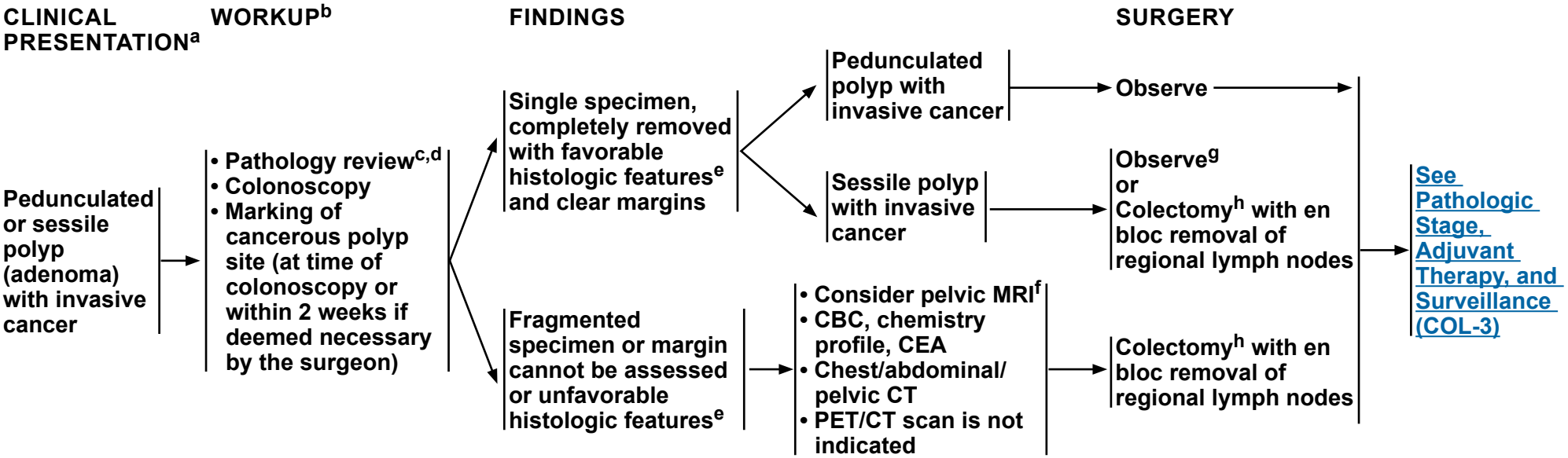

Small bowel adenocarcinoma → See the NCCN Guidelines for Small Bowel Adenocarcinoma

Appendiceal adenocarcinoma → Consider systemic therapy as per the NCCN Guidelines for Colon Cancer

Peritoneal mesothelioma or other extrapleural mesotheliomas → Consider systemic therapy as per the NCCN Guidelines for Malignant Pleural Mesothelioma (MPM-A)

[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b] See 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 are useful in treatment determination (predictive markers) and prognosis. College of American Pathologists Consensus Statement 1999. Prognostic factors in colorectal cancer. Arch Pathol Lab Med 2000;124:979-994.
[e] See Principles of Pathologic Review (COL-B) - Endoscopically removed malignant polyp.
[f] 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.
[g] Observation may be considered, with the understanding that there is significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, hematogenous metastasis, but not lymph node metastasis) than polypoid malignant polyps. See Principles of Pathologic Review (COL-B) - Endoscopically removed malignant polyp.
[h] See Principles of Surgery (COL-C 1 of 3).

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

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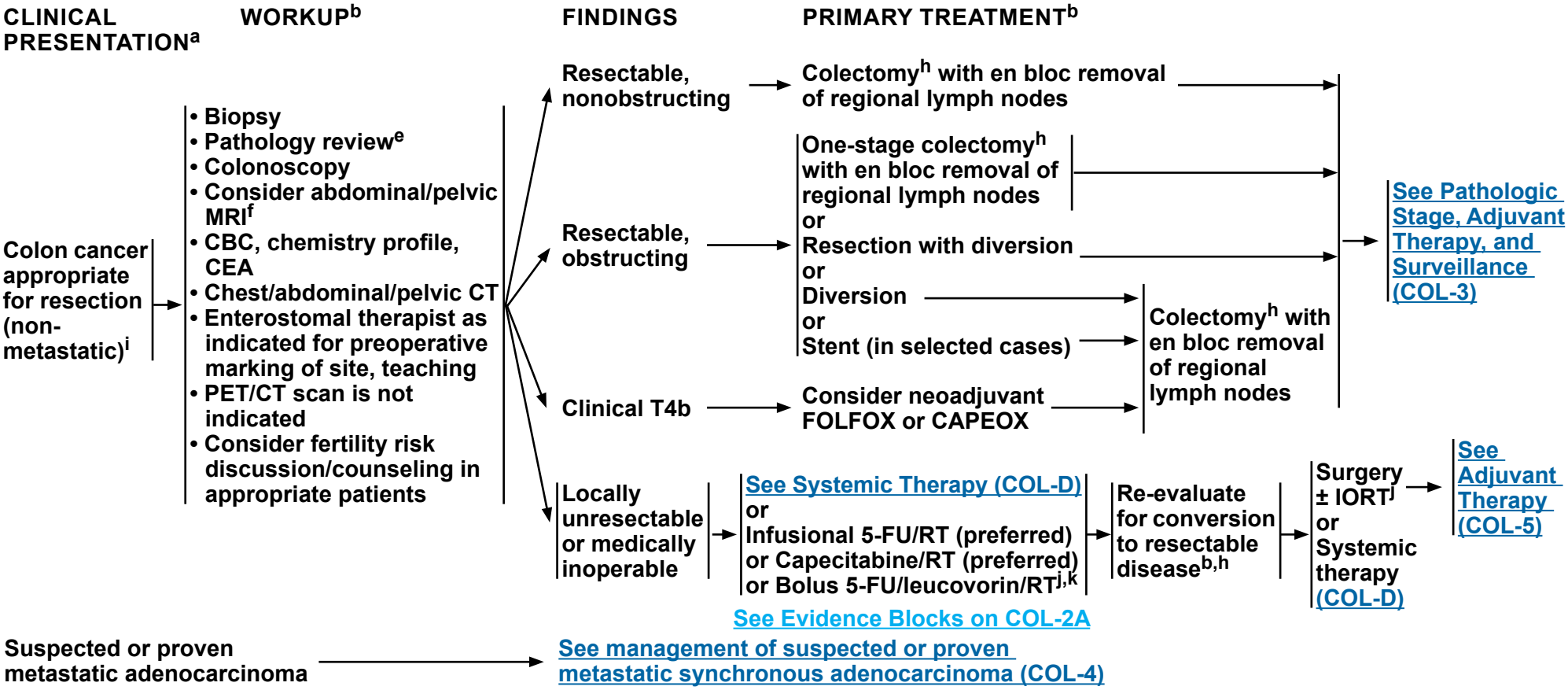

[a] All patients with colon cancer should be counseled for family history and considered for risk assessment. For patients with suspected Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b] See Principles of Imaging (COL-A).
[e] See Principles of Pathologic Review (COL-B) - Colon cancer appropriate for resection, pathologic stage, and lymph node evaluation.
[f] 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.
[h] See Principles of Surgery (COL-C 1 of 3).
[i] For tools to aid optimal assessment and management of older adults with cancer, see the NCCN Guidelines for Older Adult Oncology.
[j] See Principles of Radiation Therapy (COL-E).
[k] Bolus 5-FU/leucovorin/RT is an option for patients not able to tolerate capecitabine or infusional 5-FU.

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EVIDENCE BLOCKS FOR PRIMARY TREATMENT FOR CLINICAL T4b OR LOCALLY UNRESECTABLE OR MEDICALLY INOPERABLE (COL-2)

FOLFOX	
CapeOx	
Infusional 5-FU/RT	
Capecitabine/RT	
Bolus 5-FU/leucovorin/RT	

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PATHOLOGIC STAGE[e]	ADJUVANT TREATMENT[b,s]
Tis; T1, N0, M0; T2, N0, M0; T3-4, N0, M0[l] (MSI-H or dMMR)	Observation
T3, N0, M0[l,m] (MSS or pMMR and no high-risk features)	Observation or Consider capecitabine[o] or 5-FU/leucovorin[o]
T3, N0, M0 at high risk for systemic recurrence[m,n] or T4, N0, M0 (MSS or pMMR)	Capecitabine[o,p] or 5-FU/leucovorin[o,p] or FOLFOX[o,p,q,r] or CAPEOX[o,p,q,r] or Observation
T1-3, N1 (low-risk stage III)	Preferred: • CAPEOX (3 mo)[o,r] or • FOLFOX (3–6 mo)[o,r] (category 1 for 6 mo) or Other options include: Capecitabine (6 mo)[o] or 5-FU (6 mo)[o]
T4, N1-2; T Any, N2 (high-risk stage III)	Preferred: • CAPEOX (3–6 mo)[o,p,r] (category 1 for 6 mo) or • FOLFOX (6 mo)[o,p,r] (category 1) or Other options include: Capecitabine (6 mo)[o,p] or 5-FU (6 mo)[o,p]

See Surveillance (COL-8)

See Evidence Blocks on COL-3A

[b] See Principles of Imaging (COL-A).
[e] See Principles of Pathologic Review (COL-B).
[l] See Principles of Risk Assessment for Stage II Disease (COL-F).
[m] High-risk factors for recurrence: poorly differentiated histology (exclusive of those cancers that are MSI-H), lymphatic/vascular invasion, bowel obstruction, <12 lymph nodes examined, perineural invasion, localized perforation, or close, indeterminate, or positive margins. In high-risk stage II patients, there are no data that correlate risk features and selection of chemotherapy.
[n] There are insufficient data to recommend the use of multi-gene assay panels to determine adjuvant therapy.
[o] See Principles of Adjuvant Therapy (COL-G).
[p] Consider RT for T4 with penetration to a fixed structure. See Principles of Radiation Therapy (COL-E).
[q] 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.
[r] A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients age 70 and older has not been proven.
[s] In patients staged as T1-3, N1 (low-risk stage III), 3 months of CapeOX is non-inferior to 6 months of CapeOX for disease-free survival; non-inferiority of 3 vs. 6 months of FOLFOX has not been proven. In patients 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 disease-free survival, whereas non-inferiority of 3 vs. 6 months of CapeOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 months vs. 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CapeOX). Shi Q, et al. J Clin Oncol 2017;35 (suppl):LBA1.

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EVIDENCE BLOCKS FOR ADJUVANT THERAPY
(COL-3)

	T3, N0, M0 (MSS or pMMR and no high-risk features)	T3, N0, M0 at high risk for systemic recurrence or T4, N0, M0 (MSS or pMMR)
Capecitabine		
Bolus 5-FU/leucovorin		
Infusional 5-FU/leucovorin		
FOLFOX	—	
CapeOx	—	

	Low Risk Stage III	High Risk Stage III
CapeOx (3 months)		
CapeOx (6 months)	—	
FOLFOX (3 months)		—
FOLFOX (6 months)		
Capecitabine		
Bolus 5-FU/leucovorin		
Infusional 5-FU/leucovorin		

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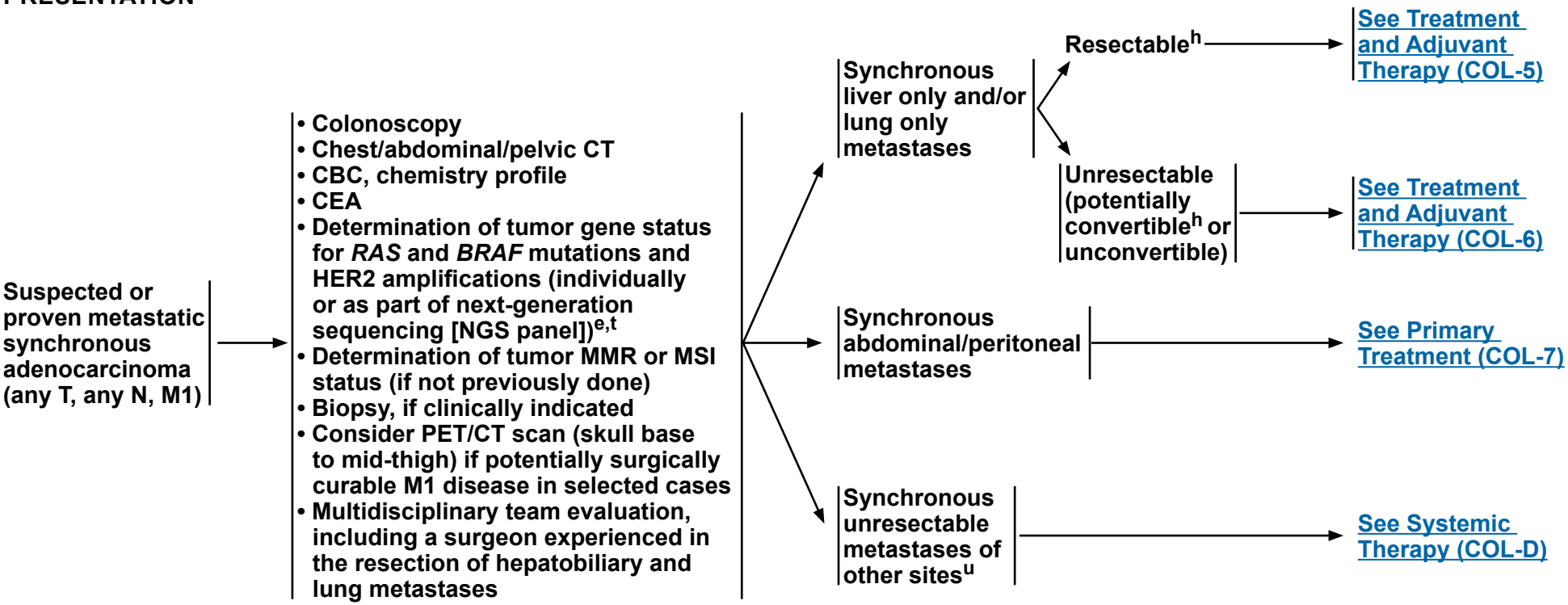

[b] See Principles of Imaging (COL-A).
[e] See Principles of Pathologic Review (COL-B 4 of 5) - *KRAS*, *NRAS*, and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing.
[h] See Principles of Surgery (COL-C 2 of 3).
[t] If known *RAS/RAF* mutation, HER2 testing is not indicated. NGS panels have the ability to pick up rare and actionable mutations and fusions.
[u] Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.

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TREATMENT
Resectable[h] synchronous liver and/or lung metastases only

ADJUVANT TREATMENT[b]
(resected metastatic disease)

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

→

FOLFOX (preferred) or CAPEOX (preferred)
or
Capecitabine or 5-FU/leucovorin
(6 MO TOTAL PERIOPERATIVE TREATMENT PREFERRED)

See Evidence Blocks on COL-5A

→ See Surveillance (COL-8)

[b] See Principles of Imaging (COL-A).
[h] See Principles of Surgery (COL-C 2 of 3).
[v] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[w] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E).

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EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY FOR RESECTABLE SYNCHRONOUS LIVER AND/OR LUNG METASTASES (COL-5)

	Neoadjuvant Therapy or Between Resection	Adjuvant Therapy
FOLFOX		
CapeOx		
FOLFIRI		—
Capecitabine	—	
5-FU/leucovorin	—	

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TREATMENT
Unresectable[h] synchronous liver and/or lung metastases only

- **Systemic therapy**
  - **FOLFIRI or FOLFOX or CAPEOX or FOLFOXIRI ± bevacizumab[x,y] or**
  - **FOLFIRI or FOLFOX or FOLFOXIRI ± panitumumab or cetuximab[z] (category 2B for FOLFOXIRI combination) (*KRAS/NRAS/BRAF* WT gene and left-sided tumors only)[e,aa]**
- **Consider colon resection[h] only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms**

→ **Re-evaluate for conversion to resectable[b,h] every 2 mo if conversion to resectability is a reasonable goal**

→ **Converted to resectable** → **Synchronized or staged resection[h] of colon and metastatic cancer**

→ **Systemic therapy ± biologic therapy (COL-D) (category 2B for biologic therapy) or Consider observation or shortened course of chemotherapy (6 MO TOTAL PERIOPERATIVE TREATMENT PREFERRED)**

→ **See Surveillance (COL-8)**

→ **Remains unresectable** → **See Systemic Therapy (COL-D)**

ADJUVANT TREATMENT[b]

See Evidence Blocks on COL-6A

See Recurrence (COL-9)

[b] See Principles of Imaging (COL-A).
[e] See Principles of Pathologic Review (COL-B 4 of 5) - KRAS, NRAS, and BRAF Mutation Testing.
[h] See Principles of Surgery (COL-C 2 of 3).
[x] 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 6–8 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.
[y] An FDA-approved biosimilar is an appropriate substitution for bevacizumab.
[z] There are conflicting data regarding the use of FOLFOX + cetuximab in patients who have potentially resectable liver metastases.
[aa] 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.

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EVIDENCE BLOCKS FOR UNRESECTABLE SYNCHRONOUS LIVER AND/OR LUNG METASTASES ONLY (COL-6)

Primary treatment	
FOLFOX	
FOLFOX/cetuximab	
FOLFOX/panitumumab	
CapeOx/bevacizumab	
FOLFIRI	
FOLFOXIRI	
FOLFOXIRI/bevacizumab	
FOLFOXIRI/panitumumab	
FOLFOXIRI/cetuximab	

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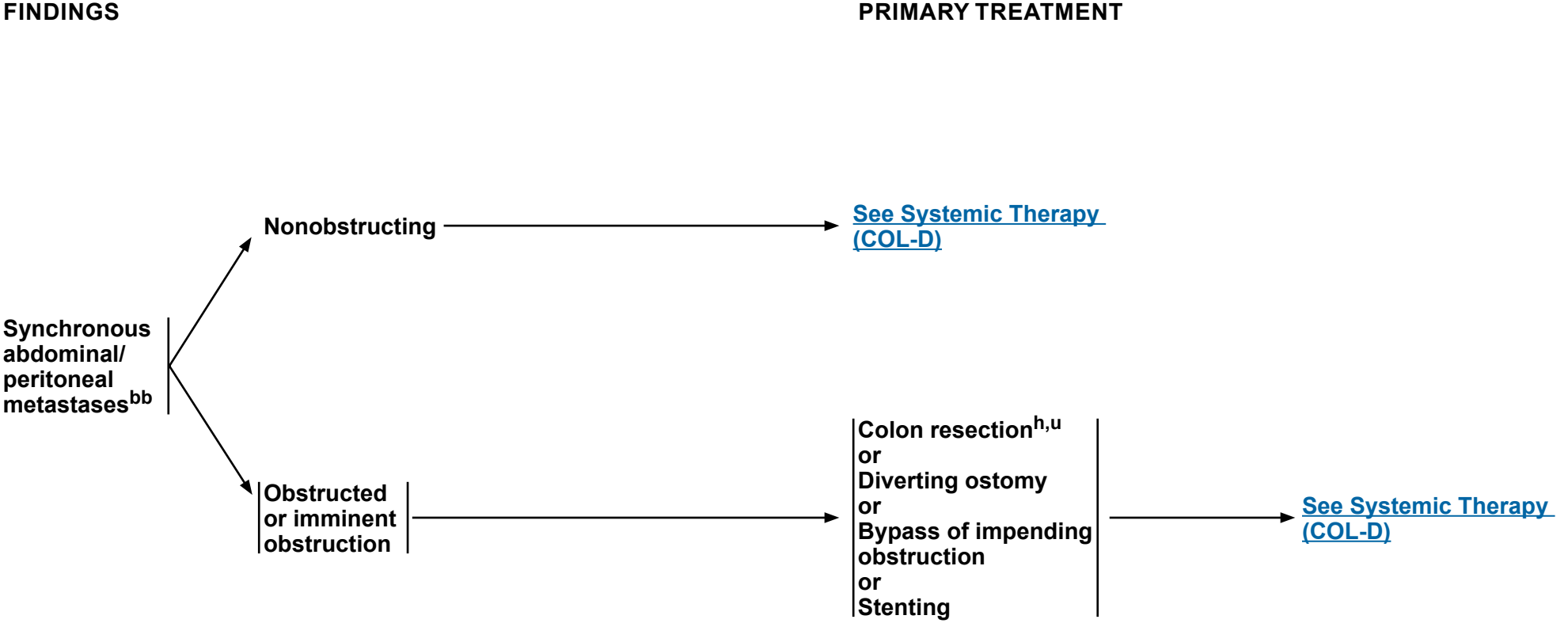

[h] See Principles of Surgery (COL-C 2 of 3).
[u] Consider colon resection only if imminent risk of obstruction, significant bleeding, perforation, or other significant tumor-related symptoms.
[bb] Complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for select patients with limited peritoneal metastases for whom R0 resection can be achieved.

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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,[cc] repeat in 3 y, then every 5 y[dd]
Stage II, III	• History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA[ee] every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • Chest/abdominal/pelvic CT every 6–12 mo (category 2B for frequency <12 mo) for a total of 5 y • Colonoscopy[a] in 1 y after surgery except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo ▸ If advanced adenoma, repeat in 1 y ▸ If no advanced adenoma,[cc] repeat in 3 y, then every 5 y[dd] • PET/CT scan is not indicated • See Principles of Survivorship (COL-H)
Stage IV	• History and physical every 3–6 mo for 2 y, then every 6 mo for a total of 5 y • CEA[ee] every 3–6 mo x 2 y, then every 6 mo for a total of 5 y • Chest/abdominal/pelvic CT scan every 3–6 mo (category 2B for frequency <6 mo) x 2 y, then every 6–12 mo for a total of 5 y • Colonoscopy[a] in 1 y after surgery except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 mo ▸ If advanced adenoma, repeat in 1 y ▸ If no advanced adenoma,[cc] repeat in 3 y, then every 5 y[dd] • See Principles of Survivorship (COL-H)

→ Serial CEA elevation or documented recurrence → See 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 Lynch syndrome, familial adenomatous polyposis (FAP), and attenuated FAP, see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.
[b] See Principles of Imaging (COL-A).
[cc] Villous polyp, polyp >1 cm, or high-grade dysplasia.
[dd] Rex DK, Kahi CJ, Levin B, et al. Guidelines for colonoscopy surveillance after cancer resection: a consensus update by the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2006;130:1865-71.
[ee] If patient is a potential candidate for further intervention.

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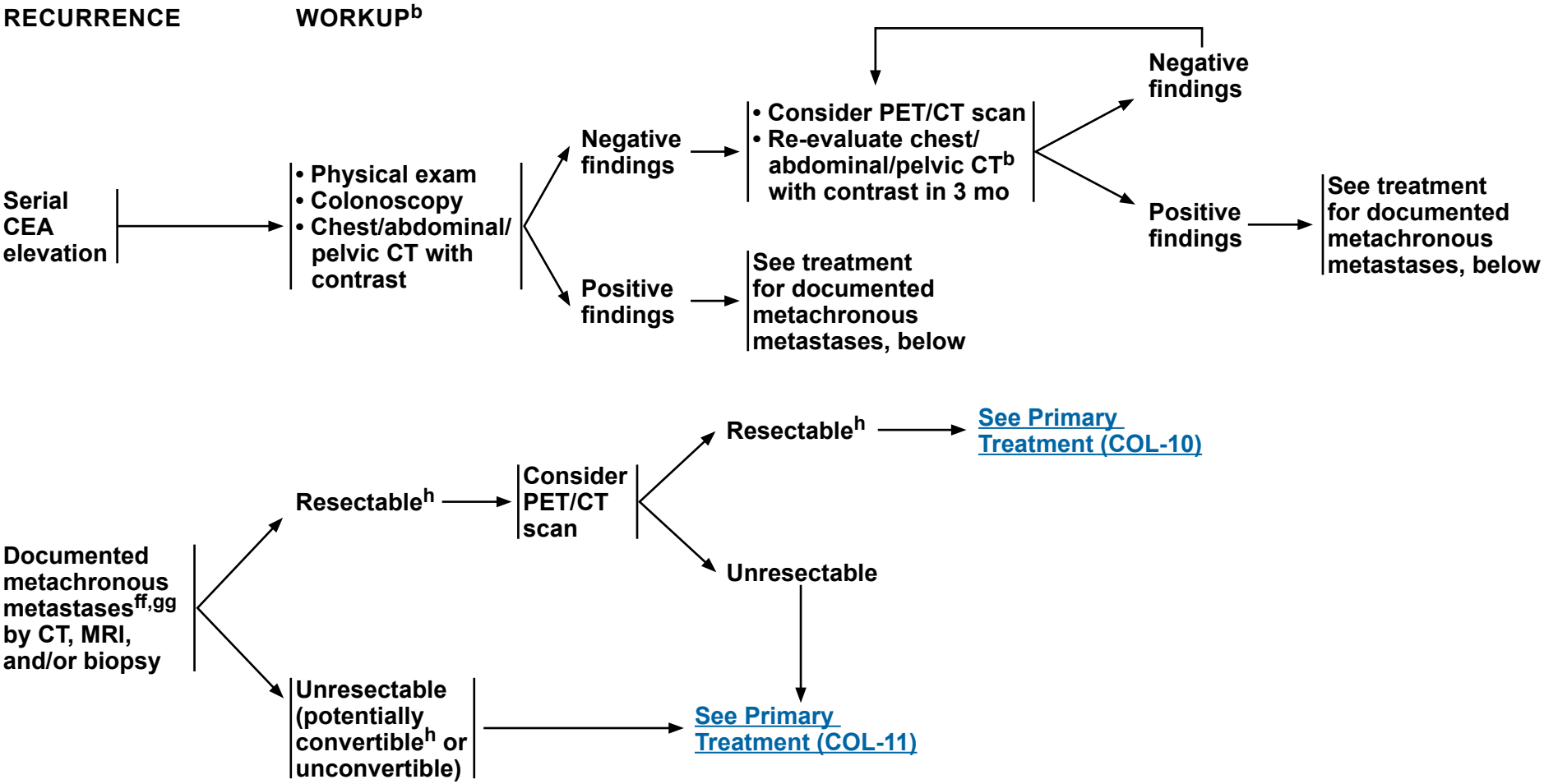

[b] See Principles of Imaging (COL-A).
[h] See Principles of Surgery (COL-C 2 of 3).
[ff] Determination of tumor gene status for *RAS* and *BRAF* mutations and HER2 amplifications (individually or as part of next-generation sequencing [NGS] panel). If known RAS/RAF mutation, HER2 testing is not indicated. Determination of tumor MMR or MSI status (if not previously done). See Principles of Pathologic Review (COL-B 4 of 5) - *KRAS*, *NRAS,* and *BRAF* Mutation Testing and Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing. NGS panels have the ability to pick up rare and actionable mutations and fusions.
[gg] Patients should be evaluated by a multidisciplinary team including surgical consultation for potentially resectable patients.

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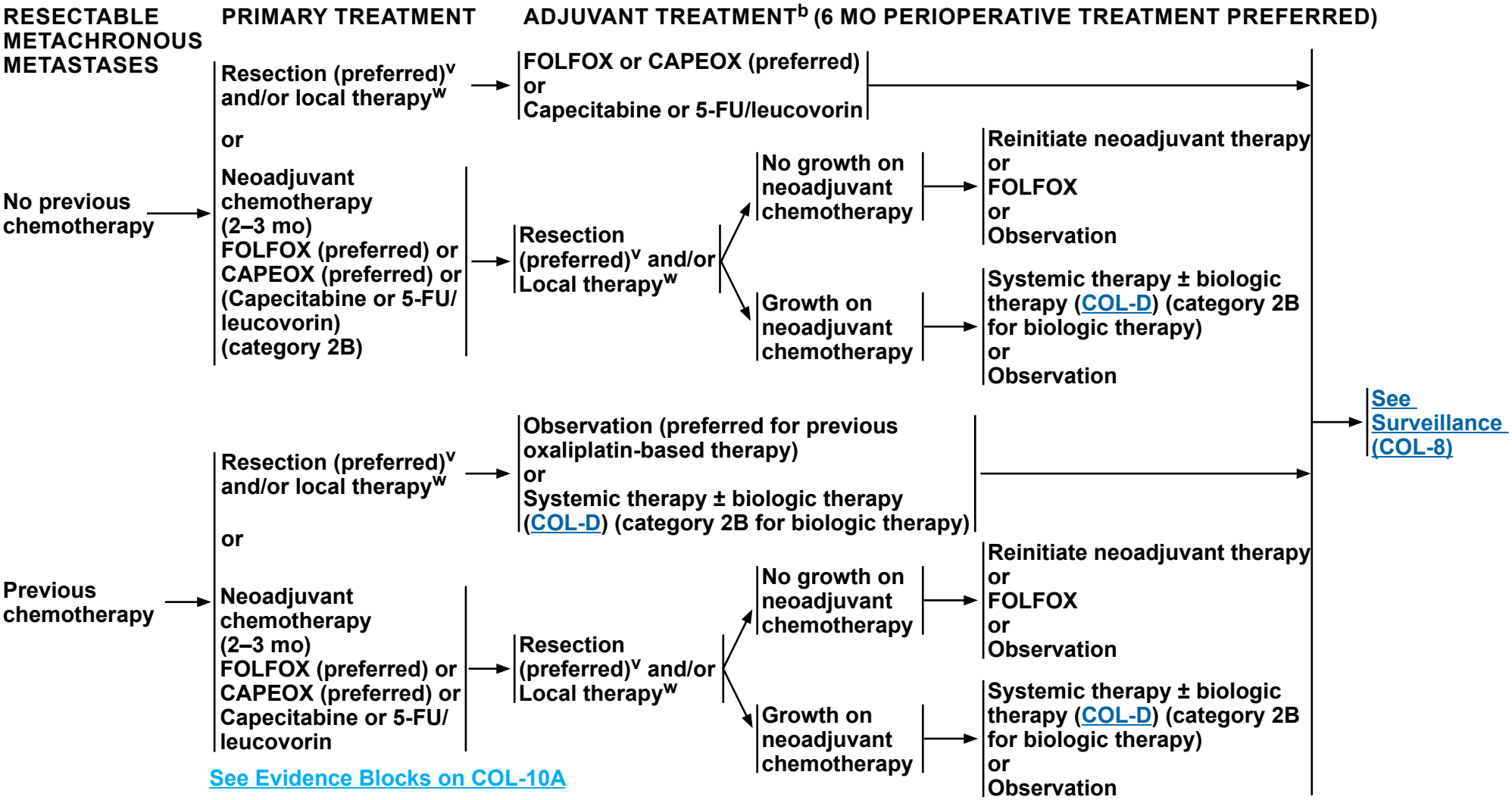

[b] See Principles of Imaging (COL-A).

[v] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.

[w] Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (COL-C and COL-E).

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EVIDENCE BLOCKS FOR NEOADJUVANT/ADJUVANT THERAPY FOR RESECTABLE METACHRONOUS METASTASES (COL-10)

	Neoadjuvant Therapy (with or without previous chemotherapy)	Adjuvant Therapy
FOLFOX		
CapeOx		
Capecitabine		
5-FU/leucovorin		

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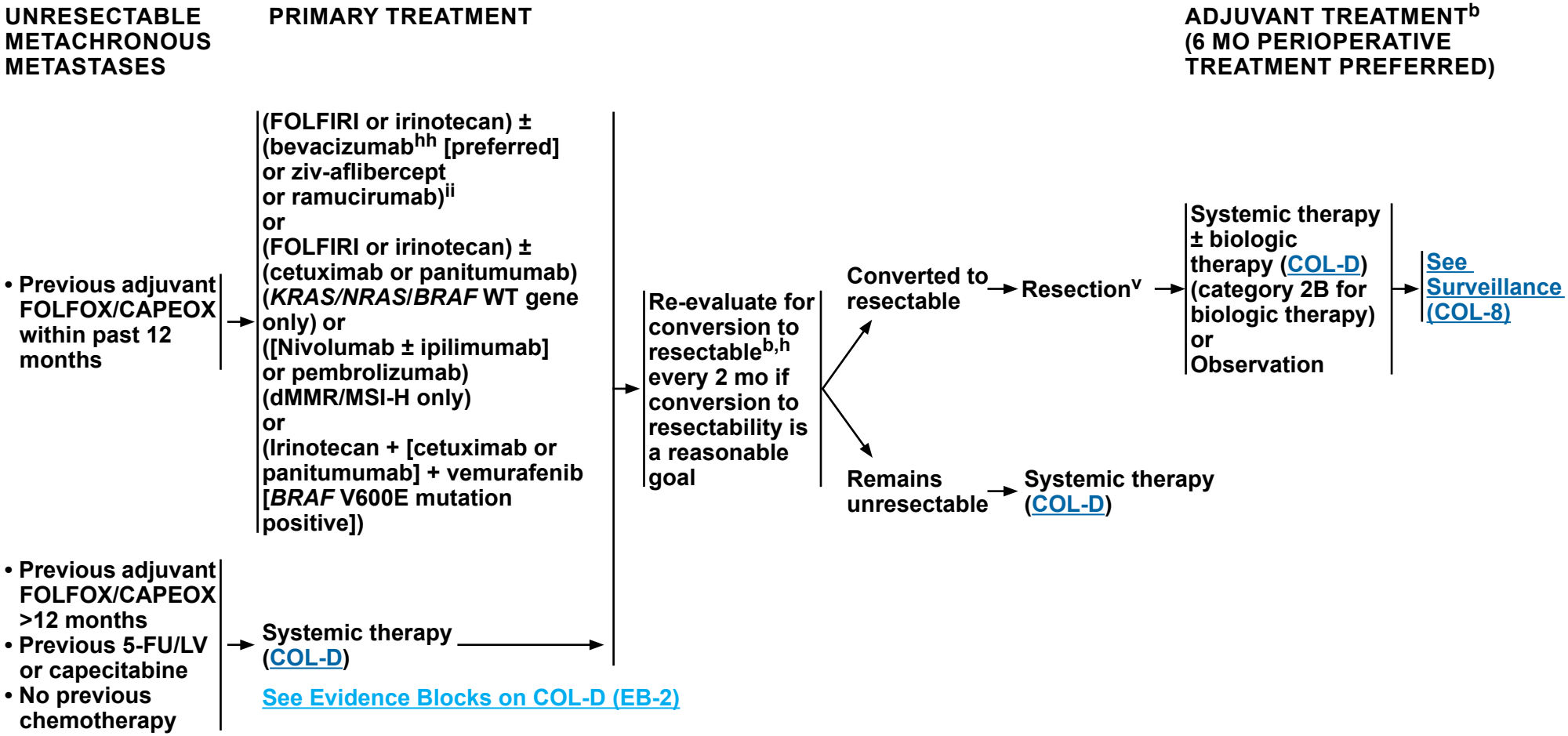

[b] See Principles of Imaging (COL-A).
[e] See Principles of Pathologic Review (COL-B 4 of 5) - *KRAS, NRAS,* and *BRAF* Mutation Testing.
[h] See Principles of Surgery (COL-C 2 of 3).
[v] Hepatic artery infusion ± systemic 5-FU/leucovorin (category 2B) is also an option at institutions with experience in both the surgical and medical oncologic aspects of this procedure.
[hh] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[ii] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.

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PRINCIPLES OF IMAGING[1-3]

Initial Workup/Staging

- Chest, abdomen, and pelvis 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 scan).
  - If IV iodinated contrast material is contraindicated because of significant contrast allergy, then MR 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 MR without IV contrast or consider PET/CT imaging.
- Consider an abdominal/pelvic 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.
- PET/CT is not routinely indicated.
  - PET/CT does not supplant a contrast-enhanced diagnostic CT or MR and should only be used to evaluate an equivocal finding on a contrast-enhanced CT or MR scan or in patients with strong contraindications to IV contrast administration.
  - Consider PET/CT (skull base to mid-thigh) if potentially surgically curable M1 disease in selected cases.
- If liver-directed therapy or surgery is contemplated, a hepatic MRI with intravenous routine extra-cellular or hepatobiliary GBCA is preferred over CT (and PET/CT) to assess exact number and distribution of metastatic foci for local treatment planning.

Monitoring

- Chest, abdomen, and pelvis CT with contrast
  - Prior to adjuvant treatment to assess response to primary therapy or resection
  - During re-evaluation of conversion to resectable disease
- PET/CT is not indicated.

Surveillance

- Stage I disease
  - Imaging is not routinely indicated and should only be based on symptoms and clinical concern for recurrent/metastatic disease.
- Stage II & III disease
  - Chest, abdomen, and pelvis CT every 6–12 months (category 2B for frequency <12 months) for a total of 5 years.
  - PET/CT is not indicated.
- Stage IV disease
  - Chest, abdomen, and pelvis CT every 3–6 months (category 2B for frequency <6 months) x 2 years, then every 6–12 months for a total of 5 years.

[1] Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology 2010;257:674-84.
[2] van Kessel CS, Buckens CF, van den Bosch MA, et al. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol 2012;19:2805-2813.
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PRINCIPLES OF PATHOLOGIC REVIEW

Endoscopically Removed Malignant Polyps

- A malignant polyp is defined as one with cancer invading through the muscularis mucosa and into the submucosa (pT1). pTis is not considered a "malignant polyp."
- Favorable histologic features: grade 1 or 2, no angiolymphatic invasion, and negative margin of resection. There is no consensus as to the definition of what constitutes a positive margin of resection. A positive margin has been defined as: 1) tumor <1 mm from the transected margin; 2) tumor <2 mm from the transected margin; and 3) tumor cells present within the diathermy of the transected margin.[1-4]
- Unfavorable histologic features: grade 3 or 4, angiolymphatic invasion, or a "positive margin." See the positive margin definition above. In several studies, tumor budding has been shown to be an adverse histologic feature associated with adverse outcome and may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps.
- There is controversy as to whether malignant colorectal polyps with a sessile configuration can be successfully treated by endoscopic removal. The literature seems to indicate that endoscopically removed sessile malignant polyps have a significantly greater incidence of adverse outcomes (residual disease, recurrent disease, mortality, and hematogenous metastasis, but not lymph node metastasis) than do pedunculated malignant polyps. However, when one closely looks at the data, configuration by itself is not a significant variable 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]

See Pathologic Stage (continued) on COL-B 2 of 6

See Lymph Node Evaluation on COL-B 3 of 6

See *KRAS*, *NRAS*, and *BRAF* Mutation Testing on COL-B 4 of 6

See references on COL-B 5 of 6

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PRINCIPLES OF PATHOLOGIC 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. For stage II carcinoma, those with PNI have a significantly worse 5-year disease-free survival 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 disease-free 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]**

See Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-B 1 of 6
See Lymph Node Evaluation on COL-B 3 of 6
See *KRAS*, *NRAS*, and *BRAF* Mutation Testing on COL-B 4 of 6
See references on COL-B 5 of 6

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PRINCIPLES OF PATHOLOGIC REVIEW

Lymph Node Evaluation

- The AJCC and College of American Pathologists recommend examination of a minimum of 12 lymph nodes to accurately stage colon cancers.[8,9,19] The literature lacks consensus as to what is the minimal number of lymph nodes to accurately identify stage II cancer. The minimal number of nodes has been reported as >7, >9, >13, >20, and >30.[20-28] The number of lymph nodes retrieved can vary with age of the patient, gender, tumor grade, and tumor site.[21] 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.[29]

Sentinel Lymph Node and Detection of Micrometastasis by Immunohistochemistry

- Examination of the lymph nodes (sentinel or routine) by intense histologic and/or immunohistochemical investigation helps to detect the presence of metastatic disease. The detection of single cells by IHC or by multiple H&E levels and/or clumps of tumor cells <0.2 mm are considered isolated tumor cells (pN0) The 8th edition of the AJCC Cancer Staging Manual and Handbook[30] defines clumps of tumor cells ≥0.2 mm in diameter or clusters of 10-20 tumor cells as micrometastasis and recommends that these micrometastases be considered as standard positive lymph nodes (pN+).
- At the present time the use of sentinel lymph nodes and detection isolated tumor cells by IHC alone should be considered investigational, and results should be used with caution in clinical management decisions.[31-40] Some studies have shown that the detection of IHC cytokeratin-positive cells in stage II (N0) colon cancer (defined by H&E) has a worse prognosis, while others have failed to show this survival difference. In some of these studies, what is presently defined as isolated tumor cells were considered to be micrometastases.[36-41] A recent metaanalysis[42] demonstrated that micrometastasis (≥ 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.[43]

See Endoscopically Removed Malignant Polyp and Colon Cancer Appropriate for Resection on COL-B 1 of 6

See Pathologic Stage on COL-B 2 of 6

See *KRAS*, *NRAS*, and *BRAF* Mutation Testing on COL-B 4 of 6

See references on COL-B 5 of 6

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PRINCIPLES OF PATHOLOGIC REVIEW

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

- **All patients with metastatic colorectal cancer should have tumor tissue genotyped for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of a next-generation sequencing (NGS) panel. Patients with any known *KRAS* mutation (exon 2, 3, 4) or *NRAS* mutation (exon 2, 3, 4) should not be treated with either cetuximab or panitumumab.[44-46] *BRAF* V600E mutation makes response to panitumumab or cetuximab highly unlikely unless given with a BRAF inhibitor.[47-49]**
- **Testing for *KRAS*, *NRAS*, and *BRAF* mutations should be performed only in laboratories that are certified under the clinical laboratory improvement amendments of 1988 (CLIA-88) as qualified to perform *high-complexity* clinical laboratory (molecular pathology) testing. No specific methodology is recommended (eg, sequencing, hybridization).**
- **The testing can be performed on formalin-fixed paraffin-embedded tissue. The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the *KRAS*, *NRAS*, and *BRAF* mutations are similar in both specimen types.[50]**

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

- **Universal MMR[a] or MSI[a] testing is recommended in all patients with a personal history of colon or rectal cancer. See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal**
- **The presence of a *BRAF* V600E mutation in the setting of MLH1 absence would preclude the diagnosis of Lynch syndrome in the vast majority of cases. However, approximately 1% of cancers with *BRAF* V600E mutations (and loss of MLH-1) are Lynch syndrome. Caution should be exercised in excluding cases with strong family history from germline screening in the case of BRAF V600E mutations.[51]**
- **Stage II MSI-H patients may have a good prognosis and do not benefit from 5-FU adjuvant therapy.[52]**
- **MMR or MSI testing should be performed only in CLIA-approved laboratories.**
- **Testing for MSI may be accomplished with a validated NGS panel, especially in patients with metastatic disease who require genotyping of *RAS* and *BRAF*.**
- **Immunohistochemistry (IHC) refers to staining tumor tissue for protein expression of the four mismatch repair MMR genes known to be mutated in Lynch syndrome LS (MLH1, MSH2, MSH6, and PMS2.) A normal IHC test implies that all four MMR proteins are normally expressed (retained). Loss (absence) of expression of one or more of the four DNA MMR proteins is often reported as abnormal or positive IHC. When IHC is reported as positive, caution should be taken to ensure that positive refers to absence of mismatch expression and not presence of expression. NOTE: Normal is the presence of positive protein staining (retained) and abnormal is negative or loss of staining of protein. Loss of protein expression by IHC in any one of the MMR genes guides further genetic testing (mutation detection to the genes where the protein expression is not observed). Abnormal MLH1 IHC should be followed by tumor testing for BRAF V600E mutation. The presence of BRAF V600E mutation is consistent with sporadic cancer. However, approximately 1% of Lynch syndrome patients with loss of MLH-1 can express BRAF V600E mutation.[51]**

See Endoscopically Removed Malignant Polyps and Colon Cancer Appropriate for Resection on COL-B 1 of 6

See Pathologic Stage on COL-B 2 of 6

See Lymph Node Evaluation on COL-B 3 of 6

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

See references on COL-B 5 of 6

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PRINCIPLES OF PATHOLOGIC REVIEW
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PRINCIPLES OF SURGERY

Colectomy

- **Lymphadenectomy**
  - **Lymph nodes at the origin of feeding vessel(s) should be identified for pathologic exam.**
  - **Clinically positive lymph nodes outside the 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 need to be examined to establish N stage.[1]**
- **Minimally invasive approaches may be considered based on the following criteria:[2]**
  - **The surgeon has experience performing laparoscopically assisted colorectal operations.[3,4]**
  - **Minimally invasive approaches are generally not indicated for locally advanced cancer or acute bowel obstruction or perforation from cancer.**
  - **Thorough abdominal exploration is required.[5]**
  - **Consider preoperative marking of lesion(s).**
- **Management of patients with carrier status of known or clinically suspected Lynch syndrome**
  - **Consider more extensive colectomy for patients with a strong family history of colon cancer or young age (<50 y).**
    See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
- **Resection needs to be complete to be considered curative.**

See Criteria for Resectability of Metastases and Locoregional Therapies Within Surgery on COL-C 2 of 3

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

Liver

- Hepatic resection is the treatment of choice for resectable liver metastases from colorectal cancer.[6]
- Complete resection must be feasible based on anatomic grounds and the extent of disease; maintenance of adequate hepatic function is required.[7]
- The primary tumor must have been resected for cure (R0). There should be no unresectable extrahepatic sites of disease.[8-11] Having a plan for a debulking resection (less than an R0 resection) is not recommended.[7]
- 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.[12]
- When hepatic metastatic disease is not optimally resectable based on insufficient remnant liver volume, approaches utilizing preoperative portal vein embolization[13] or staged liver resection[14] can be considered.
- Ablative techniques may be considered alone or in conjunction with resection. All original sites of disease need to be amenable to ablation or resection.
- Arterially directed catheter therapy, and in particular yttrium 90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.
- Re-resection can be considered in selected patients.[15]

Lung

- Complete resection based on the anatomic location and extent of disease with maintenance of adequate function is required.[16-19]
- The primary tumor must have been resected for cure (R0).
- Resectable extrapulmonary metastases do not preclude resection.[20-23]
- Re-resection can be considered in selected patients.[24]
- Ablative techniques may be considered alone or in conjunction with resection for resectable disease. All original sites of disease need to be amenable to ablation or resection.
- Ablative techniques can also be considered when unresectable and amenable to complete ablation.
- Patients with resectable synchronous metastases can be resected synchronously or using a staged approach.
- Conformal external beam radiation therapy may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable.

Evaluation for Conversion to Resectable Disease

- Re-evaluation for resection should be considered in otherwise unresectable patients after 2 months of preoperative chemotherapy and every 2 months thereafter.[25-28]
- Disease with a higher likelihood of being converted to resectable are those with initially convertible disease distributed within limited sites.
- When considering whether disease has been converted to resectable, all original sites need to be amenable to resection.[29]
- Preoperative chemotherapy regimens with high response rates should be considered for patients with potentially convertible disease.[30]

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

INITIAL THERAPY[b]

Patient appropriate for intensive therapy

- FOLFOX ± bevacizumab[c] → Progression → See COL-D 2 of 13
  or
  CAPEOX ± bevacizumab[c] → Progression → See COL-D 2 of 13
  or
  FOLFOX + (cetuximab or panitumumab)[d,e] (*KRAS/NRAS/BRAF* WT and left-sided tumors only) → Progression → See COL-D 2 of 13
- or
  FOLFIRI[f] ± bevacizumab[c] → Progression → See COL-D 3 of 13
  or
  FOLFIRI[f] + (cetuximab or panitumumab)[d,e] (*KRAS/NRAS/BRAF* WT and left-sided tumors only) → Progression → See COL-D 3 of 13
- or
  FOLFOXIRI[f] ± bevacizumab[c] → Progression → See COL-D 4 of 13
- or
  5-FU/leucovorin (infusional preferred) ± bevacizumab[g,c] → Progression → See COL-D 5 of 13
  or
  Capecitabine ± bevacizumab[g,c] → Progression → See COL-D 5 of 13

Patient not appropriate for intensive therapy

- Infusional 5-FU + leucovorin ± bevacizumab[c]
  or
  Capecitabine ± bevacizumab[c]
  or
  (Cetuximab or panitumumab)[d,e] (category 2B) (*KRAS/NRAS/BRAF* WT and left-sided tumors only)
  or
  (Nivolumab or pembrolizumab) (dMMR/MSI-H only)[d,h]
  or
  Nivolumab + ipilimumab (dMMR/MSI-H only)[d,h] (category 2B)

  → Improvement in functional status → Consider initial therapy as above[h]

  → No improvement in functional status → Best supportive care
  See NCCN Guidelines for Palliative Care

See Evidence Blocks on COL-D (EB-1)

See footnotes on COL-D (7 of 13)

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

Previous oxaliplatin-based therapy without irinotecan

SUBSEQUENT THERAPY[b,j,k]

- FOLFIRI[f] or irinotecan[f]
- or FOLFIRI[f] + (bevacizumab[c,l] [preferred] or ziv-aflibercept[l,m] or ramucirumab[l,m])
- or Irinotecan[f] + (bevacizumab[c,l] [preferred] or ziv-aflibercept[l,m] or ramucirumab[l,m])
- or FOLFIRI[f] + (cetuximab or panitumumab)[d,n,o] (*KRAS/NRAS/BRAF* WT only)
- or Irinotecan[f] + (cetuximab or panitumumab)[d,n,o] (*KRAS/NRAS/BRAF* WT only)
- or Irinotecan[f] + (cetuximab or panitumumab)[d,n] + vemurafenib (*BRAF* V600E mutation positive)
- or Dabrafenib + trametinib + (cetuximab or panitumumab)[d,n] (*BRAF* V600E mutation positive)
- or Encorafenib + binimetinib + (cetuximab or panitumumab)[d,n] (*BRAF* V600E mutation positive)
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[p] (dMMR/MSI-H only)[d,h]
- or (Trastuzumab[q] + [pertuzumab or lapatinib])[r] (HER2-amplified and RAS wild-type)

→ Irinotecan[f] + (cetuximab or panitumumab)[d,n,o] (*KRAS/NRAS/BRAF* WT only)
- or Regorafenib[s]
- or Trifluridine + tipiracil[s]
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[p] (dMMR/MSI-H only)[d,h]
- or (Trastuzumab[q] + [pertuzumab or lapatinib])[r] (HER2-amplified and RAS wild-type)

→ See Subsequent therapy

→ Regorafenib[s]
- or Trifluridine + tipiracil[s]
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[p] (dMMR/MSI-H only)[d,h]
- or (Trastuzumab[q] + [pertuzumab or lapatinib])[r] (HER2-amplified and RAS wild-type)

→ See Subsequent therapy

→ See Subsequent therapy

Regorafenib[s]
- or Trifluridine + tipiracil[s]

Regorafenib[s,t]
- or Trifluridine + tipiracil[s,t]
- or Best supportive care

See Evidence Blocks on COL-D (EB-2) and COL-D (EB-3)

[j] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.
[n] If neither previously given
[o] If no previous treatment with a checkpoint inhibitor
[r] If no previous treatment with HER2 inhibitor.
[t] If not previously given

See footnotes on COL-D (7 of 13)

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

Previous irinotecan-based therapy without oxaliplatin

SUBSEQUENT THERAPY[b,j,k]

- FOLFOX or CAPEOX
- or FOLFOX + bevacizumab[c]
- or CAPEOX + bevacizumab[c]
- or FOLFOX + (cetuximab or panitumumab)[d] (*KRAS/NRAS/BRAF* WT only)
- or Irinotecan[f] + (cetuximab or panitumumab)[d,n,o] (*KRAS/NRAS/BRAF* WT only)
- or Irinotecan[f] + (cetuximab or panitumumab)[d,n] + vemurafenib (*BRAF* V600E mutation positive)
- or Dabrafenib + trametinib + (cetuximab or panitumumab)[d,n] (*BRAF* V600E mutation positive)
- or Encorafenib + binimetinib + (cetuximab or panitumumab)[d,n] (*BRAF* V600E mutation positive)
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[p] (dMMR/MSI-H only)[d,h]
- or (Trastuzumab[q] + [pertuzumab or lapatinib])[r] (HER2-amplified and RAS WT)

→ See Subsequent therapy

See Subsequent therapy

- Irinotecan[f] + (cetuximab or panitumumab)[d,n,o] (*KRAS/NRAS/BRAF* WT only)
- or Regorafenib[s]
- or Trifluridine + tipiracil[s]
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[p] (dMMR/MSI-H only)[d,h]
- or (Trastuzumab[q] + [pertuzumab or lapatinib])[r] (HER2-amplified and RAS WT)

→ See Subsequent therapy

- FOLFOX or CAPEOX
- or ([Nivolumab ± ipilimumab] or pembrolizumab)[p] (dMMR/MSI-H only)[d,h]
- or (Trastuzumab[q] + [pertuzumab or lapatinib])[r] (HER2-amplified and RAS WT)

→ See Subsequent therapy

- Regorafenib[s]
- or Trifluridine + tipiracil[s]

- Regorafenib[s]
- or Trifluridine + tipiracil[s]

- Regorafenib[s,t]
- or Trifluridine + tipiracil[s,t]
- or Best supportive care

See footnotes on COL-D (7 of 13)

See Evidence Blocks on COL-D (EB-2) and COL-D (EB-3)

[j] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.

[n] If neither previously given
[p] If no previous treatment with a checkpoint inhibitor
[r] If no previous treatment with HER2 inhibitor.
[t] If not previously given

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

Previous FOLFOXIRI

SUBSEQUENT THERAPY[b,j,k]

- Irinotecan[f] + (cetuximab or panitumumab)[d,o] (*KRAS/NRAS/BRAF* WT only)
  or
  Irinotecan[f] + (cetuximab or panitumumab)[d,n] + vemurafenib (*BRAF* V600E mutation positive)
  or
  Dabrafenib + trametinib + (cetuximab or panitumumab)[d,n] (*BRAF* V600E mutation positive)
  or
  Encorafenib + binimetinib + (cetuximab or panitumumab)[d,n] (*BRAF* V600E mutation positive)
  or
  Regorafenib[s]
  or
  Trifluridine + tipiracil[s]
  or
  ([Nivolumab ± ipilimumab] or pembrolizumab)[p] (dMMR/MSI-H only)[d,h]
  or
  (Trastuzumab[q] + [pertuzumab or lapatinib])[r] (HER2-amplified and RAS WT)
  → See Subsequent therapy

- Regorafenib[s]
  or
  Trifluridine + tipiracil[s]
  → Regorafenib[s,t]
  or
  Trifluridine + tipiracil[s,t]
  or
  Best supportive care
  or
  ([Nivolumab ± ipilimumab] or pembrolizumab)[p] (dMMR/MSI-H only)[d,h]
  or
  (Trastuzumab[q] + [pertuzumab or lapatinib])[r] (HER2-amplified and RAS WT)
  → See Subsequent therapy

See Evidence Blocks on COL-D (EB-2) and COL-D (EB-3)

[j] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.
[n] If neither previously given
[p] If no previous treatment with a checkpoint inhibitor
[r] If no previous treatment with HER2 inhibitor.
[t] If not previously given

See footnotes on COL-D (7 of 13)

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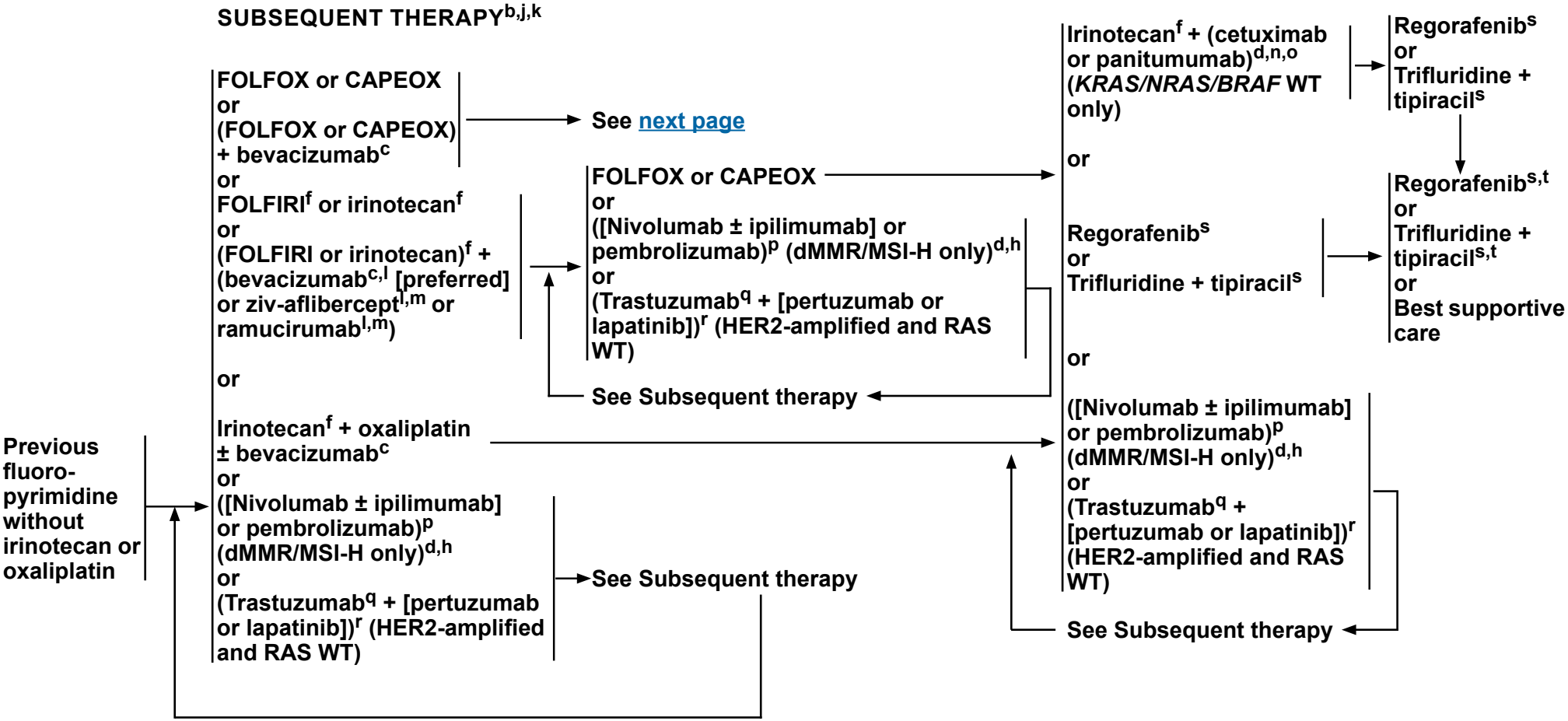
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a]



[j] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.
[n] If neither previously given
[p] If no previous treatment with a checkpoint inhibitor
[r] If no previous treatment with HER2 inhibitor.
[t] If not previously given

See Evidence Blocks on COL-D (EB-2) and COL-D (EB-3)

See footnotes on COL-D (7 of 13)

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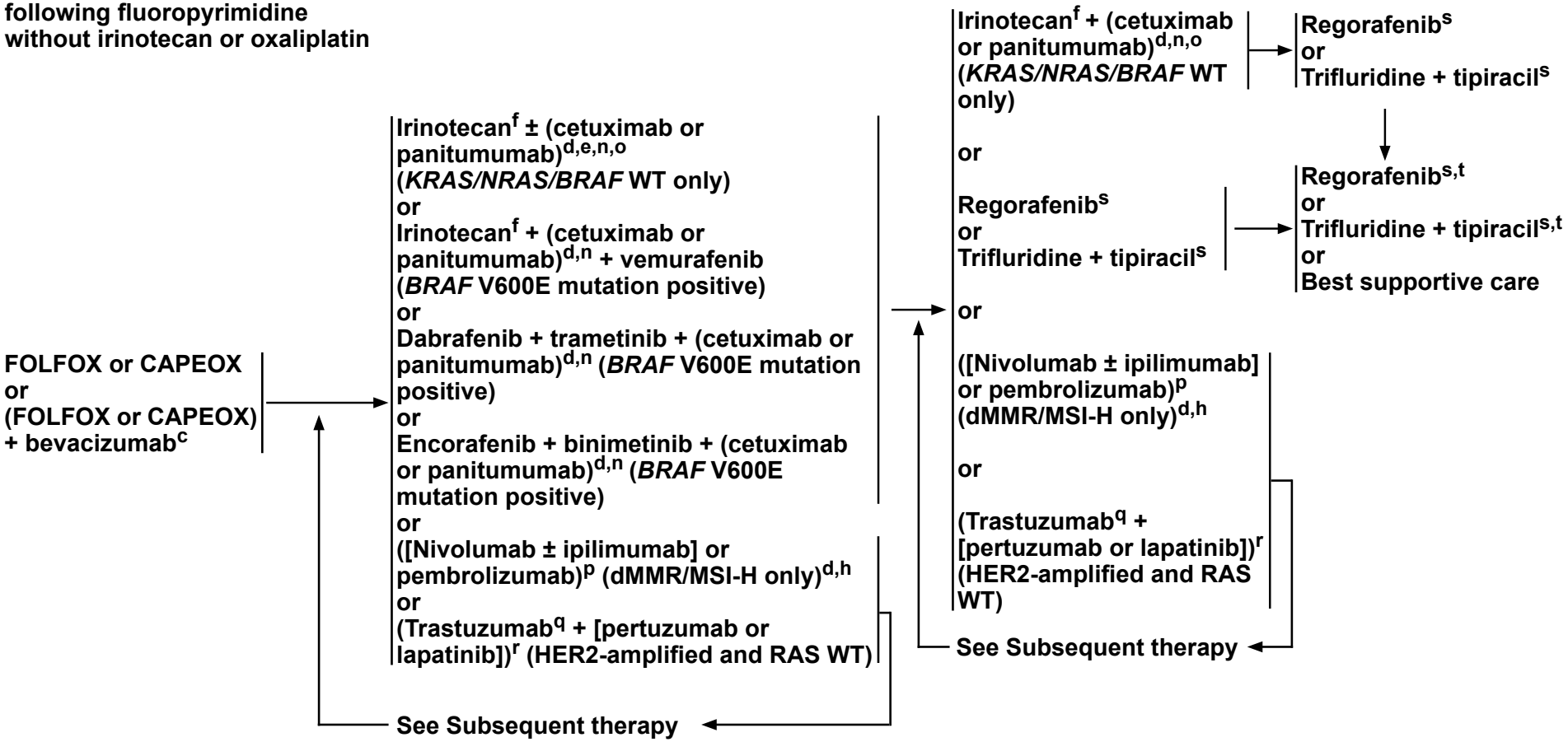
CONTINUUM OF CARE - SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a]

SUBSEQUENT THERAPY[b,j,k] following fluoropyrimidine without irinotecan or oxaliplatin



See Evidence Blocks on COL-D (EB-2) and COL-D (EB-3)

[j] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.
[n] If neither previously given
[p] If no previous treatment with a checkpoint inhibitor
[r] If no previous treatment with HER2 inhibitor.
[t] If not previously given

See footnotes on COL-D (7 of 13)

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE
COL-D (1 OF 13)

Regimen	First-Line Therapy
FOLFOX	
FOLFOX/bevacizumab	
FOLFOX/cetuximab	
FOLFOX/panitumumab	
CapeOx	
CapeOx/bevacizumab	
5-FU/leucovorin	
FOLFIRI	
FOLFIRI/bevacizumab	
FOLFIRI/cetuximab	
FOLFIRI/panitumumab	

Regimen	First-Line Therapy
FOLFOXIRI	
FOLFOXIRI/bevacizumab	
5-FU/leucovorin/bevacizumab	
Capecitabine	
Capecitabine/bevacizumab	
Cetuximab	
Panitumumab	
Nivolumab	
Pembrolizumab	
Nivolumab/ipilimumab	

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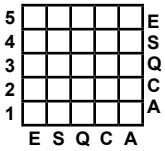

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE

Regimen	Second-Line Therapy
FOLFIRI	
FOLFIRI/bevacizumab (after prior bevacizumab)	
FOLFIRI/bevacizumab (no prior bevacizumab)	
FOLFIRI/ziv-aflibercept (after prior bevacizumab)	
FOLFIRI/ziv-aflibercept (no prior bevacizumab)	
FOLFIRI/ramucirumab (after prior bevacizumab)	
FOLFIRI/ramucirumab (no prior bevacizumab)	
FOLFIRI/cetuximab	
FOLFIRI/panitumumab	
Irinotecan	
Irinotecan/cetuximab	
Irinotecan/panitumumab	

Previous oxaliplatin-based therapy on COL-D (2 of 13)
Previous irinotecan-based therapy on COL-D (3 of 13)
Previous FOLFOXIRI on COL-D (4 of 13)
Previous fluoropyrimidine on COL-D (5 of 13)

*Evidence Block development in progress

Regimen	Second-Line Therapy
Irinotecan/cetuximab/vemurafenib	
Irinotecan/panitumumab/vemurafenib	
Dabrafenib/trametinib/cetuximab	
Dabrafenib/trametinib/panitumumab	
Encorafenib/binimetinib/cetuximab	
Encorafenib/binimetinib/panitumumab	
Larotrectinib	
Entrectinib	*
Irinotecan/bevacizumab (after prior bevacizumab)	
Irinotecan/bevacizumab (no prior bevacizumab)	
Irinotecan/ziv-aflibercept (after prior bevacizumab)	
Irinotecan/ziv-aflibercept (no prior bevacizumab)	
Irinotecan/ramucirumab (after prior bevacizumab)	
Irinotecan/ramucirumab (no prior bevacizumab)	
Irinotecan/oxaliplatin	
IROX/bevacizumab (after prior bevacizumab)	
IROX/bevacizumab (no prior bevacizumab)	

Regimen	Second-Line Therapy
Nivolumab	
Pembrolizumab	
Nivolumab/ipilimumab	
Trastuzumab/pertuzumab	
Trastuzumab/lapatinib	
FOLFOX	
FOLFOX/bevacizumab (after prior bevacizumab)	
FOLFOX/bevacizumab (no prior bevacizumab)	
CapeOx/bevacizumab (after prior bevacizumab)	
CapeOx/bevacizumab (no prior bevacizumab)	
Regorafenib	
Trifluridine/tipiracil	
CapeOx	
Panitumumab	
Cetuximab	

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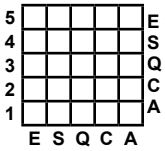

E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

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EVIDENCE BLOCKS FOR ADVANCED OR METASTATIC DISEASE

Regimen	Third-Line Therapy	Subsequent Therapy
CapeOx		
Cetuximab		
FOLFOX		
Irinotecan		—
Irinotecan/cetuximab		
Irinotecan/panitumumab		
Irinotecan/cetuximab/vemurafenib		
Irinotecan/panitumumab/vemurafenib		
Dabrafenib/trametinib/cetuximab		
Dabrafenib/trametinib/panitumumab		
Encorafenib/binimetinib/cetuximab		
Encorafenib/binimetinib/ panitumumab		
Larotrectinib		
Entrectinib	*	*

Regimen	Third-Line Therapy	Subsequent Therapy
Nivolumab		—
Pembrolizumab		—
Nivolumab/ipilimumab		—
Trastuzumab/pertuzumab		
Trastuzumab/lapatinib		
Panitumumab		
Regorafenib (previous trifluridine/tipiracil)		
Regorafenib (no previous trifluridine/tipiracil)		
Trifluridine/tipiracil (previous regorafenib)		
Trifluridine/tipiracil (no previous regorafenib)		

Previous oxaliplatin-based therapy on COL-D (2 of 13)
Previous irinotecan-based therapy on COL-D (3 of 13)
Previous FOLFOXIRI on COL-D (4 of 13)
Previous fluoropyrimidine on COL-D (5 of 13)

*Evidence Block development in progress

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE FOOTNOTES

[a] For chemotherapy references, see Chemotherapy Regimens and References (COL-D [8 of 13]).
[b] Chest/abdominal/pelvic CT with contrast or chest CT and abdominal/pelvic MRI with contrast to monitor progress of therapy. PET/CT should not be used. See Principles of Imaging (COL-A).
[c] An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
[d] See Principles of Pathologic Review (COL-B 4 of 5).
[e] 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.
[f] Irinotecan should be used with caution in patients with Gilbert's disease or elevated serum bilirubin. There is a commercially available test for *UGT1A1*. Guidelines for use in clinical practice have not been established.
[g] A treatment option for patients not able to tolerate oxaliplatin or irinotecan.
[h] These therapies are FDA approved for colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. However, a number of patients in the clinical trials had not received all three prior systemic therapies. Thirty-seven percent of patients received nivolumab monotherapy and 24% received ipilimumab/nivolumab combination therapy in first- or second-line, and 28% and 31% of patients had not received all three indicated prior therapies before treatment with nivolumab or ipilimumab/nivolumab, respectively.
[i] The use of single-agent capecitabine after progression on a fluoropyrimidine-containing regimen has been shown to be ineffective; therefore, this is not recommended.
[j] Larotrectinib or entrectinib are treatment options for patients with metastatic colorectal cancer that is *NTRK* gene fusion positive.
[k] 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.
[l] Bevacizumab is the preferred anti-angiogenic agent based on toxicity and/or cost.
[m] 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.
[n] If neither previously given.
[o] Cetuximab or panitumumab are recommended in combination with irinotecan-based therapy or as single-agent therapy for patients who cannot tolerate irinotecan.
[p] If no previous treatment with a checkpoint inhibitor.
[q] An FDA-approved biosimilar is an appropriate substitute for trastuzumab.
[r] If no previous treatment with HER2 inhibitor.
[s] Regorafenib or trifluridine + tipiracil are treatment options for patients who have progressed through all available regimens.
[t] If not previously given.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

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

mFOLFOX7[4]
Oxaliplatin 85 mg/m² IV day 1*
Leucovorin 400 mg/m² IV day 1**
5-FU 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) IV continuous infusion
Repeat every 2 weeks

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

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

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

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

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

FOLFIRI[9,10]
Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Leucovorin 400 mg/m² IV infusion to match duration of irinotecan infusion, day 1**
5-FU 400 mg/m² IV bolus day 1, then 1200 mg/m²/d x 2 days (total 2400 mg/m² over 46–48 hours) continuous infusion
Repeat every 2 weeks

FOLFIRI + bevacizumab[11,†,¶]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

* Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m²/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m2/min. J Oncol Pract 2016;12:e548-553.
** Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
† An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
‡ The majority of safety and efficacy data for this regimen have been developed in Europe, where a capecitabine starting dose of 1000 mg/m² twice daily for 14 days, repeated every 21 days, is standard. Evidence suggests that North American patients may experience greater toxicity with capecitabine (as well as with other fluoropyrimidines) than European patients, and may require a lower dose of capecitabine.
¶ Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

FOLFIRI + cetuximab (*KRAS/NRAS/BRAF* WT only)
Cetuximab 400 mg/m² IV over 2 hours first infusion, then 250 mg/m² IV over 60 minutes weekly[12]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

FOLFIRI + panitumumab[14] (*KRAS/NRAS/BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ziv-aflibercept[15]
Ziv-aflibercept 4 mg/kg IV over 60 minutes, day 1
Repeat every 2 weeks

FOLFIRI + ramucirumab[16]
Ramucirumab 8 mg/kg over 60 minutes, day 1
Repeat every 2 weeks

FOLFOXIRI[17]
Irinotecan 165 mg/m² IV day 1, oxaliplatin 85 mg/m² IV day 1,*
Leucovorin 400 mg/m² day 1, fluorouracil 1200 mg/m²/d x 2 days (total 2400 mg/m² over 48 hours) continuous infusion starting on day 1.**
Repeat every 2 weeks
The dose used in European studies was 3200 mg/m². U.S. patients have been shown to have poorer tolerance for 5-FU. The dose listed above is recommended for U.S. patients.

FOLFOXIRI + bevacizumab[18,†,¶]
Bevacizumab 5 mg/kg IV, day 1
Repeat every 2 weeks

IROX[19]
Oxaliplatin 85 mg/m² IV,*
followed by irinotecan 200 mg/m² over 30–90 minutes every 3 weeks

Bolus or infusional 5-FU/leucovorin
Roswell Park regimen[20]
Leucovorin 500 mg/m² IV over 2 hours, days 1, 8, 15, 22, 29, and 36
5-FU 500 mg/m² IV bolus 1 hour after start of leucovorin, days 1, 8, 15, 22, 29, and 36
Repeat every 8 weeks

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

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

* Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m2/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m²/min. J Oncol Pract 2016;12:e548-553.
** Leucovorin 400 mg/m² is the equivalent of levoleucovorin 200 mg/m².
† An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
¶ Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Capecitabine[8]
Capecitabine 850–1250 mg/m² PO twice daily, days 1–14
Repeat every 3 weeks

Capecitabine + bevacizumab[22,†,¶]
Bevacizumab 7.5 mg/kg IV, day 1
Repeat every 3 weeks

Irinotecan
Irinotecan 125 mg/m² IV over 30–90 minutes, days 1 and 8
Repeat every 3 weeks[23,24]
or Irinotecan 180 mg/m² IV over 30–90 minutes, day 1
Repeat every 2 weeks
or Irinotecan 300–350 mg/m² IV over 30–90 minutes, day 1
Repeat every 3 weeks

Irinotecan + cetuximab (*KRAS/NRAS/BRAF* WT only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[25]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

Irinotecan + panitumumab[14] (*KRAS*/*NRAS*/*BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Irinotecan + ramucirumab[16]
Ramucirumab 8 mg/kg IV over 60 minutes every 2 weeks

Cetuximab (*KRAS/NRAS/BRAF* WT only)
Cetuximab 400 mg/m² first infusion, then 250 mg/m² IV weekly[25]
or Cetuximab 500 mg/m² IV over 2 hours, day 1, every 2 weeks[13]

Panitumumab[26] (*KRAS/NRAS/BRAF* WT only)
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks

Regorafenib
Regorafenib 160 mg PO daily on days 1–21[27]
or
First cycle: Regorafenib 80 mg PO daily on days 1–7, then 120 mg PO daily on days 8–14, then 160 mg PO daily on days 15–21[28]
Subsequent cycles: Regorafenib 160 mg PO daily on days 1–21
Repeat every 28 days

Trifluridine + tipiracil[29]
Trifluridine + tipiracil 35 mg/m² up to a maximum dose of 80 mg per dose (based on the trifluridine component)
PO twice daily days 1–5 and 8–12
Repeat every 28 days

Pembrolizumab[30] (dMMR/MSI-H only)
Pembrolizumab 2 mg/kg every 3 weeks
or Pembrolizumab 200 mg every 3 weeks

Nivolumab[31] (dMMR/MSI-H only)
Nivolumab 3 mg/kg every 2 weeks
or Nivolumab 240 mg IV every 2 weeks
or Nivolumab 480 mg IV every 4 weeks

Nivolumab + ipilimumab[32] (dMMR/MSI-H only)
Nivolumab 3 mg/kg (30-minute IV infusion) and ipilimumab 1 mg/kg (30-minute IV infusion) once every 3 weeks for four doses, then nivolumab 3 mg/kg IV or nivolumab 240 mg IV every 2 weeks

†An FDA-approved biosimilar is an appropriate substitute for bevacizumab.
¶Bevacizumab may be safely given at a rate of 0.5 mg/kg/min (5 mg/kg over 10 minutes and 7.5 mg/kg over 15 minutes).

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - CHEMOTHERAPY REGIMENS

Trastuzumab§ + pertuzumab[33] (HER2-amplified and RAS WT)
Trastuzumab 8mg/kg IV loading dose on Day 1 of Cycle 1, then 6mg/kg IV every 21 days
Pertuzumab 840mg IV loading dose on Day 1 of Cycle 1, then 420mg IV every 21 days

Trastuzumab§ + lapatinib[34] (HER2-amplified and RAS WT)
Trastuzumab 4mg/kg IV loading dose on Day 1 of Cycle 1, then 2mg/kg IV weekly
Lapatinib 1000mg PO daily

Irinotecan + cetuximab + vemurafenib[35]
(*BRAF* V600E mutation positive)
Irinotecan 180 mg/m² IV every 2 weeks
Cetuximab 500 mg/m² IV every 2 weeks
Vemurafenib 960 mg PO twice daily

Irinotecan + panitumumab + vemurafenib[35]
(*BRAF* V600E mutation positive)
Irinotecan 180 mg/m² IV every 2 weeks
Panitumumab 6 mg/kg IV over 60 minutes every 2 weeks
Vemurafenib 960 mg PO twice daily

Dabrafenib + trametinib + cetuximab[36]
(*BRAF* V600E mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Cetuximab 400 mg/m² followed by 250 mg/m² weekly

Dabrafenib + trametinib + panitumumab[36]
(*BRAF* V600E mutation positive)
Dabrafenib 150 mg PO twice daily
Trametinib 2 mg PO daily
Panitumumab 6 mg/kg IV every 14 days

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

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

Larotrectinib[39]
(*NTRK* gene fusion positive)
100 mg PO twice daily

Entrectinib[40]
(*NTRK* gene fusion positive)
600 mg PO once daily

§ An FDA-approved biosimilar is an appropriate substitute for trastuzumab.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE - REFERENCES

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PRINCIPLES OF RADIATION THERAPY

General Principles

- **Neoadjuvant radiation therapy with concurrent fluoropyrimidine-based chemotherapy may be considered for initially unresectable non-metastatic T4 colon cancer to aid resectability.**
- **In patients with a limited number of liver or lung metastases, radiotherapy to the metastatic site can be considered in highly selected cases or in the setting of a clinical trial. Radiotherapy should not be used in the place of surgical resection. Radiotherapy should be delivered in a highly conformal manner. The techniques can include 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or stereotactic body radiation therapy (SBRT).**

Treatment Information

- **If radiation therapy is to be used, conformal external beam radiation should be routinely used and IMRT/SBRT should be reserved only 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.**
- **Image-guided radiation therapy (IGRT) with kilovoltage (kV) imaging and cone-beam CT imaging should be routinely used during the course of treatment with IMRT and SBRT.**
- **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.**
- **Intraoperative radiation therapy (IORT), if available, may be considered for patients with T4 or recurrent cancers as an additional boost.**
- **Target Volumes**
  - **Radiation therapy 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 after evaluating the cumulative dose to adjacent organs at risk.**
    - ◊ **Small bowel dose should be limited to 45 Gy.**
    - ◊ **Large bowel, stomach, and liver are critical structures that should be evaluated on the dose-volume histogram (DVH).**
    - ◊ **Fluoropyrimidine-based chemotherapy should be delivered concurrently with radiation.**
  - **If IORT is not available, additional 10–20 Gy external beam radiation therapy and/or brachytherapy could be considered to a limited volume.**

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PRINCIPLES OF RISK ASSESSMENT FOR STAGE II DISEASE[1,2,3]

- **Patient/physician discussion 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)**
  - **Assessment of other comorbidities and anticipated life expectancy.**
- **The benefit of adjuvant chemotherapy does not improve survival by more than 5%.**
- **Microsatellite Instability (MSI) or Mismatch Repair (MMR) Testing (see COL-B 4 of 5)**

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PRINCIPLES OF ADJUVANT THERAPY

- **FOLFOX is superior to 5-FU/leucovorin for patients with stage III colon cancer.[1,2] Capecitabine/oxaliplatin is superior to bolus 5-FU/leucovorin for patients with stage III colon cancer.**
- **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 stage II patients with multiple high-risk factors and is not indicated for good- or average-risk patients with stage II colon cancer.**
- **A benefit for the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 years and older has not been proven.[4]**
- **In patients staged as T1-3, N1 (low-risk stage III), 3 months of CapeOX is non-inferior to 6 months of CapeOX for disease-free survival; non-inferiority of 3 versus 6 months of FOLFOX has not been proven. In patients 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 disease-free survival, whereas non-inferiority of 3 versus 6 months of CapeOX has not been proven. Grade 3+ neurotoxicity rates are lower for patients who receive 3 months versus 6 months of treatment (3% vs. 16% for FOLFOX; 3% vs. 9% for CapeOX).[5]**

See Principles of Adjuvant Therapy - Chemotherapy Regimens and References on COL-G 2 of 2

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PRINCIPLES OF ADJUVANT THERAPY - CHEMOTHERAPY REGIMENS AND REFERENCES

mFOLFOX 6
Oxaliplatin 85 mg/m^2 IV, day 1*
Leucovorin 400 mg/m^2 IV, day 1**
5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/d x 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion.
Repeat every 2 weeks.[1,2,3]

Capecitabine[4]
Capecitabine 1000–1250‡ mg/m^2 twice daily days 1–14 every 3 weeks x 24 weeks.

CAPEOX[5]
Oxaliplatin 130 mg/m^2 IV* day 1
Capecitabine 1000‡ mg/m^2 twice daily days 1–14 every 3 weeks x 24 weeks.

5-FU/leucovorin
- **Leucovorin 500 mg/m^2 given as a 2-hour infusion and repeated weekly x 6. 5-FU 500 mg/m^2 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/LV (sLV5FU2)[7]**
  Leucovorin 400 mg/m^2 IV day 1, followed by 5-FU bolus 400 mg/m^2 and then 1200 mg/m^2/d x 2 days (total 2400 mg/m^2 over 46–48 hours) continuous infusion. Repeat every 2 weeks.**

Footnotes
* Oxaliplatin may be given either over 2 hours, or may be infused over a shorter time at a rate of 1 mg/m2/min. Leucovorin infusion should match infusion time of oxaliplatin. Cercek A, Park V, Yaeger R, et al. Faster FOLFOX: oxaliplatin can be safely infused at a rate of 1 mg/m2/min. J Oncol Pract 2016;12:e548-553.
** Leucovorin 400 mg/m^2 is the equivalent of levoleucovorin 200 mg/m^2.
‡ 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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Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SURVIVORSHIP
Colorectal Long-term Follow-up Care

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

Management of Late/Long-Term Sequelae of Disease or 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 (See 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]
See NCCN Guidelines for Survivorship
- Undergo all age and gender-appropriate cancer and preventive health screenings as per national guidelines
- Maintain a healthy body weight throughout life.
- Adopt a physically active lifestyle (at least 30 minutes of moderate-intensity activity on most days of the week). Activity recommendations may require modification based on treatment sequelae (ie, ostomy, neuropathy).
- Consume a healthy diet with emphasis on plant sources. Diet recommendations may be modified based on severity of bowel dysfunction.
- Consider daily aspirin 325 mg for secondary prevention.
- Eliminate or limit alcohol consumption, no more than 1 drink/day for women, and 2 drinks/day for men.
- 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.

References

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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
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

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

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

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American Joint Committee on Cancer (AJCC)
TNM Staging System for Colon Cancer 8th ed., 2017)

Table 2. **Prognostic Groups**

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

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NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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Discussion

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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 2019, an estimated 101,420 new cases of colon cancer and 44,180 cases of rectal cancer will occur. During the same year, an estimated 51,020 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.[2] In fact, the incidence of CRC decreased at a rate of approximately 3% per year between 2011 and 2015.[1] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[3] and is currently down by more than 50% from peak mortality rates.[1] 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.

Despite the observed improvements in the overall CRC incidence rate, a retrospective cohort study of the SEER CRC registry found that the incidence of CRC in patients younger than 50 years has been increasing.[4] The authors estimate that the incidence rates for colon and rectal cancers will increase by 90.0% and 124.2%, respectively, for patients 20 to 34 years of age by 2030. The cause of this trend is currently unknown. One review suggests that CRC that occurs in young adult patients may be clinicopathologically and genetically different from CRC in older adults, although this has not been confirmed broadly. If cancer in this population is different, there would be a need to develop specific treatment strategies for this population.[5]

This Discussion summarizes the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) 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, patient 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 staging system (Table 1 in the algorithm).[6] Furthermore, all recommendations are classified as category 2A except where noted in the text or algorithm. 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.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Colon Cancer, an electronic search of the PubMed database was performed to obtain key literature in the field of CRC, using the following search terms: (colon cancer) OR (colorectal cancer) OR (rectal cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[7]

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

The data from key PubMed articles and articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

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

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Risk Assessment

Approximately 20% of cases of colon cancer are associated with familial clustering, and first-degree relatives of patients with colorectal adenomas or invasive CRC are at increased risk for CRC.[8-12] 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).[13-15] 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.[16]

CRC is a heterogeneous disease. An international consortium recently reported a molecular classification, defining four different subtypes: CMS1 (MSI Immune), hypermutated, microsatellite unstable (see *Lynch Syndrome* and *Microsatellite Instability*, below), with strong immune activation; CMS2 (Canonical), epithelial, chromosomally unstable, with marked WNT and MYC signalling activation; CMS3 (Metabolic), epithelial, with evident metabolic dysregulation; and CMS4 (Mesenchymal), prominent transforming growth factor β activation, stromal invasion, and angiogenesis.[17] However, this classification is not yet recommended in clinical practice.

Lynch Syndrome

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases.[13,14,18,19] This hereditary syndrome results from germline mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). Although identifying a germline mutation in an MMR gene through sequencing is definitive for Lynch syndrome, patients usually undergo selection by considering family history and performing an initial test on tumor tissue before sequencing. One of two different initial tests can be performed on CRC specimens to identify individuals who might have Lynch syndrome: 1) immunohistochemical analysis for MMR protein expression, which is often diminished because of mutation; or 2) analysis for microsatellite instability (MSI), which results from MMR deficiency and is detected as changes in the length of repetitive DNA elements in tumor tissue caused by the insertion or deletion of repeated units.[20] Testing the *BRAF* gene for mutation is indicated when immunohistochemical analysis shows that *MLH1* expression is absent in the tumor. The presence of a *BRAF* mutation indicates that *MLH1* expression is down-regulated through somatic methylation of the promoter region of the gene and not through a germline mutation.[20]

Many NCCN Member Institutions and other comprehensive cancer centers now perform immunohistochemistry and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.[21-24] The cost effectiveness of this approach, referred to as universal or reflex testing, has been confirmed for 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)[25-27] and by the American Society for Clinical Pathology (ASCP), College of American Pathologists (CAP), Association for Molecular Pathology (AMP), and ASCO in a guideline on molecular biomarkers for CRC.[28] 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.[29,30] The Cleveland Clinic recently reported on its experiences implementing such a screening approach.[31]

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The NCCN Colon/Rectal Cancer Panel endorses universal MMR or MSI testing of all patients with a personal history of colon or rectal cancer to identify individuals with Lynch syndrome. This testing is also relevant for treatment selection in stage IV disease (see *Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease*, below). An infrastructure needs to be in place to handle the screening results in either case. A more detailed discussion is available in the NCCN Guidelines for Colorectal Cancer Screening.

The Role of Vitamin D in CRC

Prospective studies have suggested that vitamin D deficiency may contribute to CRC incidence and/or that vitamin D supplementation may decrease CRC risk.[32-38] Furthermore, several prospective studies have shown that low vitamin D levels are associated with increased mortality of patients with CRC.[39-42] In fact, a systematic review and meta-analysis of 5 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.[43] Another meta-analysis determined that the relationship between vitamin D levels and mortality is linear.[44]

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.[45] 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.[46]

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.[47-49] In addition, while the randomized, double-blind, phase II SUNSHINE trial reported a longer progression-free survival (PFS) for previously untreated metastatic CRC (mCRC) patients 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 months vs. 11.0 months), this difference was not significant (HR, 0.64; 95% CI, 0–0.90; P = .02).[50] 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.[51] Citing this report and the lack of level 1 evidence, the panel does not currently recommend routine screening for vitamin D deficiency or supplementation of vitamin D in patients with 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.[52-54] 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).[53,55-70] In fact, in the EPIC cohort of almost 350,000 individuals, those who adhered to 5 healthy lifestyle factors (healthy weight, physical activity, non-smoking, limited alcohol consumption, 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 ≤1 of the factors.[71] Other large studies support the conclusion that adherence to healthy lifestyle factors can reduce the risk of CRC.[72,73]

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Some data suggest that consumption of dairy may lower risk for the development of CRC.[70,74,75] However, a recent systematic review and meta-analysis of 15 cohort studies (>900,000 subjects; >5200 cases of CRC) only found an association between risk for colon cancer in men and the consumption of nonfermented milk.[76] No association was seen for rectal cancer in men or for colon or rectal cancer in women, and no association was seen for either cancer in either gender with consumption of solid cheese or fermented milk. Large cohort studies and meta-analyses suggest that other dietary factors may also lower the risk for CRC, including the consumption of fish and legumes.[77-79] Furthermore, the use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may also decrease the risk for CRC.[80-85] In fact, the USPSTF recommends that adults aged 50 to 59 years with a 10-year cardiovascular disease risk ≥10% and a life expectancy of ≥10 years and without an increased bleeding risk take low-dose aspirin daily for at least 10 years for the primary prevention of both cardiovascular disease and CRC.[86]

In addition, some data suggest that smoking, metabolic syndrome, obesity, and red/processed meat consumption are associated with a poor prognosis.[57,87-91] Conversely, post-diagnosis fish consumption may be associated with a better prognosis.[92] A family history of CRC increases risk while improving prognosis.[93] Data on the effect of dairy consumption on prognosis after diagnosis of CRC are conflicting.[94,95]

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.[96-105] Results of a small randomized study suggest that 1 year of low-dose metformin in non-diabetic patients with previously resected colorectal adenomas or polyps may reduce the likelihood of subsequent adenomas or polyps.[106] In addition, although patients with CRC and diabetes appear to have a worse prognosis than those without diabetes,[107,108] patients with CRC and diabetes treated with metformin seem to have a survival benefit over those not treated with metformin.[104,109,110] The data regarding the effects of metformin on CRC incidence and mortality, however, are not completely consistent, with some studies seeing no effect.[111,112]

Staging

Staging in colon cancer is based on the TNM (tumor, node, metastases) system. The TNM categories reflect very similar survival outcomes for rectal and colon cancer; these diseases therefore share the same staging system.[6]

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.[6] 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.[113-115] 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 node-negative patients with T4a compared with node-negative patients with T4b tumors (58.4%).[116]

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

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as N1c. Within each T stage, survival is inversely correlated with N stage (N0, N1a, N1b, N2a, and N2b).[6]

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.[6] Patients with peritoneal metastases have a shorter PFS and OS than those without peritoneal involvement.[117]

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; perineural invasion (PNI); and tumor deposits.[6,118-126] The prefixes “p” and “yp” used in TNM staging denote “pathologic staging” and “pathologic staging after neoadjuvant therapy and surgery,” respectively.[6]

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.[6] 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.[6] 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.[6] 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.[127] Patients with CRM-positive resections had a 38.2% local recurrence rate, whereas those with CRM-negative resections had a 10.0% local recurrence rate.[127]

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.[128] In addition, results from population-based studies show an association between improvement in survival and examination of greater than or equal to 12 lymph nodes.[129,130] 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 recent results suggest that this idea is not correct.[131-133] 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.[134] The number of regional lymph nodes retrieved from a surgical specimen also varies with age of the

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patient, gender, and tumor grade or site.[128,129,135,136] In addition, it has been suggested that lymph nodes in patients with a strong anti-cancer immune response are easier to find, and that such patients have an improved prognosis.[137] 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 both improved prognosis and increased lymph node retrieval.[138,139]

Regardless of the mechanism for the observed correlation, the panel recommends examination of a minimum of 12 lymph nodes. This recommendation is supported by CAP[140] and the 8th edition of the AJCC Cancer Staging Manual,[6] which also specify pathologic examination of a minimum 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.[141] 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 fewer than 12 nodes were initially identified. Patients considered to have N0 disease but for whom fewer than 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 series have suggested cutoffs of 0.1, 0.2, or 0.25 as lymph node ratios that are prognostic for OS or PFS.[142-145] A systematic review and meta-analysis of 33 studies that included greater than 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).[146] 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.[147]

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).[148] Results of studies evaluating the sentinel node for micrometastatic disease through use of hematoxylin and eosin (H&E) staining to identify small foci of tumor cells and the identification of particular tumor antigens through immunohistochemical analysis have been reported.[148-153]

There is also a potential benefit of assessing regional lymph nodes for isolated tumor cells.[151,154-157] The 8th edition of the AJCC Cancer Staging Manual considers tumor clusters smaller than 0.2 mm to be true metastases, because such micrometastases have been shown to be a poor prognostic factor.[6] One study of 312 consecutive patients with pN0 disease found that positive cytokeratin staining was associated with a higher risk of recurrence.[158] 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 immunohistochemical or reverse transcriptase polymerase chain reaction (RT-PCR) evidence of tumor cells in regional nodes.[159] A 2014 meta-analysis also found that the presence of micrometastases increases the likelihood of disease recurrence.[160]

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

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are not counted as lymph nodes replaced by tumor. Most of these tumor deposits are thought to arise from lymphovascular invasion or, occasionally, PNI.[161,162] 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.[125,126,163,164] 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 ($P < .0001$).[126]

Perineural Invasion

Several studies have shown that the presence of PNI is associated with a significantly worse prognosis.[122-124,163,165-168] For example, one retrospective analysis of 269 consecutive patients who had colorectal tumors resected at one institution found a 4-fold greater 5-year survival in patients without PNI versus patients whose tumors invaded nearby neural structures.[123] Multivariate analysis of patients with stage II rectal cancer showed that patients with PNI have a significantly worse 5-year DFS compared with those without PNI (29% vs. 82%; $P = .0005$).[124] Similar results were seen for patients with stage III disease.[122] 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).[166] PNI is therefore included as a high-risk factor for systemic recurrence.

Adenocarcinomas of the Small Bowel and Appendix

For recommendations on the management of small bowel adenocarcinoma, see the NCCN Guidelines for Small Bowel Adenocarcinoma.

Adenocarcinomas of the appendix are rare cancers for which no NCCN Guidelines exist. Data on treatment of appendiceal adenocarcinomas are quite limited. Most patients receive debulking surgery with systemic or intraperitoneal therapy (intraperitoneal therapy is discussed further in *Peritoneal Carcinomatosis*, below). Case series have shown that combination systemic therapy in patients with advanced disease can result in response rates similar to those seen in advanced CRC.[169-171] A recent analysis of the NCCN Outcomes Database found that fluoropyrimidine-based therapy is the most commonly administered systemic therapy at NCCN Member Institutions.[172] Among 99 patients with a recorded best response, the response rate was 39%, with a median PFS of 1.2 years.

Acknowledging the lack of high-level data, the panel recommends that adenocarcinomas of the appendix be treated with systemic therapy according to these NCCN Guidelines for Colon Cancer.

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.[119] The panel recommends marking the polyp site during colonoscopy or within 2 weeks of the polypectomy if deemed necessary by the surgeon.

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.[173] 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.[174,175] Favorable histologic features include lesions of grade 1 or 2, no angiolymphatic invasion, and a negative resection margin. However, in addition to the option of observation, the panel includes the

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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.[176-178]

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/abdominal/pelvic 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.[173,179-181] Laparoscopic surgery is an option.[182] Unfavorable histopathologic features for malignant polyps include grade 3 or 4, angiolymphatic invasion, or a positive margin of resection.[183,184] 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.[173,185-187] 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.[188-191]

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.[192] CT should be with IV and oral contrast. If the CT of the abdomen and pelvis is inadequate or if CT with IV contrast is contraindicated, an abdominal/pelvic MRI with contrast plus a non-contrast chest CT should be considered. The chest CT can identify lung metastases, which occur in approximately 4% to 9% of patients with colon and rectal cancer.[193-195] One series of 378 patients found that resection of pulmonary metastases resulted in 3-year recurrence-free survival of 28% and 3-year OS of 78%.[196] 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 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.

For resectable colon cancer that is causing overt obstruction, one-stage colectomy with en bloc removal of regional lymph nodes, resection with

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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.[197] A meta-analysis found that oncologic outcomes were similar for surgery and for stenting followed by elective surgery.[198] 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.[199] Another meta-analysis of comparative studies compared colectomy to diversion followed by colectomy.[200] Although 30-day mortality and morbidity were the same between the groups, the diversion group was less likely to have a permanent colostomy (OR, 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.[201-203]

If the cancer is locally unresectable or the patient is medically inoperable, systemic therapy or chemoradiation is recommended, possibly with the goal of converting the lesion to a resectable state.

Surgical Management

For resectable non-metastatic colon cancer, the preferred surgical procedure is colectomy with en bloc removal of the regional lymph nodes.[204,205] 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.[206]

There has been some recent attention focused on the quality of colectomy.[207] A retrospective observational study found a possible OS advantage for surgery in the mesocolic plane over surgery in the muscularis propria plane.[208] A comparison of resection techniques by expert surgeons in Japan and Germany showed that complete mesocolic excision (CME) with central vascular ligation resulted in greater mesentery and lymph node yields than the Japanese D3 high tie surgery.[209] 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).[210] A systematic review found that 4 of 9 prospective studies reported improved lymph node harvest and survival with CME compared with non-CME colectomy; the other studies reported improved specimen quality.[211]

Minimally Invasive Approaches to Colectomy

Laparoscopic colectomy is an option in the surgical management of colon cancer.[212-215] 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.[216] 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.[217] Non-inferiority 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.[218] 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

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approaches.[219] Long-term follow-up of participants in the CLASICC trial showed that the lack of differences in outcomes between arms continued over a median 62.9 months.[220]

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 years follow-up.[221,222] A similar RCT in Australia and New Zealand also found no differences in disease outcomes.[223] In addition, results of several recent meta-analyses have supported the conclusion that the 2 surgical approaches provide similar long-term outcomes with respect to local recurrence and survival in patients with colon cancer.[224-229] Factors have been described that may confound conclusions drawn from randomized studies comparing open colectomy with laparoscopic-assisted surgery for colon cancer.[230,231]

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.[232] A meta-analysis of 18 studies (6153 patients) found a lower rate of cardiac complications with laparoscopic colectomy compared with open resection.[233] Analyses of large national databases also support the benefits of the laparoscopic approach.[234,235]

In recent years, perioperative care has improved, with reductions in the average length of hospital stay and complication rates after surgery.[236,237] The multicenter, randomized, controlled EnROL trial therefore compared conventional and laparoscopic colectomy with an enhanced recovery program in place.[238] 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 days vs. 7 days; $P = .033$).

Robotic colectomy has been compared to the laparoscopic approach, mostly with observational cohort studies.[239-242] In general, the robotic approach appears to result 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.[182,243,244]

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-high [MSI-H], stage II disease do not require any adjuvant therapy.
- Patients with low-risk stage II disease that is microsatellite-stable (MSS) or MMR-proficient (pMMR) can be observed without adjuvant therapy or considered for capecitabine or 5-FU/leucovorin (LV). Based on results of the MOSAIC trial,[245-247] 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.

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- Patients with high-risk stage II disease that is MSS or pMMR, defined as those with poor prognostic features, including T4 tumors (stage IIB/IIC); poorly differentiated histology (exclusive of those cancers that are MSI-H); lymphovascular invasion; PNI; bowel obstruction; lesions with localized perforation or close, indeterminate, or positive margins; or inadequately sampled nodes (<12 lymph nodes), can be considered for adjuvant chemotherapy with 5-FU/LV, capecitabine, FOLFOX, or CAPEOX (capecitabine and oxaliplatin).[120,248] 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.

- For patients with low-risk (T1–3, N1) stage III disease, the preferred adjuvant treatment options are 3 months of CAPEOX[249-251] or 3 to 6 months of FOLFOX (category 1 for 6 months of FOLFOX).[245-247,251] Other treatment options include single-agent capecitabine[252] or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.[253-256]

- For patients with high-risk (T4, N1–2 or Tany, N2) stage III disease, the preferred adjuvant treatment options are 6 months of FOLFOX (category 1)[245-247] or 3 to 6 months of CAPEOX[249,250] (category 1 for 6 months).[251] Other treatment options include single-agent capecitabine[252] or 5-FU/LV in patients for whom oxaliplatin therapy is believed to be inappropriate.[253-256]

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.[257-259] For example, patients from the National Cancer Database with stage III or high-risk stage II disease treated according to these NCCN Guidelines had a survival advantage over patients whose treatment did not adhere to these guidelines.[257] 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 resulted in a lower risk of death.[259]

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 follow-up are appropriate endpoints for clinical trials involving treatment of colon cancer with 5-FU–based chemotherapy in the adjuvant setting.[260] An update of this analysis showed that most relapses occur within 2 years after surgery, and that recurrence rates were less than 1.5% per year and less than 0.5% per year after 5 and 8 years, respectively.[261] 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 more than 5 years may now be required to evaluate the effect of adjuvant therapies on OS.[262] 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.[263] 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.[263]

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

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studies.[120,245-248] 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.[264] 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 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; $P = .01$).[265] In this trial, however, approximately 64% of patients had fewer than 12 lymph nodes sampled, and thus actually may have been patients with higher risk disease who were more likely to benefit from adjuvant therapy.[266]

The benefit of oxaliplatin in adjuvant therapy for patients with stage II colon cancer has also been addressed. Results from a recent 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; $P = .258$).[267] 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; $P = .98$).[247] 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.[268] 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.[269]

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 untreated patients.[270] 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.[269] 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.[271]

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.[248,272,273] 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 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 high-risk

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features do not have a recurrence while some patients deemed to be average-risk do.[274] 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 2004 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.[248] Additional information that may influence adjuvant therapy decisions for stage II 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.[275,276]

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).[277] 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.[278] Patients determined to have defective MMR (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.[13,14,18,19] Somatic MMR defects have been reported to occur in approximately 19% of colorectal tumors,[279] 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.[280]

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; $P < .0001$).[281] In another large study, the percentage of stage IV tumors characterized as MSI-H was only 3.5%.[282] 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.[283-285] 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.[283,286]

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.[284,285,287] 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.[284] Similarly, results from another retrospective study of pooled data from adjuvant trials by Sargent et al[285] 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,[285] however, a recent study of 1913 patients with stage II CRC from the QUASAR study, half of whom

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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.[266] A recent study of patients in the CALGB 9581 and 89803 trials came to a similar conclusion.[288] 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 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. 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

Several multigene assays have been developed in hopes of providing prognostic and predictive information to aid in decisions regarding adjuvant therapy in patients with stage II or III colon cancer.[274]

Oncotype DX colon cancer assay quantifies the expression of 7 recurrence-risk genes and 5 reference genes as a prognostic classifier of low, intermediate, or high likelihood of recurrence.[289] Clinical validation in patients with stage II and III colon cancer from QUASAR[290] and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07[291] 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.[290] 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 recent 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).[292] 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.[291] 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.[293]

ColoPrint quantifies the expression of 18 genes as a prognostic classifier of low versus high recurrence risk.[294] In a set of 206 patients with stage I through III CRC, the 5-year relapse-free survival (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).[294] 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.[295] 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,

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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.[296] 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 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).[297] Similar to the other assays described here, the recurrence risk determined by ColDx is independent of other risk factors.

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, there is no evidence of predictive value in terms of the potential benefit of chemotherapy to any of the available multigene assays. The panel believes that there are insufficient data to recommend the use of multigene assays to determine adjuvant therapy.

Adjuvant Chemotherapy in Elderly Patients

Adjuvant chemotherapy usage declines with the age of the patient.[298] 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.[299-301]

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 or older with stage III disease (HR, 0.70; *P* < .001).[302] Another analysis of 5489 patients aged greater than or equal to 75 years diagnosed with stage III colon cancer between 2004 and 2007 from 4 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).[298] This study also looked specifically at the benefit of the addition of oxaliplatin to adjuvant therapy in these older stage III patients, 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 aged greater than or equal to 70 years.[303]

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 aged greater than or equal to 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).[268] 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).[267]

However, a recent 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 of age or older.[304]

As for the risks of adjuvant therapy in elderly 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).[305] For instance, the ORs for 30-day

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mortality for patients aged 70 years and aged 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 elderly 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 aged 70 years and older 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 more than 15,000 patients examined the effect of timing of adjuvant therapy after resection.[306] 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.[307] 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.[308] 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.[309] In fact, the registry study found that patients who started therapy after 8 weeks were more likely to be older than 65 years, have had an emergency resection, and/or have a prolonged postoperative admission.[308]

Leucovorin Shortage

A shortage of LV recently 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.[310] 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.[311] 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 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.[312] Finally, if none of the above options is 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

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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.[245-247] 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).[247] 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.[246]

An analysis of 5 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.[313] Another population-based analysis found that the harms of oxaliplatin in the medicare population with stage III colon cancer were reasonable, even in patients aged 75 years or older.[314] 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.[315] 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.[316]

The IDEA collaboration investigated whether limiting adjuvant treatment to 3 months of FOLFOX or CAPEOX—which would markedly decrease the 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.[251] The median follow-up was 39 months. Importantly, grade 3+ neurotoxicity rates were lower in the 3 months versus 6 months 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-month to 6-month comparison with CAPEOX (HR, 1.02; 95% CI, 0.89–1.17).

A pooled analysis of high-risk stage II patients in the IDEA collaboration failed to show non-inferiority of 3 months compared to 6 months of adjuvant treatment based on 5-year DFS (80.7% for 3 months vs. 84.0% for 6 months; HR, 1.18; 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 (81.7% vs. 82.0%). There were significantly less grade 3–5 toxicities with 3 months versus 6 months (26% vs. 40%; *P* < .0001).[317] While these results are

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interesting, the panel does not yet consider the data to be definitive regarding an optimal duration of oxaliplatin-containing adjuvant therapy regimens for stage II disease.

Based on these data, 3 to 6 months of FOLFOX (category 1 for 6 months) is listed in the guidelines as a preferred adjuvant therapy option for patients with low-risk stage III colon cancer, and 6 months of FOLFOX (category 1) is listed as a preferred adjuvant therapy option for patients with high-risk stage III colon cancer. Six months of infusional 5-FU/LV is included as another adjuvant therapy option for low- or high-risk stage III colon cancer.

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.[252] Final results of this trial were recently reported.[318] After a median follow-up of 6.9 years, the equivalencies in DFS and OS were maintained in all subgroups, including those 70 years of age or older.

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%).[249,250] 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; $P = .04$).[319] Another phase III trial compared CAPEOX to mFOLFOX6 in 408 patients with stage III or high-risk stage II colon cancer.[320] 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.[315]

The IDEA collaboration investigated whether a shortened duration of adjuvant FOLFOX or CAPEOX would be a feasible way to avoid or lessen the toxicities associated with oxaliplatin-containing adjuvant therapy in some patients with locoregional colon cancer, without impairing oncologic outcomes.[251] This study demonstrated that a 3-month duration of adjuvant CAPEOX treatment was as effective as a 6-month treatment for stage III disease, especially for the lower-risk subgroup. Furthermore, the shorter duration of adjuvant therapy was associated with significantly lower rates of adverse effects compared to the longer duration of treatment. For more information on the IDEA trial, see *Adjuvant FOLFOX and Infusional 5-FU/LV* in this Discussion.

Based on these data, 3 months of CAPEOX is listed in the guidelines as a preferred adjuvant therapy option for patients with low-risk stage III colon cancer, and 3 to 6 months of CAPEOX (category 1 for 6 months) is listed as a preferred adjuvant therapy option for patients with high-risk stage III colon cancer. Six months of single-agent capecitabine is included as another adjuvant therapy option for low- or high-risk stage III colon cancer.

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.[321] 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.[321,322] 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.[323] In addition, FOLFIRI (infusional 5-FU/LV/irinotecan) has not been shown to be superior to 5-FU/LV in the adjuvant setting.[324,325] Thus, data do not support the use of irinotecan-containing regimens in the treatment of stage II or III colon cancer.

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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).[326] Similar results were seen after a median follow-up of 5 years.[327] The results of the phase III AVANT trial evaluating bevacizumab in the adjuvant setting in a similar protocol also failed to 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.[328] 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.[329] 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*, cetuximab provided no added benefit and was associated with increases in grade 3/4 adverse events.[330] In addition, all subsets of patients treated with cetuximab experienced increases in grade 3/4 adverse events. The open-label, randomized, phase III PETACC-8 trial also compared FOLFOX with and without cetuximab.[331] 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 adverse events (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.[332] 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, [268,333] 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).[268] Grade 3 neurotoxicity, diarrhea, and dehydration were higher with FLOX than with 5-FU/LV,[268] 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,[245] 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.[333] For these reasons, FLOX is no longer recommended as adjuvant treatment for colon cancer.

Perioperative Chemoradiation

Neoadjuvant or adjuvant radiation therapy delivered concurrently with 5-FU–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.[334] Radiation therapy fields should include the tumor bed as defined by preoperative radiologic imaging and/or surgical clips. Intraoperative radiation therapy (IORT), if available, should be considered for these patients as an additional boost.[335,336] If IORT is not available, an additional 10 to 20 Gy of external beam radiation therapy (EBRT) and/or brachytherapy could be considered to a limited volume.

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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.

If radiation therapy is to be used, conformal beam radiation should be the routine choice; intensity-modulated radiation therapy (IMRT), which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to normal tissue,[337] or stereotactic body RT (SBRT; also called stereotactic ablative radiotherapy [SABR]) should be considered 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.[338]

Neoadjuvant Therapy for Resectable Colon Cancer

For the 2016 version of these guidelines, the panel added the option for neoadjuvant treatment with FOLFOX or CAPEOX for patients with resectable, clinical T4b colon cancer. The randomized phase III FOxTROT trial is assessing whether this approach improves DFS (NCT00647530). Results from the feasibility phase of the trial were reported in 2012.[339] One hundred fifty patients with T3 (with ≥5 mm invasion beyond the muscularis propria) or T4 tumors were randomly assigned to 3 cycles of preoperative therapy (5-FU/LV/oxaliplatin), surgery, and 9 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. A 2019 abstract reported more mature data from 1052 patients on the FOxTROT trial.[340] Histologic regression was seen in 59% of patients who received neoadjuvant therapy, including 4% pathologic complete responses. Neoadjuvant therapy also resulted in marked histologic downstaging as well as a decrease in incomplete resections compared to postoperative therapy (5% vs. 10%; P = .001). The 2-year rate of relapse or persistent disease (2-year failure rate) also improved with neoadjuvant therapy, although this difference was not statistically significant (14% vs. 18%; HR, 0.77; P = .11). These results support the feasibility of neoadjuvant therapy as a treatment option for colon cancer.

Management of Metastatic Disease

Approximately 50% to 60% of patients diagnosed with CRC develop colorectal metastases,[341-343] and 80% to 90% of these patients have unresectable metastatic liver disease.[342,344-347] Metastatic disease most frequently develops metachronously after treatment for locoregional CRC, with the liver being the most common site of involvement.[348] However, 20% to 34% of patients with CRC present with synchronous liver metastases.[347,349] Some evidence indicates that synchronous metastatic colorectal liver disease is associated with a more disseminated disease state and a worse prognosis than metastatic colorectal liver disease that develops metachronously. In a retrospective study of 155 patients who underwent hepatic resection for colorectal liver metastases, patients with synchronous liver metastases had more sites of liver involvement (P = .008) and more bilobar metastases (P = .016) than patients diagnosed with metachronous liver metastases.[350]

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.[351] 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.[346] Furthermore, several studies have shown rates of 5-year survival to be low in patients with metastatic liver disease not undergoing surgery.[342,352] Certain clinicopathologic factors, such as the presence of extrahepatic metastases, the presence of >3

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tumors, and a disease-free interval of less than 12 months, have been associated with a poor prognosis in patients with CRC.[349,353-357]

Other groups, including ESMO, have established guidelines for the treatment of mCRC.[358] The NCCN recommendations are discussed below.

Surgical Management of Colorectal Metastases

Studies of selected patients undergoing surgery to remove colorectal liver metastases have shown that cure is possible in this population and should be the goal for a substantial number of these patients.[342,359] Reports have shown 5-year DFS rates of approximately 20% in patients who have undergone resection of liver metastases,[354,357] and a recent meta-analysis reported a median 5-year survival of 38%.[360] 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.[361-363] 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*).[364]

Colorectal metastatic disease sometimes occurs in the lung.[341] Most of the treatment recommendations discussed for metastatic colorectal liver disease also apply to the treatment of colorectal pulmonary metastases.[196,365,366] A series of 378 patients found that resection of pulmonary metastases resulted in 3-year recurrence-free survival of 28% and 3-year OS of 78%.[196] Combined pulmonary and hepatic resections of resectable metastatic disease have been performed in very highly selected cases,[367-371] and an analysis of patients who underwent hepatic resection followed by subsequent pulmonary resection showed positive outcomes.[372]

Evidence supporting resection of extrahepatic metastases in patients with mCRC is limited. In a recent retrospective analysis of patients undergoing concurrent complete resection of hepatic and extrahepatic disease, the 5-year survival rate was lower than in patients without extrahepatic disease, and virtually all patients who underwent resection of extrahepatic metastases experienced disease recurrence.[373,374] However, a recent international analysis of 1629 patients with colorectal liver metastases showed that 16% of the 171 patients (10.4%) who underwent concurrent resection of extrahepatic and hepatic disease remained disease-free at a median follow-up of 26 months, suggesting that concurrent resection may be of significant benefit in well-selected patients (ie, those with a smaller total number of metastases).[371] A recent systematic review concluded similarly that carefully selected patients might benefit from this approach.[375]

Data suggest that a surgical approach to the treatment of recurrent hepatic disease isolated to the liver can be safely undertaken.[376-381] 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.[377] 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.[376] A recent meta-analysis of 27 studies including fewer than 7200 patients found that those with longer disease-free intervals; those whose recurrences were solitary, smaller, or unilobular; and those lacking extrahepatic disease derived more benefit from repeat hepatectomy.[382] Panel consensus is that re-resection of liver or lung metastases can be considered in carefully selected patients.[366,380,383]

Patients with a resectable primary colon tumor and resectable synchronous metastases can be treated with a staged or simultaneous resection, as discussed below in *Resectable Synchronous Liver or Lung Metastases*. For patients presenting with unresectable metastases and an

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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 *Unresectable Synchronous Liver or Lung Metastases*).[384]

Local Therapies for Metastases

The standard of care for patients with resectable metastatic disease is surgical resection. Image-guided ablation has historically been used for non-surgical patients[385-387] but is also indicated for small metastases that can be treated with margins, in combination with surgery or alone, as long as all visible disease is treated.[388] SBRT is a reasonable option for patients who cannot be resected or ablated, as discussed in subsequent paragraphs.[345,389,390] Many patients, however, are not surgical candidates and/or have disease that cannot be ablated with clear margins[387] 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.[391-393]

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

Hepatic Arterial Infusion

Placement of a hepatic arterial port or implantable pump during surgical intervention for liver resection with subsequent infusion of chemotherapy directed to the liver metastases through the hepatic artery (ie, HAIC) is an option (category 2B). In a randomized study of patients who had undergone hepatic resection, administration of floxuridine with dexamethasone through HAIC and intravenous 5-FU with or without LV was shown to be superior to a similar systemic chemotherapy regimen alone with respect to 2-year survival free of hepatic disease.[346,395] 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.[346,396] 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.[346] Results of some studies also suggest that HAIC may be useful in the conversion of patients from an unresectable to a resectable status.[397,398]

Some of the uncertainties regarding patient selection for preoperative chemotherapy are also relevant to the application of HAIC.[359] Limitations on the use of HAIC include the potential for biliary toxicity[346] 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.[392] A randomized trial compared the arterial delivery of irinotecan-loaded drug-eluting beads (DEBIRI) and reported an OS benefit (22 months vs. 15 months; $P = .031$) of DEBIRI when compared to systemic FOLFIRI.[399] A 2013 meta-analysis identified 5 observational studies and 1 randomized trial and concluded that, although DEBIRI appears to be safe and effective for patients with unresectable colorectal liver metastases, additional trials are needed.[400] A more recent trial randomized 30 patients with colorectal liver metastases to FOLFOX/bevacizumab and 30 patients to

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FOLFOX/bevacizumab/DEBIRI.[401] DEBIRI resulted in an improvement in the primary outcome measure of response rate (78% vs. 54% at 2 months; *P* = .02).

Doxorubicin-eluting beads have also been studied; the most robust data supporting their effectiveness come from several phase II trials in hepatocellular carcinoma.[402-407] A 2013 systematic review concluded that data are not strong enough to recommend TACE for the treatment of colorectal liver metastases except as part of a clinical trial.[408]

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).[409] 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.[410] In the refractory setting, a CEA level ≥90 and lymphovascular invasion at the time of primary resection were negative prognostic factors for OS.[411] 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[412] and resin[413] 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.[412,414,415]

Results from the phase III randomized controlled SIRFLOX trial (yttrium-90 resin microspheres with FOLFOX +/- bevacizumab vs. FOLFOX +/- bevacizumab) were reported.[416] 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 FOXFIREGlobal studies were performed in the same manner as the SIRFLOX trial with the intention to compile all data and allow assessment of oncologic outcomes in a larger cohort.[417] Pooled data from 1103 patients in these 3 prospective trials showed similar findings as in the SIRFLOX trial with prolongation of the liver PFS in the group treated by radioembolization but no difference in OS and PFS. Of interest was the unexpected finding of survival benefit with radioembolization plus chemotherapy compared to chemotherapy alone in the subgroup of patients with right-sided primary origin (HR, 0.67; 95% CI, 0.48–0.92). Based on these data, further investigation is needed to identify the role of radioembolization at earlier stages of disease in patients with right-sided primary origin.

Whereas very little data show any impact on patient survival and the data supporting its efficacy are limited, toxicity with radioembolization is relatively low.[416,418-420] 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.[421,422] Ablative techniques include

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radiofrequency ablation (RFA),[387,423] microwave (MW) ablation, cryoablation, and electro-coagulation (irreversible electroporation).[424] 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.[387,423,425-427]

A small number of older retrospective studies have compared RFA and resection in the treatment of liver or lung metastases.[362,428-431] Most of these studies have shown RFA to be relatively inferior to resection in terms of rates of local recurrence and 5-year OS. [428,432] Whether the differences in outcome observed for patients with liver metastases treated with RFA versus resection alone are from patient selection bias, lack of treatment assessment based on the ability to achieve margins, technologic limitations of RFA, or a combination of these factors remains unclear.[430]

A 2012 phase II trial randomized 119 patients to receive systemic treatment alone (FOLFOX with or without bevacizumab) or systemic treatment plus RFA.[433] No difference in OS was initially seen, but PFS was improved at 3 years in the RFA group (27.6% vs. 10.6%; HR, 0.63; 95% CI, 0.42–0.95; *P* = .025). A subsequent analysis following prolonged follow-up of the same population in this phase II randomized, controlled trial showed that OS was improved in the combined modality arm (HR, 0.58; 95% CI, 0.38–0.88, *P* = .01), with a 3-, 5-, and 8-year OS of 56.9%, 43.1%, and 35.9% for the combined modality arm compared to 55.2%, 30.3%, and 8.9% for the chemotherapy alone arm.[388] This study documented a long-term survival benefit for patients receiving RFA in addition to chemotherapy compared to those treated by chemotherapy only.

Data on ablative techniques other than RFA are growing.[422,434-441] However, in a comparison of RFA with MW ablation, outcomes were similar with no local tumor progression for metastases ablated with margins greater than 10 mm (A0) and a relatively better control of perivascular tumors with the use of MW (*P* = .021).[441] Similarly, 2 recent studies and a position paper by a panel of experts indicated that ablation may provide acceptable oncologic outcomes for selected patients with small liver metastases that can be ablated with sufficient margins.[386,387,429] In the same way, a 2018 systematic review confirmed that MW provides oncologic outcomes similar to resection.[442] Recent publications indicated that the significance of margin creation is particularly important for *RAS*-mutant metastases.[443-445]

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

Liver- or Lung-Directed Radiation

Local radiation therapies include arterial radioembolization with microspheres[411,412,446-454] and conformal (stereotactic) EBRT.[455]

EBRT to the metastatic site can be considered in highly selected cases in which the patient has a limited number of liver or lung metastases or the patient is symptomatic or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include three-dimensional conformal radiation therapy (CRT), SBRT,[345,389,390,456] and IMRT, which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to healthy tissue.[337,457-460]

Peritoneal Carcinomatosis

Approximately 17% of patients with mCRC have peritoneal carcinomatosis, with 2% having the peritoneum as the only site of

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metastasis. Patients with peritoneal metastases generally have a shorter PFS and OS than those without peritoneal involvement.[117,461] 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.[462-464] 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.[465,466]

Cytoreductive Debulking with Hyperthermic Intraperitoneal Chemotherapy

Several surgical series and retrospective analyses have addressed the role of cytoreductive surgery (ie, peritoneal stripping surgery) in combination with perioperative hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of peritoneal carcinomatosis without extra-abdominal metastases.[467-476] 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 cytoreductive surgery and HIPEC with mitomycin C; postoperative 5-FU/LV was given to 33 of 47 patients.[477] 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.[478] 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).[479]

Other criticisms of the Verwaal trial have been published.[479] One important point is that the trial included patients with peritoneal carcinomatosis of appendiceal origin, a group that has seen greater benefit with the cytoreductive surgery/HIPEC approach.[468,472,480,481] 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 cytoreductive surgery and early postoperative intraperitoneal chemotherapy.[472] The median OS time for patients with pseudomyxoma peritonei, which arises from mucinous appendiceal carcinomas, was not reached at the time of publication. A recent retrospective international registry study reported 10- and 15-year survival rates of 63% and 59%, respectively, in patients with pseudomyxoma peritonei from mucinous appendiceal carcinomas treated with cytoreductive surgery and HIPEC.[482] HIPEC was not shown to be associated with improvements in OS in this study, whereas completeness of cytoreduction was. Thus, for patients with pseudomyxoma peritonei, optimal treatment is still unclear.[483]

More recently, an ASCO 2018 abstract reported results from the randomized, phase III multicenter, PRODIGE 7 trial of 265 patients with colorectal peritoneal carcinomatosis.[484] Patients in this trial received standard treatment of systemic chemotherapy before and/or after cytoreductive surgery and were randomized to standard treatment plus HIPEC with oxaliplatin or standard treatment alone. 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 (HR, 1.00; 95% CI, 0.73–1.37) and no significant difference in RFS, with a median RFS of 13.1 months with HIPEC versus 11.1 months without (HR, 0.90; 95% CI, 0.69–1.90). 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 (24.1% vs. 13.6%, P = .030).

The individual components of the HIPEC approach have not been well studied. In fact, studies in rats have suggested that the hyperthermia

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component of the treatment is irrelevant.[485] Results of a retrospective cohort study also suggest that heat may not affect outcomes from the procedure.[469] In addition, a randomized trial compared systemic 5-FU/oxaliplatin to cytoreductive surgery and intraperitoneal 5-FU without heat.[486] Although terminated prematurely because of poor accrual, analysis suggested that the cytoreductive surgery plus IPEC approach may have been superior to the systemic therapy approach (2-year OS, 54% vs. 38%; *P* = .04) for patients with resectable colorectal peritoneal metastases.

In addition, significant morbidity and mortality are associated with this procedure. A 2006 meta-analysis of 2 RCTs and 12 other studies reported morbidity rates ranging from 23% to 44% and mortality rates ranging from 0% to 12%.[476] Furthermore, recurrences after the procedure are very common.[487] Whereas the risks are reportedly decreasing with time (ie, recent studies report 1%–5% mortality rates at centers of excellence[473,479]), the benefits of the approach have not been definitively shown, and HIPEC remains very controversial.[488-491]

The panel currently believes that complete cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. 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.[492-495] 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.[496] It should be noted that size alone is rarely a contraindication to resection of a tumor. Resectability differs fundamentally from endpoints that focus more on palliative measures. Instead, the resectability endpoint is focused on the potential of surgery to cure the disease.[497] 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.[343,492]

The role of PET/CT in determining resectability of patients with mCRC is discussed in *Workup and Management of Synchronous Metastatic Disease*, below.

Conversion to Resectability

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

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with significant response to conversion chemotherapy can be converted from unresectable to resectable status.[432]

Any active metastatic systemic regimen can be used in an attempt to convert a patient's unresectable status to a resectable status, because the goal is not specifically to eradicate micrometastatic disease, but rather to obtain the optimal size regression of the visible metastases. An important point to keep in mind is that irinotecan- and oxaliplatin-based chemotherapeutic regimens may cause liver steatohepatitis and sinusoidal liver injury, respectively.[498-502] 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.[498,499,502,503] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable. Some of the trials addressing various conversion therapy regimens are discussed below.

In the study 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.[494] 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,[344] 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.[353] 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.[504] The median OS time in this group was 42.4 months.

In addition, first-line FOLFOXIRI (infusional 5-FU, LV, oxaliplatin, irinotecan) has been compared with FOLFIRI (infusional 5-FU, LV, irinotecan) in two randomized clinical trials in patients with unresectable disease.[505,506] 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[505]; and 4% versus 10%, $P = .08$ in the Gastrointestinal Committee of the Hellenic Oncology Research Group (HORG) trial.[506] 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 ($P = .026$).[507]

More recent favorable results of randomized clinical trials evaluating FOLFIRI, FOLFOX, or FOLFOXIRI in combination with anti-epidermal growth factor receptor (EGFR) inhibitors for the purpose of conversion of unresectable disease to resectable disease have been reported. For instance, in the CELIM phase II trial, patients were randomized to receive cetuximab with either FOLFOX6 or FOLFIRI.[508] Retrospective analysis showed that in both treatment arms combined resectability increased from 32% to 60% after chemotherapy in patients with wild-type *KRAS* exon 2 with the addition of cetuximab ($P < .0001$). Final analysis of this trial showed that the median OS of the entire cohort was 35.7 months (95% CI, 27.2–44.2 months), with no difference between the arms.[509] Another recent RCT compared chemotherapy (mFOLFOX6 or FOLFIRI) plus cetuximab to chemotherapy alone in patients with unresectable colorectal cancer metastatic to the liver.[510] The primary endpoint was the rate of

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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 randomized, phase II VOLPI 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.[511] Of the cohort with unresectable, potentially convertible metastases, 60% were ultimately converted to resectable with FOLFOXIRI + panitumumab compared to 36.4% with FOLFOXIRI alone. ORR and disease control rate were also improved in the combination compared to FOLFOXIRI alone. A recent meta-analysis of four RCTs concluded that the addition of cetuximab or panitumumab to chemotherapy significantly increased the response rate, the R0 resection rate (from 11%–18%; RR, 1.59; $P = .04$), and PFS, but not OS in patients with wild-type *KRAS* exon 2-containing tumors.[512]

The role of bevacizumab in the patient with unresectable disease, 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.[513,514] 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. On the other 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.[515] Therefore, arguments for use of bevacizumab with oxaliplatin-based therapy in this “convert to resectability” setting are not compelling. However, because it is not known in advance whether resectability will be achieved, the use of bevacizumab with oxaliplatin-based therapy in this setting is acceptable.

When chemotherapy is planned for patients with initially unresectable disease, the panel recommends that a surgical re-evaluation be planned 2 months after initiation of chemotherapy, and that those patients who continue to receive chemotherapy undergo surgical re-evaluation every 2 months thereafter.[502,516-518] Reported risks associated with chemotherapy include the potential for development of liver sinusoidal dilatation, steatosis, or steatohepatitis.[498,503,519] To limit the development of hepatotoxicity, it is therefore recommended that surgery be performed as soon as possible after the patient becomes resectable.

Neoadjuvant and Adjuvant Therapy for Resectable Metastatic Disease

The panel recommends that a course of an active systemic therapy regimen for metastatic disease, administered for a total perioperative treatment time of approximately 6 months, be considered for most patients undergoing liver or lung resection to increase the likelihood that residual microscopic disease will be eradicated (category 2B for the use of biologic agents in the perioperative metastatic setting). Although systemic therapy can be given before, between, or after resections, the total duration of perioperative systemic therapy should not exceed 6 months. A 2012 meta-analysis identified three randomized clinical trials comparing surgery alone to surgery plus systemic therapy with 642 evaluable patients with colorectal liver metastases.[520] 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

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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.[521] Additional recent meta-analyses have also failed to observe a statistically significant OS benefit with the addition of adjuvant chemotherapy in resectable mCRC.[522-524]

The choice of chemotherapy regimen in the perioperative setting depends on several factors, including the chemotherapy history of the patient, whether disease is synchronous or metachronous, and the response rates and safety/toxicity issues associated with the regimens, as outlined in the guidelines. Biologics are not recommended in the perioperative metastatic setting, with the exception of initial therapy in unresectable patients who may be converted to a resectable state.

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.[525,526]

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.[346,527,528] In fact, results from recent studies of patients with CRC receiving preoperative therapy indicated that viable cancer was still present in most of the original sites of metastases when these sites were examined pathologically despite achievement of a complete response as evaluated on CT scan.[528-530] Therefore, during treatment with preoperative systemic therapy, frequent evaluations must be undertaken and close communication must be maintained among medical oncologists, radiologists, surgeons, and patients so that a treatment strategy can be developed that optimizes exposure to the preoperative regimen and facilitates an appropriately timed surgical intervention.[498]

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.[498-502] 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 metastatic colon cancer involves various active drugs, either in combination or as single agents. The choice of therapy is based on consideration of the goals of therapy, the type and timing of prior therapy, the mutational profile of the tumor, and the differing toxicity profiles of the constituent drugs. Although the specific regimens listed in the guideline are designated according to whether they pertain to initial therapy, therapy after first progression, or therapy after second progression, it is important to clarify that these recommendations represent a continuum of care and that these lines of treatment are blurred rather than discrete.[531] For example, if oxaliplatin is administered as a part of an initial treatment regimen but is discontinued after 12 weeks or earlier for escalating neurotoxicity, continuation of the remainder of the treatment regimen would still be considered initial therapy.

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Principles to consider at the start of therapy include: 1) preplanned strategies for altering therapy for patients exhibiting a tumor response or disease characterized as stable or progressive; and 2) plans for adjusting therapy for patients who experience certain toxicities. For example, 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 take into account not only the component drugs, but also the doses, schedules, and methods of administration of these agents, and the potential for surgical cure and the performance status of the patient.

As initial therapy for metastatic disease in a patient appropriate for intensive therapy (ie, one with a good tolerance for this therapy for whom a high tumor response rate would be potentially beneficial), the panel recommends a choice of five chemotherapy regimens: FOLFOX (ie, mFOLFOX6),[532,533] FOLFIRI ,[254] CAPEOX,[534-536] infusional 5-FU/LV or capecitabine,[254,311,537,538] or FOLFOXIRI,[505,506] with or without targeted agents.[539]

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.[533,540-542] 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.[533] A combined analysis of data from seven recent phase III clinical trials in advanced CRC provided support for a correlation between an increase in median survival and administration of all of the three cytotoxic agents (ie, 5-FU/LV, oxaliplatin, irinotecan) at some point in the continuum of care.[543] 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 gastrointestinal toxicities were significantly increased for patients with a performance status of 2.[544]

Overall, the panel does not consider one regimen (ie, FOLFOX, CAPEOX, FOLFIRI, 5-FU/LV, capecitabine, FOLFOXIRI) 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).

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[545-547] or targeted therapies (eg, EGFR inhibitors)[545,548-552] 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 stopped therapy due to progression compared to other reasons, limiting the quality of these data. The randomized FIRE-4 trial (NCT02934529) is currently under recruitment and will seek to address this question.

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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 with 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.[553] 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 months 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 months 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 pronounced for patients with *RAS/BRAF* wild-type or *BRAF* V600E mutation-positive tumors.[554]

The AIO 0207 trial was an open-label, non-inferiority, 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.[555] 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 non-inferior, 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.[556]

The randomized phase III non-inferiority SAKK 41/06 trial addressed the question of continuing bevacizumab alone as maintenance therapy after chemotherapy plus bevacizumab in first-line therapy.[557] The primary

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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 months vs. 23.8 months; HR, 0.83; 95% CI, 0.63–1.1; *P* = .2). Therefore, non-inferiority 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.[558] Intention-to-treat 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.[559] 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.[560]

Another phase III trial investigated the role of capecitabine in the maintenance phase, after initial treatment with FOLFOX or CAPEOX.[561] 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.

Biosimilars

A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing biologic therapy.[562-568] 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. Bevacizumab-awwb and -bvzr have been FDA approved for the treatment of mCRC.[562,563] Trastuzumab-anns, -dkst, -qyyp, -dttb, and -pkrb are not FDA approved for CRC, but have been approved for other cancer types (breast and gastric).[564-568] The NCCN Panel has agreed that an 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 or mCRC has become increasingly prominent, the NCCN Panel has expanded its recommendations regarding biomarker testing. Currently, determination of tumor gene status for *KRAS/RAS* and *BRAF* mutations, as well as HER2 amplifications, are recommended for patients with mCRC. Testing may be carried out for individual genes or as part of a next-generation sequencing (NGS) panel, although no specific methodology is recommended. NGS panels have the advantage of being able to pick up rare and actionable genetic alterations, such as neurotrophic tyrosine receptor kinase (*NTRK*) fusions. Specific information about each of these biomarkers may be found in the sections below.

KRAS and NRAS Mutations

EGFR has been reported to be overexpressed in 49% to 82% of colorectal tumors.[569-572] EGFR testing of colorectal tumor cells has no proven predictive value in determining likelihood of response to either cetuximab or panitumumab. Data from the BOND study indicated that the intensity of immunohistochemical staining of EGFR in colorectal tumor cells did not correlate with the response rate to cetuximab.[573] A similar conclusion was drawn with respect to panitumumab.[574] Therefore, routine EGFR testing is

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not recommended, and no patient should be considered for or excluded from cetuximab or panitumumab therapy based on EGFR test results. The RAS/RAF/MAPK pathway is downstream of EGFR; mutations in components of this pathway are being studied in search of predictive markers for efficacy of these therapies.

A sizable body of literature has shown that tumors with a mutation in codon 12 or 13 of exon 2 of the *KRAS* gene are essentially insensitive to cetuximab or panitumumab therapy.[575-583] More recent evidence shows mutations in *KRAS* outside of exon 2 and mutations in *NRAS* are also predictive for a lack of benefit to cetuximab and panitumumab.[584,585]

The panel therefore strongly recommends *RAS* (*KRAS/NRAS)* genotyping of tumor tissue (either primary tumor or metastasis) in all patients with mCRC. Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified. ASCO released a Provisional Clinical Opinion Update on extended *RAS* testing in patients with mCRC that is consistent with the NCCN Panel's recommendations.[586] A guideline on molecular biomarkers for CRC developed by the ASCP, CAP, AMP, and ASCO also recommends *RAS* testing consistent with the NCCN recommendations.[28]

The recommendation for *RAS* testing, at this point, is not meant to indicate a preference regarding regimen selection in the first-line setting. Rather, this early establishment of *RAS* status is appropriate to plan for the treatment continuum, so that the information may be obtained in a non–time-sensitive manner and the patient and provider can discuss the implications of a *RAS* mutation, if present, while other treatment options still exist. Note that because anti-EGFR agents have no role in the management of stage I, II, or III disease, *RAS* genotyping of 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.[587-589] For this reason, *RAS* genotyping can be performed on archived specimens of either the primary tumor or a metastasis. Fresh biopsies should not be obtained solely for the purpose of *RAS* genotyping unless an archived specimen from either the primary tumor or a metastasis is unavailable.

The panel recommends that *KRAS, NRAS, and BRAF* gene testing be performed only in laboratories that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform highly complex molecular pathology testing.[590] No specific testing methodology is recommended.[591] The three genes can be tested individually or as part of an NGS panel.

Approximately 40% of CRCs are characterized by mutations in codons 12 and 13 in exon 2 of the coding region of the *KRAS* gene.[281,575] A sizable body of literature has shown that these *KRAS* exon 2 mutations are predictive of lack of response to cetuximab or panitumumab therapy,[575-583,592] and FDA labels for cetuximab and panitumumab specifically state that these agents are not recommended for the treatment of CRC characterized by these mutations.[593,594] Results are mixed as far as the prognostic value of *KRAS* mutations. In the Alliance N0147 trial, patients with *KRAS* exon 2 mutations experienced a shorter DFS than patients without such mutations.[595] At this time, however, the test is not recommended for prognostic reasons.

A retrospective study by De Roock et al[596] raised the possibility that codon 13 mutations (G13D) in *KRAS* may not be absolutely predictive of non-response. Another retrospective study showed similar results.[582] However, more recent retrospective analysis of three randomized controlled phase III trials concluded that patients with *KRAS* G13D mutations were unlikely to respond to panitumumab.[597] Results from a prospective phase II single-

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arm trial assessed the benefit of cetuximab monotherapy in 12 patients with refractory mCRC whose tumors contained *KRAS* G13D mutations.[598] 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 failed to see a benefit of cetuximab monotherapy in patients with *KRAS* G13D mutations.[599] 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.[600] The panel believes that patients with any known *KRAS* mutation, including G13D, should not be treated with cetuximab or panitumumab.

In the AGITG MAX study, 10% of patients with wild-type *KRAS* exon 2 had mutations in *KRAS* exons 3 or 4 or in *NRAS* exons 2, 3, and 4.[601] In the PRIME trial, 17% of 641 patients without *KRAS* exon 2 mutations were found to have mutations in exons 3 and 4 of *KRAS* or mutations in exons 2, 3, and 4 of *NRAS*. A predefined retrospective subset analysis of data from PRIME revealed that PFS (HR, 1.31; 95% CI, 1.07–1.60; *P* = .008) and OS (HR, 1.21; 95% CI, 1.01–1.45; *P* = .04) were decreased in patients with any *KRAS* or *NRAS* mutation who received panitumumab plus FOLFOX compared to those who received FOLFOX alone.[584] These results show that panitumumab does not benefit patients with *KRAS* or *NRAS* mutations and may even have a detrimental effect in these patients.

Updated analysis of the FIRE-3 trial (discussed in *Cetuximab or Panitumumab vs. Bevacizumab in First-line Therapy,* below) was recently published.[602] 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 months vs. 12.2 months; *P* = .004). On the other hand, patients with *KRAS/NRAS* wild-type tumors showed no difference in PFS between the regimens (10.4 months vs. 10.2 months; *P* = .54). This result indicates that cetuximab likely has a detrimental effect in patients with *KRAS* or *NRAS* mutations.

The FDA indication for panitumumab was updated to state that panitumumab is not indicated for the treatment of patients with *KRAS* or *NRAS* mutation-positive disease in combination with oxaliplatin-based chemotherapy.[594] The NCCN Colon/Rectal Cancer Panel believes that *RAS* mutation status should be determined at diagnosis of stage IV disease. Patients with any known *RAS* mutation should not be treated with either cetuximab or panitumumab.

BRAF V600E Mutations

Although mutations in *RAS* indicate a lack of response to EGFR inhibitors, many tumors containing wild-type *RAS* still do not respond to these therapies. Therefore, studies have addressed factors downstream of *RAS* as possible additional biomarkers predictive of response to cetuximab or panitumumab. Approximately 5% to 9% of CRCs are characterized by a specific mutation in the *BRAF* gene (V600E)[603,604] *BRAF* mutations are, for all practical purposes, limited to tumors that do not have *KRAS* exon 2 mutations.[603-605] 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,[606-608] 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.[604,609] A planned subset analysis of the PRIME trial also found that mutations in *BRAF* indicated a

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poor prognosis but were not predictive of benefit to panitumumab added to FOLFOX in first-line treatment of mCRC.[584] 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.[605]

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.[610-612] 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).[613] Furthermore, data from the multicenter randomized controlled PICCOLO trial are consistent with this conclusion, with a suggestion of harm seen for the addition of panitumumab to irinotecan in the non–first-line setting in the small subset of patients with *BRAF* mutations.[614]

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).[615] 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* mutations.[616]

Despite uncertainty over its role as a predictive marker, it is clear that mutations in *BRAF* are a strong prognostic marker.[281,604,605,617-622] 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).[281] 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.[604] 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).[618] The OS for patients with *BRAF* mutations in the COIN trial was 8.8 months, while those with *KRAS* exon 2 mutations and wild-type *KRAS* exon 2 tumors had OS times of 14.4 months and 20.1 months, respectively.[605] 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.[623] Results from a recent systematic review and meta-analysis of 21 studies, including 9885 patients, suggest that *BRAF* mutation may accompany specific high-risk clinicopathologic characteristics.[624] 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 with a BRAF inhibitor (eg, vemurafenib; see *Vemurafenib, Irinotecan, and Cetuximab or Panitumumab*, below). The panel recommends *BRAF* genotyping of tumor tissue (either primary tumor or metastasis[625]) at diagnosis of stage IV disease. Testing for the *BRAF* V600E mutation can be performed on formalin-fixed paraffin-embedded tissues and is usually performed by PCR amplification and direct DNA

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sequence analysis. Allele-specific PCR is another acceptable method for detecting this mutation, or *BRAF* status can be determined by NGS.

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%).[626-628] Specific molecular diagnostic methods have been proposed for HER2 testing in CRC,[629] 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 in the Non-First-Line Setting,* below).[626,630] Based on this, the NCCN Guidelines recommend testing for HER2 amplifications for patients with mCRC. If the tumor is already known to have a *KRAS*/*NRAS* or *BRAF* mutation, HER2 testing is not required. As HER2-targeted therapies are still under investigation, enrollment in a clinical trial is encouraged.

Evidence does not support a prognostic role of HER2 overexpression.[631] 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.[627,628,632,633] For example, in a cohort of 97 patients with *RAS/BRAF*–wild type mCRC, median PFS on first-line therapy without an EGFR inhibitor was similar regardless of HER2 status.[627] However, in second-line therapy with an EGFR inhibitor, the PFS was significantly shorter in those with HER2 amplification compared with those without HER2 amplification (2.9 months vs. 8.1 months; HR, 5.0; $P < .0001$).

dMMR/MSI-H Status

The percentage of stage IV colorectal tumors characterized as MSI-H (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.[282,634,635] 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 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.[636] 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 *Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the Non-First-Line Setting,* below). The NCCN Guidelines 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).

NTRK Fusions

Three *NTRK* genes encode the tropomyosin receptor kinase (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.[637] Recent studies have estimated that about 0.2% to 1% of CRCs carry *NTRK* gene fusions.[638,639] A study of 2314 CRC specimens, of which

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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.[640] These results may support limiting testing for *NTRK* fusions to those with wild-type *KRAS*, *NRAS*, and *BRAF.* TRK inhibitors are treatment options for patients with mCRC that is *NTRK* gene fusion-positive (see *Larotrectinib or Entrectinib for NTRK Fusion-positive Disease in the Non-First-Line Setting,* below).

Severe Fluoropyrimidine-Associated Toxicity

Dihydropyrimidine dehydrogenase is the enzyme that catabolizes fluoropyrimidines.[641,642] Individuals with certain variants of the dihydropyrimidine dehydrogenase gene, *DPYD*, have a significantly elevated risk for severe, life-threatening toxicity after a standard dose of fluoropyrimidine because these variants result in a truncated protein and prolonged systemic exposure to fluoropyrimidine.[643-647] Pretreatment *DPYD* testing of all patients has the potential to identify the estimated 1% to 2% of the population with truncating alleles and an increased risk of severe toxicity.[648] These patients could be offered alternative regimens or receive dose reductions.[642] Two prospective studies have shown *DPYD* genotyping and fluoropyrimidine dose individualization to be feasible in clinical practice, improve patient safety, and be cost effective.[649-651] In a prospective study, 22 patients with the *DPYD*2A* variant allele (of 2038 patients screened; 1.1%) were given a fluoropyrimidine dose reduction of 17% to 91% (median 48%).[651] Results showed a significant reduction in the risk of grade ≥3 toxicity compared with historic controls (28% vs. 73%; $P < .001$). None of the patients died from drug toxicity, compared with a 10% death rate in the historical control group. Another prospective study identified 85 patients with any of the four *DPYD* variant alleles (8% of 1103 patients screened) who received an initial fluoropyrimidine dose reduction of either 25% or 50% depending on the specific allele.[650] This study reported that the RR of severe fluoropyrimidine-related toxicity was reduced for genotype-guided dosing for all studied alleles compared to the historical cohorts. Universal pretreatment *DPYD* genotyping remains controversial, however, and the NCCN Panel does not support it at this time.

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[513,652] and inferior to FOLFOX in the Intergroup trial[653]) at any point in the therapy continuum. 5-FU in combination with irinotecan or oxaliplatin should be administered via an infusional biweekly regimen,[254] or capecitabine can be used with oxaliplatin.[654]

The Dutch CAIRO trial showed promising results for the use of capecitabine/irinotecan (CapeIRI) in the first-line treatment of mCRC.[541] 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.[513] 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).[655] 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.[656] A similar trial by the Spanish group found similar results in 77 patients.[657] Preliminary results from a randomized phase II study conducted in France were presented in 2009,

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showing a manageable toxicity profile for CapeIRI/Bev in this setting.[658] 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.[659] 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.[660] Because of the concerns about the toxicity of the CapeIRI combination, which may differ between American and European patients, 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.[661-665] These regimens are not recommended for the treatment of patients with CRC.

Results from 2 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.[666,667] 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.[666] Similar results were observed in the CAIRO2 trial with the addition of cetuximab to a regimen containing capecitabine, oxaliplatin, and bevacizumab.[667] 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).

First-line Systemic Therapy

FOLFOX for First-line Therapy

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 resected patients, respectively, when chemotherapy in conjunction with surgery was compared with surgery alone.[668] The partial response rate after preoperative FOLFOX was 40%, and operative mortality was less than 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.[669]

The addition of bevacizumab is an option when FOLFOX is chosen as initial therapy,[515,670] as is the addition of panitumumab or cetuximab for patients with disease characterized by wild-type *KRAS* exon 2 (see discussions on *Bevacizumab; Cetuximab and Panitumumab: KRAS, NRAS, and BRAF Status* and *Primary Tumor Sidedness;* and *Cetuximab or Panitumumab vs. Bevacizumab in First-line Therapy*, below).[577,671,672] 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 recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.[673]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy.[674] 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.[675] Other trials

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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.[676] A recent meta-analysis of RCTs also concluded that intermittent delivery of systemic therapy does not compromise OS compared to continuous treatment.[677] Therefore, the panel recommends adjusting the schedule/timing of the administration of this drug as a means of limiting this adverse effect. 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.[678] 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 ($P = .046$).[678]

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.[679] 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.[680-687] 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.[688] 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.[534-536,689,690] 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 determined to be noninferior to FOLFOX as first-line treatment of metastatic disease.[534] Meta-analyses of RCTs also showed that CAPEOX and FOLFOX had similar benefits for patients with mCRC.[691,692]

Use of oxaliplatin has been associated with an increased incidence of peripheral sensory neuropathy (see *FOLFOX*, above).[693] Discontinuation of oxaliplatin from FOLFOX or CAPEOX should be strongly considered after 3 months of therapy (the OPTIMOX1 approach[675]), or sooner for unacceptable neurotoxicity, with other drugs in the regimen maintained until tumor progression. A recent Turkish Oncology Group Trial showed that this stop-and-go approach is safe and effective in first-line therapy with CAPEOX/bevacizumab.[694] 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.[688]

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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[695]; 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[670,695]; and 3) North American patients may experience a higher incidence of adverse events with certain doses of capecitabine compared with patients from other countries.[696] These toxicities may necessitate modifications in the dosing of capecitabine.[670,695,697] 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, a recent 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).[698]

The addition of bevacizumab is an option if CAPEOX is chosen as initial therapy.[515,670] 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 recent registry-based cohort analysis of greater than 2000 patients support the equivalence of these combinations.[673]

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.[533] 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.[699] 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 elderly patients with mCRC.[700] In this population of patients, aged ≥75 years, grade 3–4 toxicities were increased with the addition of irinotecan (52.2% vs. 76.3%), without an improvement in PFS or OS.

Toxicities associated with irinotecan include both early and late forms of diarrhea, dehydration, and severe neutropenia.[701,702] 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,[702-704] although severe irinotecan-related toxicity is not experienced by all patients with these polymorphisms.[704] Results from a dose-finding and pharmacokinetic study suggest that dosing of irinotecan should be individualized based on UGT1A1 genotype.[705] The maximum tolerated dose of intravenous 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

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indicating that a reduced starting dose of the drug should be used in patients known to be homozygous for UGT1A1*28.[701] A practical approach to the use of UGT1A1*28 allele testing with respect to patients receiving irinotecan has been presented,[704] 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 recent 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.[706] A phase III trial in Japan also showed that FOLFIRI plus bevacizumab is non-inferior to mFOLFOX6 plus bevacizumab with regard to PFS.[707] 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 (see discussions on *Bevacizumab; Cetuximab and Panitumumab*: *KRAS, NRAS, and BRAF Status and Primary Tumor Sidedness;* and *Cetuximab or Panitumumab vs. Bevacizumab in First-line Therapy*, below).[583,604,671,708,709]

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.[254,654,670,710-712] 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 2 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.[713]

Results were recently published from the open-label phase III AVEX trial, in which 280 patients aged 70 years or older were randomized to capecitabine with or without bevacizumab.[714] The trial met its primary endpoint, with the addition of 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 for first-line therapy

FOLFOXIRI is also listed as an option for initial therapy in patients with unresectable metastatic disease. Use of FOLFOXIRI compared with FOLFIRI as initial therapy for the treatment of metastatic disease has been investigated in 2 randomized phase III trials.[505,506] 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,[505] 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).[506] Both studies showed some increased toxicity in the FOLFOXIRI arm (eg, significant increases in neurotoxicity and neutropenia,[505] diarrhea, alopecia, and neurotoxicity[506]), 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.[507] The improvements in PFS and OS were maintained.

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The panel includes the possibility of adding bevacizumab to FOLFOXIRI 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.[715] 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).[716]

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.[717] 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%).

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.[718] 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.[514,719,720] 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).[711] A study of previously untreated patients receiving bevacizumab plus IFL also provided support for the inclusion of bevacizumab in initial therapy.[514] 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.[515] 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).[515] 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.[515] 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.[515]

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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 recent 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).[721] FOLFOXIRI with bevacizumab is also an accepted combination (see *FOLFOXIRI*, above), although no RCTs have compared FOLFOXIRI with and without bevacizumab.

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.[722] 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) in 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).[723]

Several meta-analyses have shown a benefit for the use of bevacizumab in first-line therapy for mCRC.[724-732] A meta-analysis of 6 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.[733] However, subgroup analyses showed that the advantage was limited to irinotecan-based regimens. In addition, a recent 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).[734] 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,[735,736] but, overall, the addition of bevacizumab to first-line chemotherapy appears to offer a modest clinical benefit.

Only limited data directly address whether bevacizumab should be used with chemotherapy in the perioperative treatment of resectable metastatic disease.[737] The randomized phase III HEPATICA trial, which closed prematurely due to poor accrual, found that global quality of life scores were higher in patients receiving CAPEOX plus bevacizumab than those receiving CAPEOX alone after resection of liver metastases, but no conclusions could be drawn regarding the primary endpoint of DFS.[738] Furthermore, data regarding the lack of efficacy of bevacizumab in the adjuvant setting in stage II and III colon cancer[326,328] have prompted some to reconsider the role of bevacizumab in the adjuvant setting of resectable colorectal metastases. However, the panel does not recommend the use of bevacizumab in the perioperative stage IV setting.

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 gastrointestinal perforation (7.1%) being the most common causes of fatality.[739] Venous thromboembolisms, on the other hand, were not increased in patients receiving bevacizumab with chemotherapy versus those receiving chemotherapy alone.[740] Another meta-analysis showed that bevacizumab was associated with a significantly higher risk of hypertension, gastrointestinal hemorrhage, and perforation, although the overall risk for hemorrhage and perforation is quite low.[741] The risk of stroke and other arterial events is increased in patients receiving bevacizumab, especially in those aged 65 years or older. Gastrointestinal perforation is a rare but important side effect of bevacizumab therapy in patients with CRC.[670,742] Extensive prior intra-abdominal surgery, such as peritoneal stripping, may predispose patients to gastrointestinal perforation. A small cohort of

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patients with advanced ovarian cancer had an unacceptably high rate of gastrointestinal perforation when treated with bevacizumab.[743] This result illustrated that peritoneal debulking surgery may be a risk factor for gastrointestinal perforation, whereas the presence of an intact primary tumor does not seem to increase the risk for gastrointestinal perforation. The FDA recently approved a safety label warning of the risk for necrotizing fasciitis, sometimes fatal and usually secondary to wound healing complications, gastrointestinal perforation, or fistula formation after bevacizumab use.[718]

Use of bevacizumab may interfere with wound healing.[670,718,742] A retrospective evaluation of data from 2 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; $P = .28$).[742] However, when chemotherapy plus bevacizumab or chemotherapy alone was administered before surgery, with a delay between bevacizumab administration and surgery 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 (ie, bevacizumab excluded from the sixth cycle of therapy).[744] 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 or less versus at more than 8 weeks before resection of liver colorectal metastases in patients receiving oxaliplatin- or irinotecan-containing regimens.[745] The panel recommends an interval of at least 6 weeks (which corresponds to 2 half-lives of the drug[718]) 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 recent retrospective meta-analysis of 5 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.[746] Although this meta-analysis has been criticized,[747,748] the results are supported by recent results from the NSABP Protocol C-08 trial.[326] 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.[593,594] 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.[749]

Recent meta-analyses of RCTs have concluded that EGFR inhibitors provide a clear clinical benefit in the treatment in patients with *RAS* wild-

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type mCRC.[585,750] Patients with known *KRAS* or *NRAS* mutations should not be treated with either cetuximab or panitumumab, either alone or in combination with other anticancer agents, because they have virtually no chance of benefit and the exposure to toxicity and expense cannot be justified (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.[593,594] Based on case reports and a small trial, administration of panitumumab seems to be feasible for patients experiencing severe infusion reactions to cetuximab.[751-753] 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.[581,583,754-757] A recent NCCN task force addressed the management of dermatologic and other toxicities associated with anti-EGFR inhibitors.[758] Cetuximab and panitumumab have also been associated with a risk for venous thromboembolic and other serious adverse events.[759,760]

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).[666,667] Several trials that 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.[761-769] For example, outcomes of 75 patients with mCRC treated with cetuximab, panitumumab, or cetuximab/irinotecan in first-line or subsequent lines of therapy at 3 Italian centers were analyzed based on sidedness of the primary tumor.[762] 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.[766] The study showed that patients with all *RAS* wild-type, right-sided primary tumors (cecum to hepatic flexure) had longer OS if treated with bevacizumab than if treated with cetuximab in first line (HR, 1.36; 95% CI, 0.93–1.99; P = .10), whereas patients with all *RAS* wild-type, left-sided primary tumors (splenic flexure to rectum) had longer OS if treated with cetuximab than if treated with bevacizumab (HR, 0.77; 95% CI, 0.59–0.99; P = 0.04).[770] OS was prolonged with cetuximab versus bevacizumab in the left-sided primary group (39.3 months vs. 32.6 months) but shortened in the right-sided primary group (13.6 months vs. 29.2 months). Retrospective analyses of other contemporary studies have confirmed this finding.[769]

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.[761,762,764] The panel believes that primary tumor sidedness is a surrogate for the non-random distribution of molecular subtypes across the colon and that the on-going analysis of genomic differences between right- and left-sided tumors[771] 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.

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Evidence also suggests that sidedness is predictive of response to EGFR inhibitors in subsequent lines of therapy,[761,762,764] 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.[583] 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).[583] The statistically significant benefit in PFS for patients with KRAS exon 2 wild-type tumors receiving cetuximab was confirmed in a recent publication of an updated analysis of the CRYSTAL data.[604] This recent 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.[772] 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).[773]

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.[614,709,774,775]

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 objective response rate (61% vs. 37%; odds ratio, 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.[577] Although data supporting the statistically significant benefits in objective response rate 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).[776]

Furthermore, in the recent 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 or mCRC and wild-type *KRAS* exon 2.[605] 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.[605]

Notably, more recent trials examining the efficacy of the addition of cetuximab to oxaliplatin-containing regimens in the first-line treatment of patients with advanced 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.[777]

However, results from the randomized phase III CALGB/SWOG 80405 trial of greater than 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

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treatment of mCRC.[672] 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.[778] Therefore, the panel recommends cetuximab plus FOLFOX as an initial therapy option for *RAS/BRAF* wild-type patients with advanced or metastatic disease.

The New EPOC trial, which was stopped early because it met protocol-defined futility criteria, found a lack of benefit to cetuximab with chemotherapy in the perioperative metastatic setting (>85% received FOLFOX or CAPEOX; patients with prior oxaliplatin received FOLFIRI).[779] In fact, with less than half of expected events observed, PFS was significantly reduced in the cetuximab arm (14.8 vs. 24.2 months; HR, 1.50; 95% CI, 1.00–2.25; *P* < .048). The panel thus cautions that cetuximab in the perioperative setting may harm patients. The panel therefore does not recommend the use of FOLFOX plus cetuximab in patients with resectable disease and should be used with caution in those with unresectable disease that could potentially be converted to a resectable status.

Panitumumab with FOLFOX: Panitumumab in combination with either FOLFOX[584,671] or FOLFIRI[708] 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.[584] 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 NRAS and Other KRAS Mutations, above).[584]

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.[602] This trial did not meet its primary endpoint of investigator-read objective response rate in the 592 randomized patients (62.0% vs. 58.0%; P = .18). PFS was nearly identical between the arms of the study, 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.[780,781] While the rate of adverse events was similar between the arms, more skin toxicity was observed in those receiving cetuximab.

Results of the phase III CALGB/SWOG 80405 trial, comparing FOLFOX/FOLFIRI with cetuximab or bevacizumab, were recently reported.[672] In this study, patients with wild-type *KRAS* exon 2 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).

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, were also published.[782] 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

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FOLFOX/panitumumab showed a longer PFS compared to FOLFOX/bevacizumab in patients with wild-type *RAS* (12.8 vs. 10.1 months; HR, 0.68; 95% CI, 0.48–0.96; *P* = .029).[783] Although these data are intriguing, definitive conclusions are hindered by the small sample size and limitations of subset analyses.[784]

Economic analyses suggest that bevacizumab may be more cost effective than EGFR inhibitors in first-line therapy for mCRC,[785] although more recent analyses have shown the opposite.[786,787]

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.

Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the First-Line Setting

Limited data exist to support the use of checkpoint inhibitor therapy for first-line treatment of dMMR/MSI-H mCRC. An abstract on the phase II CheckMate-142 trial reported results for nivolumab in combination with ipilimumab in 45 patients with previously untreated MSI-H/dMMR mCRC.[788] ORR was found to be 60% (95% CI, 44.3%–74.3%), with a median follow-up of 13.8 months. After 19.9 months of follow-up, investigator-assessed ORR was 64% (95% CI, 49%–78%), disease control rate was 84% (95% CI, 71%–94%), and duration of response had not been reached. After 19.9 months of follow-up, 20% of patients had grade 3 or 4 treatment-related adverse events and adverse events led to discontinuation in 11% of patients. Additional results from CheckMate-142 (including nivolumab alone or in combination with ipilimumab as subsequent therapy) are discussed in *Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease in the Non-First-Line Setting,* below.

Based on the limited data supporting the use of checkpoint inhibitors in the first-line setting, the panel recommends pembrolizumab or nivolumab, alone or in combination with ipilimumab, as options for first-line treatment of MSI-H/dMMR mCRC only for patients who are not appropriate for intensive therapy. The recommendation for nivolumab in combination with ipilimumab in this setting is category 2B due to concerns about potential toxicity from the combination therapy.

Second-line or Subsequent Systemic Therapy

Decisions regarding therapy after progression of metastatic disease depend on previous therapies. The panel recommends against the use of mitomycin, alfa-interferon, taxanes, methotrexate, pemetrexed, sunitinib, sorafenib, erlotinib, or gemcitabine, either as single agents or in combination, as therapy in patients exhibiting disease progression after treatment with standard therapies. These agents have not been shown to be effective in this setting. Furthermore, no objective responses were observed when single-agent capecitabine was administered in a phase II study of patients with CRC resistant to 5-FU.[789]

The recommended therapy options after first progression for patients who have received prior 5-FU/LV-based or capecitabine-based 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 [790] or infusional 5-FU/LV.[791] In the study of Rougier et al,[791] median PFS was 4.2 months for irinotecan versus 2.9 months for 5-FU (*P* = .030), whereas Cunningham et al[790] 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.[792] 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.[793]

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A meta-analysis of randomized trials found that the addition of a targeted agent after first-line treatment improves outcomes but also increases toxicity.[794] 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.[795] 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* 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[579] is recommended. For patients with wild-type *KRAS/NRAS/BRAF* progressing on therapies that *did* contain an EGFR inhibitor, administration of an EGFR inhibitor is not recommended in subsequent lines of therapy. No data support switching to either cetuximab or panitumumab after failure of the other drug, and the panel recommends against this practice.

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.[796] 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.[575] 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.[575] 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.[797] The primary endpoint of OS was improved with panitumumab (10.0 months 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.[709] These results were confirmed in the final results of Study 181.[775] Furthermore, re-analysis of samples from the trial showed that the benefit of the combination was limited to participants with no *RAS* mutations.[798] 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.[774] 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.[614]

Cetuximab has been studied both as a single agent[573,579,754,799] and in combination with irinotecan[573] 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.[800] Importantly, *KRAS* status was not determined in this study and toxicity was higher in the cetuximab-containing arm (eg, rash, diarrhea, electrolyte imbalances).[800]

In a retrospective analysis of the subset of patients with known *KRAS* exon 2 tumor status receiving cetuximab monotherapy as second-line therapy,[754] the benefit of cetuximab versus best supportive care was shown to be enhanced in patients with *KRAS* exon 2 wild-type tumors.[579]

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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.[579]

The randomized, multicenter, open-label, non-inferiority phase III ASPECCT trial compared single-agent cetuximab with single-agent panitumumab in the chemotherapy-refractory metastatic setting.[801] The primary non-inferiority 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 adverse events 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, .82–1.07).[802]

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.[803] 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).

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.[804] This study met its primary endpoint, with patients continuing on bevacizumab having a modest improvement in OS (11.2 months 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.[805]

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).[806] 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.[807] 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.[808] 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).[809]

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

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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.[810]

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.[811] 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 progression through a first-line non-bevacizumab–containing regimen showed that the addition of bevacizumab to second-line FOLFOX modestly improved survival.[811] 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).[811] 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.[811]

Ziv-Aflibercept

Ziv-aflibercept is a recombinant protein that has part of the human VEGF receptors 1 and 2 fused to the Fc portion of human IgG1.[812] It is designed to function as a VEGF trap to prevent activation of VEGF receptors 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).[813] 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.[814]

Adverse events 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.[813] 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 FOLFIRI-naïve patients. No data suggest activity of FOLFIRI plus ziv-aflibercept in patients who 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.[815] 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.[810]

Ramucirumab

Another anti-angiogenic agent, ramucirumab, is a human monoclonal antibody that targets the extracellular domain of VEGF receptor 2 to block VEGF signaling.[816] 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.[817] 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;

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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 status, time to progression on first-line therapy, and age.[818]

Rates of discontinuation due to adverse events 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 adverse events were neutropenia, hypertension, diarrhea, and fatigue. In addition, a meta-analysis of 6 phase III trials showed that ramucirumab did not increase the risk of arterial thromboembolic events, venous thromboembolic events, high-grade bleeding, or high-grade gastrointestinal bleeding compared to placebo controls.[819] 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 who 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.[810]

Systemic Therapy Options for BRAF V600E Mutation-positive Disease in the Non–First-line Setting

The NCCN Panel recommends three drug combinations as subsequent treatment options for patients with mCRC that harbors the *BRAF* V600E mutation: 1) vemurafenib, irinotecan, and cetuximab or panitumumab; 2) dabrafenib, trametinib, and cetuximab or panitumumab; or 3) encorafenib, binimetinib, and cetuximab or panitumumab. The results of clinical trials supporting each of these regimens are detailed below.

Vemurafenib, Irinotecan, and Cetuximab or Panitumumab: Vemurafenib is an inhibitor of the BRAF V600-mutated kinase, thereby blocking the downstream signaling though the BRAF/MEK/ERK pathway.[820]

The phase II SWOG S1406 trial that tested a combination of vemurafenib, cetuximab, and irinotecan was thus tested in patients with *BRAF* V600E-mutated mCRC.[821] Ninety-nine patients with *BRAF*-mutant, *RAS* wild-type tumors who received 1 or 2 prior regimens were randomized to irinotecan and cetuximab with or without vemurafenib. An abstract presented at the 2017 ASCO Annual Meeting reported that the primary endpoint of median PFS was improved in the vemurafenib arm (4.4 vs. 2.0 months; HR, 0.42; 95% CI, 0.26–0.66; *P* < .001). Disease response was also improved with addition of vemurafenib, with response rates of 16% versus 4% (*P* = .08) and disease control rates of 67% versus 22% (*P* = .001). Grade 3/4 adverse events that were higher in the vemurafenib arm included neutropenia (28% vs. 7%), anemia (13% vs. 0%), and nausea (15% vs. 0%).

Dabrafenib, Trametinib, and Cetuximab or Panitumumab: Another treatment option for BRAF V600E mutation-positive mCRC is a combination of the BRAF inhibitor, dabrafenib, with the MEK inhibitor, trametinib, and either cetuximab or panitumumab. A phase I study investigated the combination of dabrafenib plus panitumumab, trametinib plus panitumumab, or a combination of all three therapies in patients with BRAF V600E mutation-positive mCRC.[822] Response rates were 10%, 21%, and 0% for dabrafenib plus panitumumab, dabrafenib plus trametinib plus panitumumab, and trametinib plus panitumumab, respectively. The most common grade 3 or 4 adverse events noted for the dabrafenib, trametinib, and panitumumab combination were diarrhea (7%), nausea (2%), and dermatitis acneform (10%). Seventy percent of patients treated with the triplet therapy had a grade 3 or 4 adverse event.[822]

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Encorafenib, Binimetinib, and Cetuximab or Panitumumab: 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.[823,824] 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 adverse events were fatigue (13%), anemia (10%), increased creatine phosphokinase (10%), increased AST (10%), and urinary tract infections (10%).[824]

Subsequently, the randomized portion of the BEACON trial has reported similarly encouraging results, including a positive OS result.[825] 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. Confirmed ORR was 26% (95% CI, 18%–35%) for the triplet compared to 2% (95% CI, 0%–7%) for control ($P < .0001$). Median OS was 9 months for the triplet regimen compared to 5.4 months for control (HR, 0.52; 95% CI, 0.39–0.70; $P < .0001$). Median OS for the doublet regimen was 8.4 months. Adverse events were as expected based on previous studies. Grade 3 or higher adverse events occurred in 58% of patients on the triplet regimen, 50% on the doublet, and 61% on the control arm.[825]

Systemic Therapy Options for HER2-amplified Disease in the Non–First-line Setting

Two drug combinations are recommended by the panel as options for subsequent treatment of mCRC with HER2 amplifications: trastuzumab plus either pertuzumab or lapatinib. 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.[826] 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 adverse events, with hypokalemia and abdominal pain being most common.[826]

Trastuzumab Plus Lapatinib: The combination of trastuzumab plus the dual HER2/EGFR inhibitor, lapatinib, was studied in the multicenter, phase II HERACLES trial.[626] 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 adverse events, including fatigue (four patients), skin rash (one patient), and increased bilirubin (one patient).[626]

Pembrolizumab, Nivolumab, and Ipilimumab for dMMR/MSI-H Disease 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.[827]

A recent 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.[828] All patients had progressive metastatic disease; the patients in the colorectal arms had progressed

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through two to four previous therapies. The primary endpoints were the immune-related objective response rate and the 20-week immune-related PFS rate. The immune-related objective response rates were 40% (95% CI, 12%–74%) in the dMMR 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 not reached 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; $P < .001$).

Nivolumab is another humanized IgG4 PD-1 blocking antibody,[829] which was studied with or without ipilimumab in patients with mCRC in the phase II, multi-cohort CheckMate-142 trial.[830,831] 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 adverse events occurred in 20% of patients, with increased amylase and increased lipase being most common.[831] 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 disease control rate for at least 12 weeks was 80%. PFS and OS were 71% and 85%, respectively, at 1 year. In addition, significant, clinically meaningful improvements were observed in patient-reported outcomes of functioning, symptoms, and quality of life. Grade 3 to 4 treatment-related adverse events occurred in 32% of patients, but were manageable.[830]

Based on these data, the panel recommends pembrolizumab, nivolumab, or nivolumab plus ipilimumab as subsequent-line treatment options in patients with metastatic MMR-deficient CRC. These therapies are only options for patients who have not previously received a checkpoint inhibitor. Clinical trials are ongoing to confirm the benefit of these drugs in this setting.

Although PD-1 immune checkpoint inhibitors are generally well tolerated, serious adverse reactions—many immune-mediated—occur in as many as 21% to 41% of patients.[828,830-832] The most common immune-mediated side effects are to the skin, liver, kidneys, gastrointestinal tract, lungs, and endocrine systems.[833-835] 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.[833,836-838]

Larotrectinib or Entrectinib for NTRK Fusion-positive Disease in the Non–First-line Setting

Recent studies have estimated that about 0.2% to 1% of CRCs carry *NTRK* gene fusions.[638,639] Two targeted therapies, larotrectinib and entrectinib, 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.[839,840]

A pooled analysis of three studies (a phase I including adults, a phase I/II involving children, and a phase II involving adolescents and adults) studied the safety and efficacy of larotrectinib in patients with *NTRK* gene fusion-positive tumors, including four patients with colon cancer.[637] For the whole population, the ORR was 75% (95% CI, 61%–85%) by independent review and 80% (95% CI, 67%–90%) by investigator assessment,[637] although the package insert cites a 25% ORR for colon tumors specifically.[840] Larotrectinib was found to be well-tolerated as the majority

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(93%) of adverse events were grades 1 or 2 and no treatment-related adverse events of grades 3 or 4 occurred in more than 5% of patients.[637]

A pooled analysis of multiple global phase I/II studies tested the efficacy and safety of entrectinib in 54 adult patients with advanced or metastatic *NTRK* gene fusion-positive solid tumors, including four patients with CRC.[841] For the whole population, ORR was 57.4% (95% CI, 43.2%–70.8%), median PFS was 11.2 months (95% CI, 8.0–14.9), and median OS was 20.9 months (95% CI, 14.9–not reached) by independent review. Notably, a similar ORR (50% vs. 59.5%) was observed among those with central nervous system metastasis, indicating that entrectinib has activity in this population.[841] The package insert sites a 25% ORR for CRCs specifically.[839] Entrectinib was found to be well-tolerated as most treatment-related adverse effects were grade 1 or 2 and managed with dose reduction, leading few (3.9%) patients to discontinue therapy due to treatment-related adverse effects.[841]

Based on these results the panel added larotrectinib and entrectinib 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.

Regorafenib

Regorafenib is a small-molecule inhibitor of multiple kinases (including VEGF receptors, 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.[842] The phase III CORRECT trial randomized 760 patients who progressed on standard therapy to best supportive care with placebo or regorafenib.[843] 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 months 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.[844] Patients with progressive mCRC were randomized 2:1 to receive regorafenib or placebo after 2 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; $P < .001$).

Regorafenib has only shown activity in patients who have 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; no data inform the best order of these therapies.

The most common grade 3 or higher adverse events in the regorafenib arm of the CORRECT trial were hand-foot skin reaction (17%), fatigue (10%), hypertension (7%), diarrhea (7%), and rash/desquamation (6%).[843] Severe and fatal liver toxicity occurred in 0.3% of 1100 patients treated with regorafenib across all trials.[842] In a meta-analysis of four studies that included 1078 patients treated with regorafenib for CRC, gastrointestinal 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.[845] In the subset of 500 patients with CRC, the incidence of all-grade hand-foot skin reaction was 46.6%.

The randomized, phase II ReDOS trial investigated the use of an alternative dose schedule to reduce the toxicities related to regorafenib treatment.[846] 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 adverse events were also lower among the dose-escalation group compared to the standard dosing group. Based on these results, the

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panel agreed that a dose-escalation strategy is an appropriate alternative approach for regorafenib dosing.

The phase IIIb CONSIGN trial assessed the safety of regorafenib in 2872 patients from 25 countries with refractory mCRC.[847] The REBECCA study also assessed the safety and efficacy of regorafenib in a cohort of 654 patients with mCRC within a compassionate use program.[848] The safety profile of regorafenib in both of these trials was consistent with that seen in the CORRECT trial.

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.[849,850]

Results of the double-blind, randomized, controlled, international phase III RECOURSE trial were published in 2015,[851] followed shortly thereafter by approval of trifluridine-tipiracil by the FDA.[852] With 800 patients with mCRC who progressed through at least 2 prior regimens randomized 2:1 to receive trifluridine-tipiracil or placebo, the primary endpoint of OS was met (5.3 months vs. 7.1 months; HR, 0.68; 95% CI, 0.58–0.81; $P < .001$).[851] Improvement was also seen in the secondary endpoint of PFS (1.7 months vs. 2.0 months; HR, 0.48; 95% CI, 0.41–0.57; $P < .001$). The most common adverse events associated with trifluridine-tipiracil in RECOURSE were neutropenia (38%), leukopenia (21%), and febrile neutropenia (4%); one drug-related death occurred.[851] A postmarketing surveillance study did not reveal any unexpected safety signals[853] and a subgroup analysis of the RECOURSE trial reported similar efficacy and safety regardless of age, geographical origin, or *KRAS* mutation status.[854]

The panel added trifluridine-tipiracil as an additional treatment option for patients who have progressed through standard therapies. It can be given before or after regorafenib; no data inform the best order of these therapies. 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).

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 intravenous contrast of the chest, abdomen, and pelvis.[192] MRI with intravenous contrast should be considered if CT is inadequate. The panel also recommends tumor *KRAS/NRAS and BRAF* gene status testing at diagnosis of metastatic disease and consideration of testing for HER2 amplifications for all patients with *KRAS/NRAS* wild-type metastatic colon cancer (see *Biomarkers for Systemic Therapy*, above).

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 recent randomized clinical trial of patients with resectable metachronous metastases assessed the role of PET/CT in the workup of potential curable disease.[855] 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

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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.[856]

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).[857] False-positive PET/CT scan results can occur in the presence of tissue inflammation after surgery or infection.[857] An MRI with intravenous 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 *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.

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.[858-866] 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.[859,861,867,868] In addition, emerging data suggest that chemotherapy, followed by resection of liver metastases before resection of the primary tumor, might be an effective approach in some patients, although more studies are needed.[869-876]

If a patient with resectable liver or lung metastases is a candidate for surgery, the panel recommends the following options: 1) synchronous or staged colectomy with liver or lung resection[348,356] followed by adjuvant chemotherapy (FOLFOX [preferred], CAPEOX [preferred], 5-FU/LV, or capecitabine[250,668]); 2) neoadjuvant chemotherapy for 2 to 3 months (ie, FOLFOX [preferred],[347] CAPEOX [preferred], or FOLFIRI [category 2B]), followed by synchronous or staged colectomy with liver or lung resection; or 3) colectomy followed by adjuvant chemotherapy (see neoadjuvant options above) and a staged resection of metastatic disease. 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.

Unresectable Synchronous Liver or Lung Metastases

For patients with metastatic disease that is deemed to be potentially convertible (see *Conversion to Resectability*, above),[877] 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

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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 the patient is an appropriate candidate for intensive therapy. Debulking surgery or ablation without curative intent is not recommended.

For patients with liver-only or lung-only disease that is deemed unresectable (see *Determining Resectability*, above), the panel recommends chemotherapy corresponding to initial therapy for metastatic disease (eg, FOLFIRI, FOLFOX, or CAPEOX chemotherapy alone or with bevacizumab; FOLFIRI or FOLFOX with panitumumab or cetuximab; FOLFOXIRI alone or with bevacizumab).

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.[878] Other retrospective analyses also have shown a potential benefit.[879-881] Separate analyses of the SEER database and the National Cancer Database also identified a survival benefit of primary tumor resection in this setting.[882,883]

On the other hand, a different analysis of the National Cancer Database came to the opposite conclusion.[884] 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.[885] 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. Furthermore, complications from the intact primary lesion are uncommon in these circumstances,[384] 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.[886] However, other systematic reviews and meta-analyses have concluded that, whereas data may not be strong, resection of the primary tumor may provide a survival benefit.[878,887-889] Another systematic review and meta-analysis identified five studies that compared open to laparoscopic palliative colectomies in this setting.[890] 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

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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 gastrointestinal perforation in the setting of bevacizumab is not decreased by removal of the primary tumor, because large bowel perforations, in general, and perforation of the primary lesion, in particular, are rare.

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 cytoreductive surgery and/or intraperitoneal chemotherapy can be considered in experienced centers for selected patients with limited peritoneal metastases for whom R0 resection can be achieved. 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.[855,891,892] Specifically, Joyce et al[891] reported that the preoperative PET changed or precluded curative-intent liver resection in 25% of patients. A recent randomized clinical trial assessed the role of PET/CT in the workup of patients with resectable metachronous metastases.[855] 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 history of the patient and through the absence of colectomy.

Patients with resectable disease are classified according to whether they have undergone previous chemotherapy. For patients who have resectable metastatic disease, treatment is resection with 6 months of perioperative chemotherapy (pre- or postoperative or a combination of both), with choice of regimens based on previous therapy. For patients without a history of chemotherapy use, FOLFOX or CAPEOX is preferred, with capecitabine or 5-FU/LV as category 2B options. There are also cases when perioperative chemotherapy is not recommended in metachronous disease. In particular, patients with a history of previous chemotherapy and an upfront resection can be observed or may be given

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

Patients determined to have unresectable disease through cross-sectional imaging scan (including those considered potentially convertible) should receive an active systemic therapy regimen based on prior chemotherapy history (see *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.[893] Quality of life is an outcome that is rarely measured but of unquestioned clinical relevance.[894] 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.[894] PFS is often used as a surrogate, but its correlation with OS is inconsistent at best, especially when subsequent lines of therapy are administered.[894-896] 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.[897]

A recent study, in which individual patient data from three RCTs were pooled, tested endpoints that take into account subsequent lines of therapy: duration of disease control, which is the sum of PFS times of each active treatment; and time to failure of strategy, which includes intervals between treatment courses and ends when the planned lines of treatment end (because of death, progression, or administration of a new agent).[895] 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.[898,899] Further evaluation of these and other surrogate endpoints is warranted.

Posttreatment 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,[261] and a recent study found that 95% of recurrences occurred in the first 5 years.[900]

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[901-903] and in multiple meta-analyses of RCTs designed to compare low- and high-intensity programs of surveillance.[904-909] Intensive postoperative surveillance has also been suggested to be of benefit to patients with stage I and IIA disease.[910] 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.[911]

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Results from the recent 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).[912] 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).[913] 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 two months, with imaging performed if CEA increases were seen twice, in 3223 patients at 11 hospitals treated for non-mCRC in the Netherlands.[914] 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.[915]

The randomized phase III PRODIGE 13 trial will compare 5-year OS after intensive radiologic monitoring (abdominal ultrasound, chest/abdomen/pelvis CT, and CEA) with a lower intensity program (abdominal ultrasound and chest x-ray) in patients with resected stage II or III colon or rectal tumors.[916]

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 who are potentially curable of 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.[909]

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,[917] 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

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curative surgery.[904,917] 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.[909] 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.[904,918] Routine CEA monitoring and CT scanning are not recommended beyond 5 years. Use of PET/CT to monitor for disease recurrence is not recommended.[918,919] The CT that accompanies a 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.[909,920] Furthermore, use of post-treatment surveillance colonoscopy has not been shown to improve survival through the early detection of recurrence of the original CRC.[909] The recommended frequency of post-treatment surveillance colonoscopies is higher (ie, annually) for patients with Lynch syndrome.[29]

CT scan is recommended to monitor for the presence of potentially resectable metastatic lesions, primarily in the lung and liver.[904] Hence, CT scan is not routinely recommended in asymptomatic patients who are not candidates for potentially curative resection of liver or lung metastases.[904,918]

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).[921,922] 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.[261,900] The American Society of Colon and Rectal Surgeons also released surveillance guidelines, which are also very similar to NCCN surveillance recommendations.[923] 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.[924]

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

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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. A recent analysis of patients with resected or ablated colorectal liver metastases found that the frequency of surveillance imaging did not correlate with time to second procedure or median survival duration.[925] Those scanned once per year survived a median of 54 months versus 43 months for those scanned 3 to 4 times per year (*P* = .08), suggesting that annual scans may be sufficient in this population.

Managing an Increasing CEA Level

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

In a recent retrospective chart review at Memorial Sloan Kettering Cancer Center, approximately half of elevations in CEA levels after R0 resection of locoregional CRC were false positives, with most being single high readings or repeat readings in the range of 5 to 15 ng/mL.[926] In this study, false-positive results greater than 15 ng/mL were rare, and all results greater than 35 ng/mL represented true positives. Following a systematic review and meta-analysis, the pooled sensitivity and specificity of CEA at a cutoff of 10 ng/mL were calculated at 68% (95% CI, 53%–79%) and 97% (95% CI, 90%–99%), respectively.[927,928] 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 recent systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT in this setting.[929] The pooled estimates of sensitivity and specificity for the detection of tumor recurrence were 94.1% (95% CI, 89.4–97.1%) and 77.2% (95% CI, 66.4–85.9), respectively. Use of PET/CT scans in this scenario is permissible within these guidelines. The panel does not recommend a so-called blind or CEA-directed laparotomy or laparoscopy for patients whose workup for an increased CEA level is negative,[930] 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.[931] 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

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therapeutic relationship with a primary care physician throughout their lifetime.[932]

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).[933-938] 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.[939-945] Specific management interventions to address these and other side effects are described in a review,[946] and a survivorship care plan for patients with CRC have been published.[947]

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.[932]

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.[948] 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.[949] More recent data support the conclusion that physical activity improves outcomes. In a cohort of more than 2000 survivors of non-mCRC, those who spent more time in recreational activity had a lower mortality than those who spent more leisure time sitting.[950] In addition, recent 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.[951] Similar results were seen in other studies and in recent meta-analyses of prospective studies.[952-955]

A retrospective study of patients with stage II and III colon cancer enrolled in NSABP trials from 1989 to 1994 showed that patients with a BMI of 35 kg/m^2 or greater had an increased risk of disease recurrence and death.[956] 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.[957] 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.[958] A meta-analysis of prospective cohort studies found that pre-diagnosis obesity was associated with increased CRC-specific and all-cause mortality.[959]

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Other analyses confirm the increased risk for recurrence and death in obese patients.[89,960-963]

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.[964] 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.[965] However, several possible explanations for this so-called “obesity paradox” have been suggested.[966] 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.[967] There is also some evidence that higher postdiagnosis intake of total milk and calcium may be associated with a lower risk of death in patients with stage I, II, or III CRC.[95] Recent analysis of the CALGB 89803 trial found that higher dietary glycemic load was also associated with an increased risk of recurrence and mortality in patients with stage III disease.[968] 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.[969] The link between red and processed meats and mortality in survivors of non-mCRC has been further supported by recent data from the Cancer Prevention Study II Nutrition Cohort, in which survivors with consistently high intake had a higher risk of CRC-specific mortality than those with low intake (RR, 1.79; 95% CI, 1.11–2.89).[87]

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,[970] also provides “a teachable moment” for the promotion of overall health, and an opportunity to encourage patients to make choices and changes compatible with a healthy lifestyle. In addition, a recent trial showed that telephone-based health behavior coaching had a positive effect on physical activity, diet, and BMI in survivors of CRC, suggesting that survivors may be open to health behavior change.[971]

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 to no more than 1 drink/day for women and 2 drinks/day for men; and quit smoking.[970] 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.[972]

Secondary Chemoprevention for CRC Survivors

Limited data suggest a link between post-colorectal-cancer-diagnosis statin use and increased survival.[112,973,974] A meta-analysis that included 4 studies found that post-diagnosis statin use increased OS (HR, 0.76; 95% CI, 0.68–0.85; $P < .001$) and cancer-specific survival (HR, 0.70; 95% CI, 0.60–0.81; $P < .001$).[973]

Abundant data show that low-dose aspirin therapy after a diagnosis of CRC decreases the risk of recurrence and death.[975-981] 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–

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0.92) and OS (HR, 0.95; 95% CI, 0.90–1.01).[975] 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.[977,982-987] 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.[988]

Based on these data, the panel believes that survivors of CRC can consider taking 325 mg aspirin daily to reduce their risk of recurrence and death. Importantly, aspirin may increase the risk of gastrointestinal bleeding and hemorrhagic stroke, and these risks should be discussed with CRC survivors.[989]

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 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 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 chemotherapy would likely convert a patient from an unresectable to a resectable 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, abdominal, and pelvic 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. Recommended initial therapy options for advanced or metastatic disease depend on whether the patient is appropriate for intensive therapy. The more intensive initial therapy options include FOLFOX, FOLFIRI, CAPEOX, and FOLFOXIRI. Addition of a biologic agent (eg, bevacizumab, cetuximab, panitumumab) is an option in combination with some of these regimens, 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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